Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tirzepatide for managing overweight and obesity [ID6179]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

First committee meeting:

1. **Company submission** from Eli Lilly and Company
   a. **Company summary of information for patients (SIP)**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. All About Obesity
   b. Association for the Study of Obesity (ASO)
   c. British Obesity Metabolic Surgery Society (BOMSS)
   d. Diabetes UK

4. **Expert personal perspectives** from:
   a. Sarah Le Brocq – patient expert, nominated by All About Obesity (*see item 3a)
   b. Dimitris Papamargaritis, Associate Professor and Honorary Consultant in Diabetes and Endocrinology – clinical expert, nominated by ASO (*see item 3b)

5. **External Assessment Report** prepared by Warwick Evidence

6. **External Assessment Report – factual accuracy check**

7. **External Assessment Report - factual accuracy check (additional data request)**

8. **External Assessment Report – addendum**

Second committee meeting:

9. **Questions sent to NHS England**

10. **NHS England submission**
    a. **Response to questions**

11. **Issues for stakeholders letter**

12. **Response to letter from Eli Lilly and Company**

13. **Response to letter from consultees and commentators:**
    a. British Obesity and Metabolic Surgery Society (BOMSS)
    b. Diabetes UK
    c. Novo Nordisk

14. **Response to NHS England response from Eli Lilly and Company**

15. **Evidence request sent to company**

16. **Company response to evidence request**
    a. Appendix for Q1

17. **EAG critique of company responses**

After second committee meeting:

18. **Summary of committee's preferred assumptions at ACM2**

19. **Company response to committee's preferred assumptions**

20. **EAG report after ACM2**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tirzepatide for managing overweight and obesity ID6179

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
ACS	Acute coronary syndrome
AESI	Adverse events of special interest
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
AOM	Anti-obesity medication
ASCVD	Atherosclerotic cardiovascular disease
BGR	Brook–Gelman–Rubin
BHF	British Heart Foundation
BMI	Body mass index
BNF	British National Formulary
BPD	Borderline personality disorder
CAD	Coronary artery disease
CBT	Cognitive behavioural therapy
CCC	Complex chronic conditions
CEM	Cost effectiveness model
CfB	Change from baseline
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disorder
CPAP	Continuous positive airway pressure
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DMC	Data Monitoring Comittee
DPP-4	Dipeptidyl peptidase 4
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAS	Efficacy analysis set
eGFR	Estimated glomerular rate
EMA	European Medicines Agency
eMIT	Electronic market information tool
ERG	Evidence review group
ETD	Estimated treatment difference
FAS	Full analysis set
FCE	Finished consultant episode
FDA	US Food and Drugs Administration
FPG	Fasting plasma glucose

FSG	Fasting serum glucose
GCP	Good clinical practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
GORD	Gastro-oesophageal reflux disease
GPM	General population mortality
GPRD	General Practice Research Database
HbA1c	Glycated haemoglobin
HCRU	Healthcare resource utilisation
HDL	High-density lipoprotein
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IBT	Intensive behavioural therapy
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPS	Individual patient simulation
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IWQOL	Impact of Weight on Quality of Life
IWRS	Interactive web response system
LSM	Least squares mean
LVH	Left ventricular hypertrophy
LYG	Life years gained
MCMC	Markov Chain Monte Carlo
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	Multiple endocrine neoplasia syndrome type 2
MGB	Mini gastric bypass
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NBSR	National Bariatric Surgery Registry
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence

NIHR	The National Institute for Health and Care Research
NMA	Network meta-analysis
OAGB	One-anastomosis gastric bypass
OECD	Organisation for Economic Co-operation and Development
OHID	Office for Health Improvement and Disparities
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
PCA	Prescription cost analysis
PCOS	Polycystic ovary syndrome
PGIS	Patient Global Impression of Status
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services and Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QW	Once weekly
RCT	Randomised controlled trial
REML	Restricted maximum likelihood
RYGB	Roux-en-Y gastric bypass
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
SPB	Systolic blood pressure
SUCRA	Surface under the cumulative ranking curve
SWMS	Specialist weight management services
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse events
TEM	Treatment effect modifier
THIN	The Health Improvement Network
TIA	Transient ischemic attack
TID	Three times daily
TLR	Targeted literature review
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TZP	Tirzepatide
UKPDS	United Kingdom prospective diabetes study
VBA	Visual basic for application

VLDL	Very-low-density lipoprotein cholesterol
WBC	White blood cell
WHO	World Health Organisation

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The decision problem addressed within this submission is broadly consistent with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal; any differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

The population defined in the final scope is consistent with the anticipated marketing authorisation for tirzepatide. Under the full anticipated marketing authorisation, tirzepatide (Mounjaro®) is indicated for [redacted]

[redacted]

[redacted]

As per the update to the NICE guidelines for obesity identification, assessment and management (CG189), it is anticipated that tirzepatide would be used for lower BMI thresholds for people with certain ethnic backgrounds.

The expected eligible population for tirzepatide in NHS England clinical practice, and the focus of this submission, is **adults with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity**, which represents a narrower population than the anticipated marketing authorisation for tirzepatide in this indication. For transparency and comprehensiveness, clinical data and economic analyses will also be provided in additional relevant subpopulations, and for the entire indication.

The target population for tirzepatide is narrower than the anticipated marketing authorisation because it reflects a population with a substantial unmet need for a more effective treatment than current pharmacological options for chronic weight management in NHS England clinical practice.[1-3] It is well-established that ≥10% weight loss is associated with substantial clinical benefits among people with obesity who have comorbidities, and that further benefits can be derived through ≥15% or even ≥20% weight loss.[4-6] Weight loss of this magnitude reduces the burden of existing comorbidities, reduces the risk of developing further weight-related comorbidities and significantly improves health-related quality of life (Section B.1.3.3). Given the substantial clinical, economic, and humanistic burden associated with obesity, particularly among those with weight-related comorbidities (Section B.1.3.2), adults with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity are expected to derive substantial benefits from treatment with tirzepatide in NHS clinical practice based on the efficacy results from clinical trials.[3]

Based on the benefits of substantial weight loss highlighted above, the NICE guidelines for obesity management (CG189) and the accompanying quality standard (QS127) recommend a "higher level of intervention" for individuals with obesity and weight-related comorbidities compared to individuals without weight-related comorbidities.[7, 8] Furthermore, HM Government

has recently announced the initiation of a two-year pilot program, aimed at expanding access to pharmacological treatments for obesity to enable a broader population of people with obesity to benefit from these treatments.[9] Given that tirzepatide represents a more efficacious option than current pharmacological options for chronic weight management in NHS clinical practice, the anticipated positioning for tirzepatide aligns with current NICE clinical guidelines, and is also expected to support ongoing public health efforts aimed at reducing the prevalence of obesity in the UK.[9, 10]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults who have a BMI of: • ≥30 kg/m^2 (obesity) or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) and at least one weight-related comorbidity	Adults who have a BMI of ≥30 kg/m^2 (obesity) and at least one weight-related comorbidity. For transparency and comprehensiveness, clinical data and economic analyses will also be provided in additional relevant subpopulations, and for the entire indication.	The population addressed in this submission will be adults who have a BMI of ≥30 kg/m^2 (obesity) and at least one weight-related comorbidity; this represents a narrower population than the population defined in the NICE final scope. The anticipated positioning for tirzepatide is narrower than the NICE scope as it reflects a population with a substantial unmet need for a more effective treatment option than current pharmacological options for weight management in NHS England clinical practice, given that individuals with obesity and weight-related comorbidities have been demonstrated to particularly benefit from significant weight loss.[4, 7, 8, 11-14] As such, adults with a BMI of ≥30 kg/m^2 and at least one weight-related comorbidity are expected to derive substantial benefits from treatment with tirzepatide in NHS clinical practice. As a more effective treatment than current pharmacological options for weight management in NHS clinical practice, the anticipated positioning of tirzepatide is also aligned with the NICE guidelines for chronic weight management (CG189) and the accompanying quality standard (QS127), which recommend a greater level of intervention for people with obesity and weight-related comorbidities.[7, 8]
Intervention	Tirzepatide	Tirzepatide	N/A – In line with the NICE final scope.

Comparator(s)	• Standard management without tirzepatide (including a reduced calorie diet and increased physical activity) • Semaglutide (for the population for whom semaglutide is recommended in TA875) • Liraglutide (for the population for whom liraglutide is recommended in TA664) • Orlistat (prescription dose)	• Standard management without tirzepatide (including a reduced calorie diet and increased physical activity) • Semaglutide as an adjunct to diet and exercise (for the population of patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity, given that no data are available specifically for the population for whom semaglutide is recommended in TA875 [Section B.3.2.3.2])[2] • Liraglutide as an adjunct to diet and exercise (for the population for whom liraglutide is recommended in TA664)[1]	Consistent with the conclusions of the Committee across three previous appraisals in obesity and overweight management [TA875, TA664],[1, 2] orlistat is not widely used in clinical practice due to its reported poor efficacy and undesirable side effects, which lead to poor adherence and treatment outcomes.[1, 2] This is highlighted by data published by NHS England, which demonstrate a consistent decline in the prescription of orlistat over the last decade.[15] Based on these data demonstrating the limited role of orlistat within current UK clinical practice, and the clear Committee determination made in prior appraisals in this indication, orlistat should not be considered a relevant comparator for tirzepatide for the treatment of overweight and obesity.
Outcomes	The outcome measures to be considered include: • BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • adverse effects of treatment • health-related quality of life	Due to the long-term follow-up required to collect direct evidence for the incidence of T2DM, CV events and mortality, data on these outcomes is not currently available. The probability of each event occurring is therefore determined using surrogate endpoints employed in risk equations, including BMI, systolic blood pressure (SBP), total cholesterol and high-density lipoprotein (HDL). A detailed explanation of how the incidence of these outcomes is determined in the model is provided in Section B.3.3.2.
Subgroups to be considered	None.	• Adults who have a BMI of ≥35 kg/m^2, non-diabetic hyperglycaemia and a high risk of cardiovascular disease (i.e. the population of patients for whom treatment with	People who are eligible for liraglutide are a subset of the population of relevance for this submission. The subgroup of adults with a BMI of ≥35 kg/m^2, non-diabetic hyperglycaemia and a high risk of cardiovascular disease is to be considered

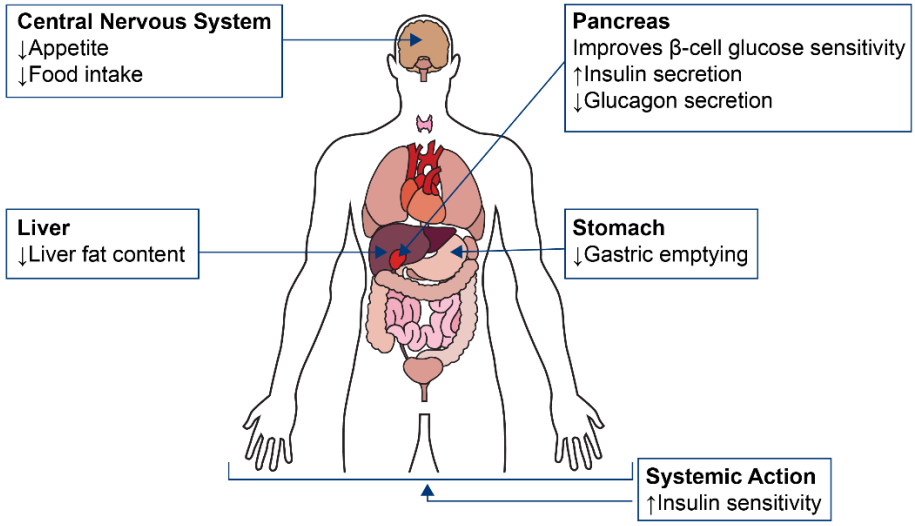
		liraglutide is recommended in TA664).[1] • Adults with a BMI of ≥30 kg/m^2 (irrespective of any weight-related comorbidities, i.e., including those with and those without comorbidities) • Adults with a BMI of ≥35 kg/m^2 (irrespective of any weight-related comorbidities).	in order to accurately compare tirzepatide with liraglutide. For transparency and comprehensiveness, clinical data and economic analyses are also provided in additional relevant subpopulations, and for the entire indication.
Special considerations including issues related to equity or equality			The following equality issues should be considered relevant for this appraisal: • Socioeconomic inequalities • BMI variations between different ethnicities • Access inequalities for treatment of other disabilities If tirzepatide is approved, any recommendations should include similar wording to previous appraisals [TA875, TA664][1, 2], to adjust BMI thresholds for certain populations.

Abbreviations: AE: Adverse event; AESI: Adverse event of special interest; BMI: Body mass index; EQ-5D: EuroQol-5D; HbA1c: glycated haemoglobin; N/A: Not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; SAE: Serious adverse event; SF-36: 36-Item Short Form Health Survey; SWMS: specialist weight management services.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of tirzepatide in the treatment of obesity is presented in Table 2. The draft Summary of Product Characteristics (SmPC) is located in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Tirzepatide (Mounjaro®)
Mechanism of action	Tirzepatide is a synthetic, long-acting, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist. Tirzepatide is made up of 39 amino acids, and has a C20 fatty diacid moiety which is highly selective to both GIP and GLP-1 receptors.[16] GIP and GLP-1 receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, leukocytes, gut and kidney, and GIP receptors are also present on adipocytes. These GIP and GLP-1 receptors are activated by binding to GIP and GLP-1, respectively. As a GIP and GLP-1 receptor agonist, tirzepatide mimics the complementary actions of these incretin hormones (Figure 1). Tirzepatide results in clinically meaningful weight loss by acting upon GIP and GLP-1 receptors within the brain, leading to reduced appetite and decreased energy intake. In addition, tirzepatide delays gastric emptying, further reducing appetite and caloric intake.[16-18] In addition to its effects on body weight control, tirzepatide has multiple glucoregulatory actions, including a key role in enhancement of glucose-stimulated insulin secretion in pancreatic beta cells and control of glucagon secretion from pancreatic alpha cells. In people with T2DM, the effect of incretins is diminished.[19] Tirzepatide is therefore also licensed as a treatment for T2DM.[16] **Figure 1. Complementary actions of GLP-1 and GIP**  **Abbreviations:** GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide 1 **Adapted from:** Samms, 2020[20]
Marketing authorisation/CE mark status	Marketing authorisation for tirzepatide in this indication is expected to be granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) in [redacted].

Indications and any restriction(s) as described in the SmPC	The anticipated marketing authorisation for tirzepatide in this indication is for [redacted] • [redacted] • [redacted] Tirzepatide is also currently indicated for the treatment of adults with insufficiently controlled T2DM: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes.[16] **Contraindications:**[16] • Hypersensitivity to the active substance or to any of the following excipients: sodium phosphate dibasic heptahydrate, sodium chloride, concentrated hydrochloric acid, sodium hydroxide (for pH adjustment), water for injections • Pregnancy **Special warnings and precautions for use:**[16] • **Acute pancreatitis:** Tirzepatide has not been studied in patients with a history of pancreatitis, and should be used with caution in these patients. Acute pancreatitis has been reported in patients treated with tirzepatide. Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis. • **Hypoglycaemia**: Patients receiving tirzepatide in combination with an insulin secretagogue or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin. • **Gastrointestinal effects:** Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea. These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure. Patients treated with tirzepatide should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications. • **Severe gastrointestinal disease:** Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients. • **Diabetic retinopathy**: Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring. • **Elderly:** Only very limited data are available from patients aged ≥ 85 years.
Method of administration and dosage	Tirzepatide is administered via subcutaneous (SC) injection once weekly (QW), using a pre-filled pen device. The dose should be injected in the abdomen, thigh, or upper arm, rotating the injection site with each dose. The dose can be administered at any time of day, with or without meals.[16] Tirzepatide is initiated at 2.5 mg QW. After 4 weeks, it is increased to 5 mg QW. If needed, the dose can be increased in 2.5 mg increments every 4

<table>
<tr><td></td><td>weeks up to 15 mg. The recommended maintenance doses are 5 mg, 10 mg and 15 mg.</td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations are required.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The following list prices for tirzepatide are confidential subject to approval. The prices are for a 4-week supply of pre-filled pen devices for SC injection. Packs are available for the recommended maintenance doses (5 mg, 10 mg and 15 mg), and for the intermediate titration doses required when following the dose escalation recommendations.
<table>
<tr><th>Tirzepatide dose</th><th>List price</th></tr>
<tr><td>2.5 mg</td><td>[redacted]</td></tr>
<tr><td>5 mg</td><td>[redacted]</td></tr>
<tr><td>7.5 mg</td><td>[redacted]</td></tr>
<tr><td>10 mg</td><td>[redacted]</td></tr>
<tr><td>12.5 mg</td><td>[redacted]</td></tr>
<tr><td>15 mg</td><td>[redacted]</td></tr>
</table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>N/A</td></tr>
</table>

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide 1; MHRA: Medicines and Healthcare Products Regulatory Agency; OSA: obstructive sleep apnoea; QW: once weekly; SmPC: summary of product characteristics; T2DM: type 2 diabetes mellitus.

B.1.3 Health condition and position of the technology in the treatment pathway

Overview and impact of obesity upon health

- Obesity is a chronic, progressive disease, defined by the World Health Organisation (WHO) as abnormal or excessive fat accumulation that presents a risk to health, with a BMI ≥30 kg/m^2.[7, 21]
- In 2021, it was estimated that 26% of adults in England had obesity, and projections from the Organisation for Economic Co-operation and Development (OECD) indicate that this will increase to 35% in 2030.[22, 23]
- Life expectancy is reduced by about 2–4 years in people with a BMI of 30–35 kg/m^2, and 8–10 years in people with a BMI of 40–50 kg/m^2 compared with people without obesity.[11]
- Obesity is associated with numerous comorbidities, including T2DM, CVD, hypertension, osteoarthritis, certain types of cancer, OSA and non-alcoholic fatty liver disease (NAFLD).[11] Nearly all aspects of health-related quality of life (HRQoL) are adversely affected by obesity, but physical functioning and mobility are particularly reduced.[5, 24]
- Weight-related stigma and perceived weight-based discrimination can affect the education, careers and self-confidence of people living with obesity, as well as have an impact on their physical and psychological health.[25, 26]
- There is a considerable economic burden associated with obesity, with government estimates indicating that the NHS spent £6.1 billion on obesity-related ill-health in 2014–15.[27] Costs to wider society are also significant, and were estimated to be £27 billion in 2014–15.[27]

Clinical pathway of care and current treatment options

- Within England, obesity management is currently delivered through a tiered system; current NICE guidelines recommend four tiers of weight management.[7, 8]
    - Tier 1 provides interventions at a population level, whereas Tier 2 provides community-based support and advice, including behavioural interventions, dietary changes and physical activity programs.[28, 29]
    - Most specialist weight management services (SWMS) are provided by a specialist-led Tier 3 service and involve multidisciplinary assessments and longer-term support.
    - Tier 4 provides similar support to Tier 3, but also manages surgical interventions for obesity.[30]
- Interventions for managing obesity include lifestyle changes (such as a reduced calorie diet and increased physical activity); pharmacotherapy (including semaglutide, liraglutide and orlistat); and bariatric surgery.[7]
- Bariatric surgery and orlistat currently have a limited role in obesity management in clinical practice;[1, 2] therefore, the relevant comparators considered in this appraisal are a reduced calorie diet and increased physical activity, semaglutide and liraglutide.
- There has been growing criticism of the current tiered system for obesity management.[29] As such, HM Government has recently announced the initiation of a two-year pilot exploring how incretin-based therapies can be delivered within primary care;[9] it is also anticipated that there will be substantial changes to the current NICE guidelines for obesity prior to the anticipated publication date for this appraisal (currently 27 March 2024).[31] Moreover, NICE has very recently published draft guidance on the use of digital weight management technologies, aimed at further improving access to weight management treatments.[32]

Unmet need

- Studies have demonstrated that ≥10% weight loss is associated with substantial and clinically meaningful benefits, and that further benefits can be derived through ≥15% or even ≥20% weight loss.[4-6]
    - Benefits associated with weight loss of this magnitude include reducing the severity of existing comorbidities, reducing the risk of developing further weight-related comorbidities, and significantly improving HRQoL.[5, 6, 13, 33, 34]
- Evidence suggests that lifestyle interventions alone are often associated with only modest weight loss and limited clinical benefits; a UK cohort study (n=176,495) demonstrated that the probability of achieving a 5% weight reduction with lifestyle intervention alone was low among both men (1 in 8) and women (1 in 7).[3, 35-37]

- Despite the increasing prevalence of obesity and ongoing public health efforts aimed at reducing the burden of obesity in the UK, the availability of highly effective and tolerable pharmacological treatment options is limited:[7, 10, 38]
    - Liraglutide is currently only recommended by NICE for a narrow population of individuals with a BMI ≥35 kg/m^2 with prediabetes and a high risk for CVD, and uptake of this treatment option has been poor.[1, 39]
    - Semaglutide is only recommended by NICE for use in SWMS, which are not consistently available in the UK.[2, 39]
    - Orlistat is not widely used in clinical practice due to its reported poor efficacy and undesirable side effects which lead to poor adherence and treatment outcomes.[1, 2, 15]

Proposed use of tirzepatide

- Given the changing landscape for obesity management and the potential move towards prescribing incretin-based therapies outside of current hospital-based SWMS, the Company anticipates that tirzepatide would be delivered both in primary care and in secondary care, with appropriate access to nutritional and exercise support as per the anticipated license.
- Tirzepatide represents a novel, tolerable and more efficacious option compared with current pharmacological treatments for weight management in NHS clinical practice;[3] a positive recommendation for tirzepatide in individuals with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity would therefore help to address the significant unmet need in this population, thereby reducing the substantial clinical, humanistic and economic burden associated with obesity and supporting ongoing public health efforts to reduce the prevalence of obesity in England.

B.1.3.1 Disease overview

Obesity is a chronic, progressive disease that is considered one of the greatest long-term health challenges facing the UK. The WHO defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health.[21] Several methods exist in screening for and diagnosing obesity and each of them uses a different approach to reflect the extent of body fat. the most common method among these is BMI, which is used as a practical measure in the diagnosis of obesity. A BMI ≥25 kg/m^2 is considered overweight, and a BMI ≥30 kg/m^2 is considered obese,[21] though overweight and obesity can be further classified into BMI categories:

- Overweight: 25–29.9 kg/m^2
- Obesity class 1: BMI 30–34.9 kg/m^2
- Obesity class 2: BMI 35–39.9 kg/m^2
- Obesity class 3: BMI ≥40 kg/m^2

It is well-established that certain ethnicities are more prone to central adiposity and cardiometabolic risks at lower BMIs; therefore, lower BMI thresholds for obesity are recommended to assess people with South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. This is reflected in the NICE guidelines (CG189) by lower BMI thresholds for these groups of ≥27.5 kg/m^2 rather than ≥30 kg/m^2.[11] Differences between sexes may also need to be taken into consideration when measures of obesity other than BMI are used (such as waist circumference or body fat percentage).

Alongside BMI measurements, clinical judgement is also required as BMI is not a direct measure of central adiposity, which is more closely related to risk of complications and negative health outcomes.[11] As such, the NICE guidelines (CG189) recommend calculating waist-to-height ratio as a practical estimate for central adiposity, as well as to help assess and predict patients' health risks.[7]

B.1.3.1.1 *Aetiology*

Obesity is driven by an imbalance between energy intake and expenditure, leading to excessive fat deposition.[40] As a multifactorial disease, obesity is caused by an interplay between various genetic, biological, psychological, social, and environmental factors, most of which are outside the control of an individual with obesity.[41] The relative contribution of each of these factors has been studied extensively, but the WHO Consultation on Obesity suggest that behavioural and environmental factors are the key drivers behind the significant increase in the prevalence of obesity during the past two decades.[42] Key lifestyle factors linked to obesity include consumption of food and drink high in fat and sugar, excessive alcohol consumption, and physical inactivity.[11, 43] In 2021, 27% of adults in England were classified as inactive, leading to an elevated risk of obesity among other negative impacts on overall health.[44, 45]

While environmental factors impact peoples' lifestyles, particularly their food choices, the extent to which environmental factors affect people can vary significantly based on genetics; studies have found that obesogenic environments can accentuate the risk of obesity in adults who are also genetically susceptible to obesity.[46] Overall, genetics contribute around 47–80% of the variation in adiposity between different people, though there is a large number of obesity-related genes, and the mechanisms behind them are not all well-understood.[47]

Hormone signalling also plays an important role in the development of obesity.[48] Dysfunctional neuroendocrine signalling leads to abnormal feeding behaviour and imbalances in energy homeostasis, resulting in surplus energy levels. The energy-surplus condition resulting from the loss of metabolic homeostasis eventually leads to obesity and overweight.[49] Incretin hormones such as GLP-1 and GIP are involved in the regulation of body weight, maintenance of energy balance and glucose homeostasis.[50] Notably, increased secretion of GLP-1 is associated with reduced appetite and food intake, which may lead to weight loss.[51] Furthermore, resistance to the actions of these hormones appears to be associated with obesity.[50, 52, 53]

B.1.3.1.2 *Epidemiology*

Over the past 50 years, there has been a substantial increase in the prevalence of obesity both globally and within the UK.[23, 54] As such, in 2021, it was estimated that 26% of adults in England had obesity, and OECD projections indicate that this will increase to 35% in 2030.[22, 23]

Epidemiological data in the UK indicate that the prevalence of obesity varies by sex, age, education, ethnicity, geography and socio-economic background. Men are more likely to have obesity than women, and obesity is more prevalent in the North of England and the Midlands than the South of England. In addition, higher prevalence of overweight and obesity are reported in areas of greater deprivation.[38] Certain ethnicities are also associated with a higher prevalence of obesity and related risk of ill health.[38] For example, compared with the general population, the prevalence of obesity in the UK is lower in men of Bangladeshi and Chinese family origin, whereas it is higher for women of African, Caribbean and Pakistani family origin.[10]

B.1.3.2 Burden of disease

B.1.3.2.1 *Morbidity and mortality*

Obesity is one of the leading causes of death and disability both worldwide and in the UK, and has a substantial impact on length of life; life expectancy is reduced by approximately 2–4 years in people with a BMI of 30–35 kg/m^2, and 8–10 years in people with a BMI of 40–50 kg/m^2

compared to people without obesity.[11, 55] This is largely driven by the burden of weight-related comorbidities, which can further contribute to an individual's obesity and considerably impact their HRQoL.

B.1.3.2.2 *Weight-related comorbidities*

Obesity is a multisystem disease, putting patients at increased risk of numerous comorbidities, including numerous cardiovascular, respiratory, musculoskeletal, and metabolic conditions as well as certain types of cancers (Table 3).[11] Obesity can also have an impact on mental health, leading to an increased incidence of psychiatric disorders such as depression and anxiety among people with obesity, as discussed in greater detail below.[56]

Table 3. Summary of key comorbidities associated with obesity

Class of comorbidity	Comorbidities
Cancer/malignancy	Postmenopausal breast, endometrial, colon and rectal, gallbladder, prostate, ovarian, endometrial renal cell, oesophageal adenocarcinoma, pancreatic, and kidney cancer
Cardiovascular	Acute coronary syndrome (ACS), coronary artery disease (CAD), obesity-associated cardiomyopathy, essential hypertension, left ventricular hypertrophy, cor pulmonale, accelerated atherosclerosis, pulmonary hypertension of obesity, dyslipidaemia, congestive heart disease (CHD), left ventricular hypertrophy (LVH), cardiomyopathy, pulmonary hypertension, lymphoedema (legs)
Gastrointestinal	Gall bladder disease (cholecystitis, cholelithiasis), gastro-oesophageal reflux disease (GORD), reflux esophagitis, non-alcoholic steatohepatitis (NASH), NAFLD, fatty liver infiltration, acute pancreatitis
Genitourinary	Stress incontinence
Metabolic/endocrine	T2DM, prediabetes, metabolic syndrome, insulin resistance, and dyslipidaemia
Musculoskeletal	Pain in back, hips, ankles, feet and knees; osteoarthritis (especially in the knees and hips), plantar fasciitis, back pain, coxavera, slipped capital femoral epiphyses, Blount disease and Legg-Calvé-Perthes disease, and chronic lumbago
Neurological	Stroke, dementia, idiopathic intracranial hypertension, and meralgia paraesthesia
Obstetric and perinatal	Pregnancy-related hypertension, foetal macrosomia, very low birthweight, neural tube defects, preterm birth, increased caesarean delivery, increased postpartum infection and pelvic dystocia, preeclampsia, hyperglycaemia, gestational diabetes
Psychological	Depression, anxiety, personality disorder, and obesity stigmatisation
Respiratory/pulmonary	OSA, Pickwickian syndrome (obesity hypoventilation syndrome), higher rates of respiratory infections, asthma, hypoventilation, pulmonary emboli risk
Surgical	Increased surgical risk and postoperative complications, deep venous thrombosis, including wound infection, pulmonary embolism, and postoperative pneumonia
Reproductive (Women)	Anovulation, early puberty, polycystic ovary syndrome (PCOS), infertility, hyperandrogenism, and sexual dysfunction
Reproductive (Men)	Hypogonadotropic hypogonadism, decreased libido, and sexual dysfunction
Extremities	Venous varicosities, lower extremity venous and/or lymphatic oedema

Abbreviations: ACS: Acute coronary syndrome; CHD: Chronic heart failure; GORD: Gastroesophageal reflux disease; LVH: Left ventricular hypertrophy; NAFLD: non-alcoholic fatty liver disease; OSA: Obstructive sleep apnoea; NASH: non-alcoholic steatohepatitis; PCOS: Polycystic ovary syndrome; T2DM: Type 2 diabetes mellitus.
Source: Fruh, 2017[57]

Within the wide range of comorbidities associated with obesity, some are particularly common and can have a substantial impact on morbidity and mortality. One such comorbidity is CVD and its related clinical events, including acute coronary syndrome (ACS) and stroke, which are strongly associated with obesity and results in substantially increased morbidity and mortality for patients with obesity. In the UK, around 168,000 people died from CVD in 2021, making it responsible for approximately 25% of all deaths.[58] T2DM also has a well-established link with obesity; it is estimated that obesity is responsible for 80–85% of a patient's risk of developing T2DM.[59] Additionally, obesity is the most common risk factor for the development of OSA, which has been associated with a 1.9-times increased risk in all-cause mortality and 2.65-times increased risk of cardiovascular mortality.[60] NAFLD is also known to be closely linked to obesity and insulin resistance, though the aetiology of NAFLD is not completely understood.[61] NAFLD can progress to liver fibrosis, liver failure, cirrhosis and hepatocellular cancer, and all-cause mortality increases exponentially with the fibrosis stage (1–4).[62, 63]

B.1.3.2.3 *Weight-related stigma*

Obesity has numerous additional adverse impacts on the lives' of people living with obesity, and is associated with a social stigma, which can affect education, careers and self-confidence.[25] People with obesity have poorer job prospects and are less likely to be employed than people of a healthy weight, translating into approximately 10% reduced earnings .[23]

Weight-related stigma can also have a substantial impact on the mental health of people with obesity, leading to depression, anxiety and lowered self-esteem. A systematic review and meta-analysis of 25 studies reported that anxiety is more prevalent in people with obesity compared with people with normal weight.[64, 65] Additionally, weight-related stigma can impact individuals' physical health and negatively impact their obesity; individuals who have experienced weight-related discrimination are reported to be less active and less likely to exercise in the future than those who do not perceive any weight-based discrimination.[26] Furthermore, weight-related stigma is also associated with higher caloric intake and a reduced quality diet, as well as unhealthy eating behaviours such as binge eating and skipping meals.[66]

B.1.3.2.4 *HRQoL*

Considering the numerous comorbidities and adverse impacts of weight-related stigma on people's lives, it is unsurprising that there is a significant association between BMI and HRQoL, with nearly all aspects of HRQoL being adversely affected by obesity.[5] A study using data collected during the Health Survey for England 2003 (12,188 respondents) demonstrated that obesity significantly reduced HRQoL, with a reduction of 0.027 EQ-5D points relative to people without obesity.[67] Furthermore, a more recent large-scale population-based retrospective study in the UK (N=64,631) reported that the mean (SD) EQ-5D score for individuals with normal weight was 0.85 (0.20), which was higher than for individuals classified as having overweight (0.81 [0.22]), and individuals who were obese (BMI 30–40 kg/m^2; 2.73 [0.27]), and morbidly obese (BMI ≥ 40 kg/m^2; 0.62 [0.32]).[68]

Obesity has a particularly prominent impact on psychological and physical functioning, and studies have reported that patients with obesity have substantially reduced mental, physical and mobility component scores by various measures of HRQoL.[5, 24] In a study among people scheduled for bariatric surgery (N=446) conducted from 2013 to 2016 in Scotland, a strong positive correlation between BMI values and Impact of Weight on Quality of Life (IWQOL) Physical Function score (higher IWQOL score indicating worsening of QoL) was reported.[69] For each 10 kg/m^2 increase in BMI, there was a decrease of 14.2 (95% CI: 10.7 to 17.7; p<0.0001) in

IWQOL-Lite Physical Function score. Furthermore, 25.8% of the participants reported they were "unable to work due to illness or disability".[69] Certain comorbidities including T2DM, heart disease, and osteoarthritis may exacerbate the negative impact of obesity on HRQoL and the impact of obesity on HRQoL also differs according to sex, age and ethnicity.[24, 70]

B.1.3.2.5 *Socioeconomic impact*

There is a considerable economic impact associated with obesity. In the UK, government estimates indicate that NHS England spent £6.1 billion on obesity-related ill-health in 2014–15, which is projected to increase to £9.7 billion by 2050.[27] This high cost burden is largely a result of obesity-related comorbidities, both in the long-term management of these diseases and in the short-term costs associated with clinical events such as stroke and knee replacement. The cost of bariatric surgery is also high and further contributes to the substantial economic burden associated with obesity in England. In addition to the economic burden on the NHS, obesity produces substantial costs to wider society due to lost productivity; government estimates indicate that the cost of obesity to wider society was £27 billion in 2014–15, which is predicted to increase to £50 billion in 2050.[27] Studies have observed that obesity is associated with absenteeism, disability pension and overall work impairment, all of which are likely to contribute to lost work-hours.[71]

B.1.3.3 Impact of weight loss

While there is a large body of evidence demonstrating that as little as 5% weight loss in people with obesity is associated with significant improvements in clinical outcomes across a range of comorbidities, more substantial weight loss (≥10% or even ≥15%) has been demonstrated to result in even further clinical benefits in terms of achieving improvement in or remission of existing comorbidities.[5, 6, 33, 34] This is exemplified in a review by Ryan *et al.* (2017), in which the clinical impact of different magnitudes of weight loss (5%, 10%, and 15%) was examined.[4] Although glycaemic measurements and triglycerides were reported to improve with limited weight loss (from 2.5%), greater weight loss was associated with greater improvements in these outcomes. Additional weight loss (5–10%) was also associated with further benefits, both in reducing systolic and diastolic blood pressure, and increasing HDL cholesterol. Notably, the review by Ryan *et al.* highlighted that some weight-related comorbidities, such as OSA and NAFLD, may require at least 10–15% weight loss for clinically meaningful improvements to be observed, highlighting the value of further weight loss on clinical outcomes.[4]

As well as improving the impact of existing weight-related comorbidities, significant weight loss can also meaningfully reduce the risk of developing additional weight-related comorbidities. In a UK primary care database study, ten different obesity-related outcomes were evaluated in people who had a BMI of 25–50 kg/m^2 (N=571,961) who had been managed with a reduced calorie diet, pharmacological treatment, referral to a dietitian, or bariatric surgery. Overall, this study reported that, assuming an initial BMI of 40 kg/m^2, a 13% reduction in body weight was associated with a relative risk reduction of 41% in T2DM, 40% in OSA, 22% in hypertension, 19% in dyslipidaemia, and 18% in asthma.[72]

Beyond the benefits highlighted above, weight loss can also lead to considerable improvements in HRQoL, particularly in physical functioning.[73-75] A systematic literature review (SLR) and meta-analysis including studies assessing the impact of lifestyle and pharmacological intervention among people with overweight and obesity reported that 5–10% weight loss was associated with improvement in HRQoL, and that physical HRQOL was more markedly improved with weight loss compared with mental HRQoL.[13] Moreover, in studies evaluating bariatric surgery where the

greatest weight loss was achieved (≥20%), a more apparent improvement in HRQoL was reported.[13]

B.1.3.4 Clinical care pathway

B.1.3.4.1 *NICE clinical guidelines*

Within the NHS in England, obesity management is currently delivered through a tiered system. The current NICE guidelines for obesity identification, assessment and management (CG189) and the accompanying quality standard (QS127) recommend four tiers of weight management depending on a patient's BMI, waist circumference and comorbidities, but also taking other factors into consideration, such as special education needs and disabilities.[7, 8] The primary goal of weight management in England clinical practice is to achieve clinically meaningful weight loss (defined by NICE as weight loss of at least 5–10%).[11] Tiers 1 and 2 are managed under local authorities. Tier 1 provides universal interventions such as health promotion at a population level, whereas Tier 2 provides community-based support and advice. Treatments in Tier 2 may include a combination of behavioural interventions, dietary changes and physical activity programs which usually run for up to 12 weeks, although policies vary locally.[28, 29] Orlistat can also be provided in Tier 2 services for eligible individuals (BMI ≥30 kg/m^2, or ≥27 kg/m^2 with associated with risk factors).[28] However, as noted in Table 1, orlistat is not widely used in clinical practice due to its reported poor efficacy and undesirable side effects which lead to poor adherence and treatment outcomes.[1, 2]

Tiers 3 and 4 provide SWMS, although SWMS are not limited to these tiers. SWMS is defined in CG189 as a specialist primary, community or secondary care-based multidisciplinary team offering a combination of surgical, dietetic, pharmacological and psychological obesity management interventions.[7]

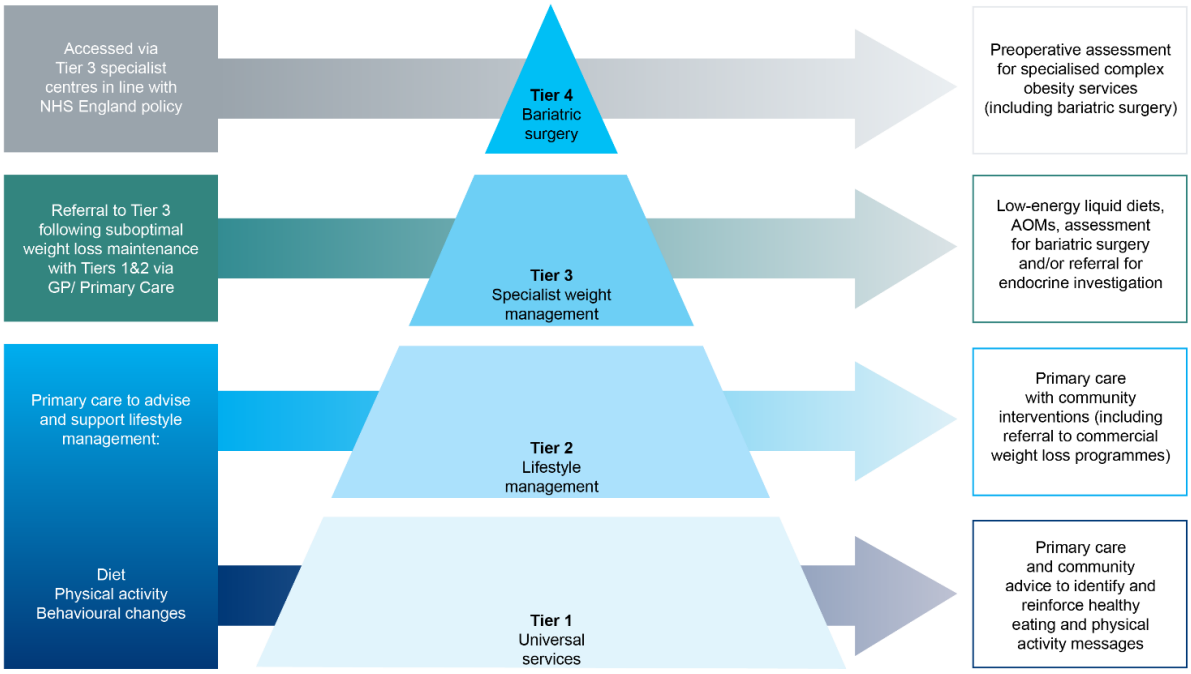
According to CG189, patients can be considered for referral to Tier 3 services if one or more of the following eligibility criteria are fulfilled,[7] although it should be noted that approximately one third of the population of England and Wales do not have access to Tier 3 services (Section B.1.3.5):[39]

- the underlying causes of overweight or obesity need to be assessed
- the person has complex disease states or needs that cannot be managed adequately in Tier 2 (for example, the additional support needs of people with learning disabilities)
- conventional treatment has been unsuccessful
- drug treatment is being considered for a person with a BMI of >50 kg/m^2
- specialist interventions (such as a very-low-calorie diet) may be needed
- surgery is being considered

As part of the Tier 3 services, patients may also be assessed for and referred onto Tier 4 services, which provide similar support to Tier 3, but also manage bariatric surgery.[76] In England, bariatric surgery is only available for patients with a BMI ≥40 kg/m^2, or between 35–40 kg/m^2 and other significant disease accessing SWMS. However, bariatric surgery is rarely used in clinical practice, with only around 0.1% of eligible patients actually receiving this treatment.[1, 2] The NHS England National Obesity Audit (NOA) reported that only 4409 people received bariatric surgery

between 2021–22.[77] As such, bariatric surgery is not considered a relevant comparator for tirzepatide and was not included in the final scope.

Figure 2. Tiered system for management of obesity in the NHS



Abbreviations: AOM: Anti-obesity medication; GP: general practitioner; NHS: national health service.
Adapted from: Hazlehurst et al., 2020[29]

B.1.3.4.2 *Current treatment options and relevant comparators for tirzepatide*

Excluding bariatric surgery, interventions for managing obesity in NHS England clinical practice include lifestyle interventions (such as a reduced calorie diet and increased physical activity) and pharmacological treatments. Pharmacological treatments for obesity that are currently recommended by NICE include orlistat, liraglutide and semaglutide.[1, 2, 11] However, as discussed previously (Table 1), orlistat is not widely used in clinical practice due to its reported poor efficacy and undesirable side effects which lead to poor adherence and treatment outcomes, and is therefore not considered a relevant comparator for tirzepatide, aligning with the Committee conclusions in previous appraisals in obesity and overweight management [TA875, TA664].[1, 2]

The comparators considered in the population of relevance to this appraisal (BMI of ≥30 kg/m^2 and at least one weight-related comorbidity) are **semaglutide** as an adjunct to a reduced calorie diet and increased physical activity, and a **reduced calorie diet and increased physical activity alone**. For completeness, **liraglutide** as an adjunct to diet and exercise is also considered as a comparator within the relevant narrower subpopulation, though uptake in NHS clinical practice is low. For the broader populations considered in this appraisal (the entire indication, adults with a BMI of ≥30 kg/m^2 and adults with a BMI of ≥35 kg/m^2), a reduced calorie diet and increased physical activity alone is considered. This consideration of relevant comparators is based on the populations for whom treatment with semaglutide and liraglutide are recommended by NICE (Table 4), which are both narrower than the target population for tirzepatide (adults with a BMI≥30 kg/m^2 and at least one weight-related comorbidity). Further explanation of the comparators considered in the economic evaluation is provided in in Section B.3.2.3.2.

Table 4. NICE-recommended pharmacological treatments for obesity

Treatment	NICE-recommended eligible population

Semaglutide 2.4 mg [TA875][2]	Semaglutide 2.4 mg (SC formulation) is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:
	• It is used for a maximum of 2 years, and within a SWMS providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
	• They have **at least 1 weight-related comorbidity** and:
	  ○ A BMI of at least 35.0 kg/m^2, or
	  ○ A BMI of 30.0 kg/m^2 to 34.9 kg/m^2 and meet the criteria for referral to specialist weight management services in NICE's guideline on obesity: identification, assessment and management.

Liraglutide 3.0 mg [TA664][1]	Liraglutide 3.0 mg is indicated in secondary care by a specialist multidisciplinary tier 3 weight management service. Liraglutide is recommended as an option for managing patients with obesity, alongside a reduced-calorie diet and increased physical activity in adults **fulfilling all the following criteria**: • BMI ≥35.0 kg/m^2 (or at least 32.5 kg/m^2 for members of ethnic minority groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population) • Non-diabetic hyperglycaemia • A high risk of CVD based on risk factors such as hypertension and dyslipidaemia

Abbreviations: BMI: Body mass index; CVD: cardiovascular disease; NICE: National Institute for Health and Care Excellence; SWMS: specialist weight management service.

B.1.3.5 Anticipated use of tirzepatide in NHS England clinical practice

As outlined in Section B.1.3.4, obesity management is currently delivered through a tiered system. However, there has been growing criticism of this system, and some consider that the approaches taken to date have not been effective in treating many patients with obesity.[29] In particular, there has been critique of the wide inequality in access to treatment based on geographic location, with fewer services being located in Integrated Care Systems (ICSs) with the highest prevalence of obesity and highest levels of deprivation.[29] An evidence review for referral to bariatric surgery published in February 2023 indicated that approximately one third of the population of England and Wales do not have access to Tier 3 services.[39] These sentiments are also reflected in the 'Get It Right First Time' program within the NHS, which aims to improve the treatment and care of patients; as part of the recently published recommendations for endocrinology, it is noted that only 44% of hospitals offer Tier 3 services, and therefore that improved access to weight assessment and management is needed.[78] HM Government has also recently acknowledged that the recommendations for the Tier in which pharmacotherapies can be delivered may be limiting patient access.[9] For instance, NICE currently only recommends semaglutide for use in SWMS (Table 4), meaning that there would be only ~35,000 people who could access this treatment once it is launched, despite many more people being eligible for this treatment.[9]

Given these challenges, HM Government has recently announced the initiation of a two-year pilot, which will explore how pharmacological treatments for obesity can be made available to more people by expanding SWMS outside of hospital settings, including exploring how these services could be safely delivered in primary care.[31] Moreover, the Company understands that

the NICE clinical guidelines for obesity management will be further updated in the coming months;[31] as such, it is expected that there will be substantial changes to the current recommendations for obesity management prior to the anticipated publication date for this appraisal (currently 27 March 2024). Finally, NICE have very recently published draft guidance for the use of digitally enabled technologies to support treatment with pharmacological treatments in SWMS, aimed at further improving access to these interventions.[32] In the context of this changing landscape, and the potential move towards prescribing incretin-based therapies outside of current hospital-based SWMS, the Company anticipates that tirzepatide would be delivered **both in primary care and in secondary care** for individuals with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity.

As part of the proposed treatment setting for the delivery of tirzepatide, the Company anticipates that tirzepatide would be provided alongside appropriate nutritional and exercise support, as per the anticipated license. However, unlike in the current system, the Company anticipates that this support could be provided outside of SWMS using appropriate triaging and an assessment of the individual needs of the patient and their obesity. In this respect, the Company considers that tirzepatide should not be limited to Tiers 3 or 4 or other SWMS services only. Tier 2 services, which deliver diet and exercise support, are currently provided in primary care with community interventions (Figure 2). If the revised system consistently expands provision of such support in primary care, then tirzepatide does not need to be limited to SWMS. Furthermore, with nearly a decade of GLP-1 RA usage in primary care for T2DM, NHS primary care services have demonstrated the ability to consistently support a large patient population to initiate and stay on injectable incretin therapies. With the NHS Long Term Plan promoting care closer to home,[79] the Company considers that the public health benefits arising from ease of access to highly efficacious therapies greatly outweigh any potential concerns relating to the mode of delivery (primary or secondary care) for the lifestyle changes that are required alongside treatment with tirzepatide.

B.1.3.6 Unmet need and role of tirzepatide

Despite the increasing prevalence of obesity, the availability of highly efficacious and tolerable treatment options for patients with obesity is limited in the NHS. Lifestyle modifications such as dietary changes, exercise, and behavioural therapy are often recommended as the initial management strategy for people with obesity. However, studies have demonstrated that lifestyle modifications alone are often associated with only modest weight loss and limited clinical benefits;[35, 37] a UK cohort study conducted in 2015 using electronic health records from 6,704 men and 99,791 women with obesity (excluding individuals who received bariatric surgery) reported that during a maximum of 9 years follow up, the annual probability of achieving a 5% weight reduction was low among both men and women, with only 1 in 8 men and 1 in 7 women achieving this weight loss target.[36] Moreover, the SURMOUNT-1 trial demonstrated that patients receiving placebo (as an adjunct to diet and exercise) achieved only minor improvements in weight loss outcomes.[3] In addition, use of semaglutide and liraglutide is limited to narrow populations within SWMS, which restricts access to these treatments.[1, 2] Finally, orlistat is associated with efficacy and tolerability issues which limits its use in clinical practice.[1, 2, 15]

As highlighted in Section B.1.3.2, studies among people with obesity have demonstrated that weight loss can significantly reduce the burden of existing comorbidities, reduce the risk of developing additional comorbidities, and provide considerable benefits in terms of HRQoL, both in physical and psychological domains.[5, 6, 13, 33, 34] While 5–10% weight loss can lead to considerable clinical benefits, and indeed is the current target for weight loss in SWMS,[11] additional benefits can be achieved through further weight loss, and evidence suggests that

weight loss of at least 10–15% may be needed to meaningfully alleviate the burden of certain comorbidities, such as OSA and NAFLD.[4] Results from pivotal trial for semaglutide, STEP-1, indicate that only 50.5% of patients achieved ≥15% weight loss at Week 68 after receiving SC semaglutide 2.4mg, while results from pivotal liraglutide trial, SCALE, indicate that only 14.4% patients achieved ≥15% weight loss at Week 56 after receiving liraglutide.[2, 12, 80] As such, there remains a substantial unmet need for a highly effective pharmacological treatment that allows a greater proportion of patients with a BMI ≥30 kg/m^2 with weight-related comorbidities to benefit from ≥10% or even ≥15% weight loss.

In the SURMOUNT-1 randomised controlled trial (RCT), tirzepatide 5, 10 and 15 mg, each as an adjunct to a reduced calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week) were shown to provide substantial and sustained weight loss up to 72 weeks, and have also demonstrated an acceptable safety profile.[3] At Week 72, tirzepatide met both coprimary primary endpoints, with 89% and 91% of participants receiving 10 and 15 mg tirzepatide achieving ≥5% weight loss, respectively, versus 35% with placebo. Moreover, tirzepatide 10 and 15 mg demonstrated a mean body weight reduction of >20% at week 72, which was significantly greater than placebo and also represents substantial degree of weight reduction in response to pharmacological intervention as compared with findings reported in other phase 3 clinical trials investigating anti-obesity medications.[3] In fact, 50% and 57% of participants in the 10 mg and 15 mg groups, respectively, had a reduction in body weight of 20% or more, versus 3% in the placebo group.[3] Additionally, a significantly greater proportion of participants on tirzepatide achieved body weight reductions of ≥10% and ≥15% from baseline than placebo.[3]

Considering this unprecedented efficacy, tirzepatide is anticipated to provide substantial clinical benefits to patients who have a BMI of ≥30 kg/m^2 in the presence of at least one weight-related comorbidity and would address a substantial unmet need in this expected eligible population. The availability of a pharmacological treatment that facilitates this magnitude of weight loss could also help alleviate the substantial cost burden of obesity-related events and treatments, and would also contribute to ongoing public health efforts to reduce the prevalence and impact of obesity in the UK.

B.1.4 Equality considerations

The following inequalities should be considered relevant for this appraisal:

Socioeconomic inequalities:

People in deprived areas often face significant barriers to accessing affordable, healthy food and to regularly exercising, translating into a higher prevalence of overweight and obesity in people of lower socioeconomic status.[27] This is highlighted by the data published by Office for Health Improvement and Disparities (OHID) for 2020/21 which demonstrate that the prevalence of excess weight is 9% higher than the least deprived areas.[81] Links between obesity and other measures of socioeconomic background are also apparent based on the OHID obesity profile education data; the percentage of people with no formal qualifications who are affected by obesity is almost 16% higher than among people with a degree.[81] The draft health inequalities briefing published by NICE in February 2023 indicated that the difference in the prevalence of obesity based on socioeconomic status may be particularly pronounced for women, with 39% of women in the most deprived areas being reported as having obesity, compared with 22% in the least deprived areas.[82]

BMI variations between different ethnicities:

Some ethnicities develop comorbidities related to excess adipose tissue at lower BMIs. NICE therefore recommends that lower BMI thresholds should be used for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background to prompt earlier intervention in these populations.[7]

Access inequalities for treatment of other medical conditions:

There are often barriers associated with accessing treatments for other medical conditions among people with overweight and obesity. According to a report by the Royal College of Surgeons, around 31% of NHS Clinical Commissioning Groups include measures to restrict elective surgery, such as hip and knee replacements, for patients with obesity.[83] This means that patients above a certain BMI are required to lose weight prior to being considered eligible for elective surgery.[84] However, many patients are unable to reduce their weight, which prevents them from accessing these procedures, resulting in a cycle of poor mobility and limited physical activity which can lead to further weight gain. In addition, people with obesity are also at a higher risk for anaesthetic complications, which can make performing both elective and non-elective surgeries particularly challenging for these patients.[85] As such, the Royal College of Anaesthetists recommends that additional specialist staff, equipment and post-operative care are provided compared to people without obesity.[86] Given that certain hospitals may have limited resources and/or expertise managing patients with obesity, this may cause delays or other access challenges for patient with obesity requiring surgery.

B.2 Clinical effectiveness

Evidence of tirzepatide in weight management

- Tirzepatide 5, 10 and 15 mg are currently being investigated for weight management as part of the SURMOUNT clinical trial programme. The SURMOUNT clinical trial program consists of nine Phase 3 trials investigating the safety and efficacy of tirzepatide for weight management in various populations and treatment settings.
- The main clinical evidence presented in this submission is from the SURMOUNT-1 trial, which is a Phase 3, randomised, placebo-controlled trial that evaluated the efficacy and safety of tirzepatide 5, 10 and 15 mg (each adjunct to a reduced-calorie diet [500-calorie deficit] and increased physical activity [increased to at least 150 minutes per week]) for adults with a BMI ≥30kg/m^2 (obesity), or a BMI ≥27kg/m^2 (overweight) and at least one weight-related comorbidity.
- The main phase of the SURMOUNT-1 trial ran over 72 weeks. An extension phase of 2 years is ongoing for participants with prediabetes at baseline and is expected to be completed by May 2024.

Efficacy

- Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for mean percent change in body weight from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority versus placebo, which was evaluated as a key secondary endpoint.
    - In the tirzepatide 10 and 15 mg groups, the mean percent change in body weight from baseline was −21.4% and −22.5%, respectively, compared to −2.4% of the placebo group.
    - In the tirzepatide 5 mg group, the mean percent change in body weight from baseline was −16.0%.
- Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority versus placebo, which was evaluated as a key secondary endpoint.
    - In the tirzepatide 10 and 15 mg groups, 96.2% and 96.3% of participants achieved a body weight reduction of ≥5%, respectively, compared to 27.9% of the placebo group.
    - In the tirzepatide 5 mg group, 89.4% of participants achieved a body weight reduction of ≥5%, respectively.
- Tirzepatide 10 mg and 15 mg were each associated with significantly greater percentages of participants achieving reductions of ≥10%, ≥15%, or ≥20% at Week 72 compared to placebo.
    - In the tirzepatide 10 and 15 mg groups, 85.9% and 90.1% of participants achieved a body weight reduction of ≥10%, respectively, compared to 13.5% of the placebo group.
    - In the tirzepatide 10 and 15 mg groups, 73.6% and 78.2% of participants achieved a body weight reduction of ≥15%, respectively, compared to 6.0% of the placebo group.
    - In the tirzepatide 10 and 15 mg groups, 55.5% and 62.9% of participants achieved a body weight reduction of ≥20%, respectively, compared to 1.3% of the placebo group.

Safety

- The SURMOUNT-1 trial demonstrated that tirzepatide 5, 10 and 15 mg have an acceptable safety profile, with gastrointestinal (GI) events (including nausea, diarrhoea and constipation) representing the most common treatment-emergent adverse events (TEAEs).
    - Most GI TEAEs were transient, mild to moderate in severity, and occurred primarily during the dose-escalation period.
- A total of 137 (5.4%) participants permanently discontinued from study drug due to an AE or death, including 21 (3.3%) participants in the placebo group and 30 (4.8%), 46 (7.2%), and 40 (6.3%) participants in the tirzepatide 5, 10 and 15 mg groups, respectively.
    - The most common reasons for discontinuation were GI AEs.
    - Eleven deaths were reported across all treatment groups, but none were considered by the investigator to be related to the study drug.
- The side effects of tirzepatide treatment can be managed by following the guidance in the SmPC and monitored via routine pharmacovigilance.

Network meta-analysis

- While a reduced calorie diet and increased physical exercise represents one of the key comparators used in NHS clinical practice, no direct head-to-head evidence is available for the other relevant comparators for tirzepatide; therefore, a network meta-analysis (NMA) was conducted to assess the relative efficacy of tirzepatide versus semaglutide and liraglutide in the populations considered in the economic analysis.
- The NMA was conducted based on a robust SLR, thus the evidence informing the NMA was systematically identified and extracted.
- A rigorous assessment of feasibility was conducted and all six studies included in the NMA were considered to be relatively homogenous with respect to treatment effect modifiers (TEMs), study design, patient populations, reported outcomes, comparability of placebo arms and reporting timepoints.
- NMA analyses included change from baseline (CfB) in weight (%), CfB in HDL, CfB in SBP and CfB in total cholesterol; these endpoints are used to inform the economic model.
- An NMA was conducted using the efficacy estimand for use in the model base case. NMA analyses were conducted both for the whole SURMOUNT-1 trial population and for the populations considered in the economic model for whom indirect treatment comparisons were required (BMI ≥30 kg/m^2 with one weight-related comorbidity [base case population] and BMI ≥35 kg/m^2 with prediabetes and a high CVD risk).
    - An NMA was not relevant for the BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2 (each irrespective of comorbidities) subgroups given that the only comparator in these subpopulations is a reduced calorie diet and increased physical activity (Section B.3.2.3.2), and head-to-head evidence for this comparison is available from SURMOUNT-1 post-hoc analyses (Section B.2.7.3).
- In order to ensure that the most appropriate model was selected for each analysis, four models were used for each analysis and their fit assessed. These models were fixed effect (FE) and random effect (RE) models, and FE and RE models with an adjustment for baseline risk (BR).
    - When RE model fail to converge or model fit of FE and RE models were similar based on deviance information criterion (DIC) and deviance statistics, FE models were chosen for ease of interpretation.[87]
- Based on the efficacy estimand analyses in the population with a BMI ≥30 kg/m^2 with one weight-related comorbidity, all three doses of tirzepatide had a statistically superior CfB in weight (%) compared to placebo, and the 10 mg and 15 mg doses of tirzepatide also demonstrated statistically superior weight loss compared to semaglutide.
- For CfB HDL, all three doses of tirzepatide were statistically superior to both placebo and semaglutide.
- For CfB total cholesterol, all three doses of tirzepatide were statistically superior compared to placebo. The 15 mg dose of tirzepatide also had a numerically superior decrease in total cholesterol compared to semaglutide.
- For CfB in SBP, all three doses of tirzepatide had a statistically superior decrease in SBP compared to placebo. The 10 mg and 15 mg doses of tirzepatide also had a numerically superior decrease in SBP compared to semaglutide.
- The efficacy estimand analyses results in the whole trial population were congruent with the comparative efficacy findings for diet and exercise and semaglutide in the base case population.
- In the whole trial population, and BMI ≥35 kg/m^2 with prediabetes and high CVD risk subpopulation, all three doses of tirzepatide were numerically or statistically superior to liraglutide for all endpoints.
- Additional analyses using the treatment regimen estimand were also conducted; these were largely consistent with the efficacy estimand analyses that informed the model base case.

Summary

- There is a considerable unmet need for a more effective and tolerable treatment compared to current pharmacological options for individuals with obesity (BMI ≥30 kg/m^2) and at least one weight-related comorbidity, given the substantial clinical, humanistic, and economic burden associated with weight management in this population.
- The SURMOUNT-1 trial and the NMA have demonstrated that tirzepatide leads to significantly

greater weight loss vs current pharmacological treatments for weight management. Tirzepatide would therefore help to address the substantial unmet need in individuals with obesity (BMI≥30 kg/m^2) and at least one weight-related comorbidity and would consequently represent an important advancement for weight management in the UK.

Tirzepatide is currently being investigated in a series of clinical trials known as the SURMOUNT program. The objective of the SURMOUNT trial program is to comprehensively investigate the safety and efficacy of tirzepatide for weight management in a variety of populations and treatment settings.

In total, the programme consists of nine individual Phase 3 studies. Full results are available for two of the trials in this clinical trial programme: SURMOUNT-1 and SURMOUNT-2. Top-line results are also available for SURMOUNT-3 and SURMOUNT-4, with full results anticipated in October 2023. Section B.2.2 provides an overview of the SURMOUNT trials for which results are currently available, while Section B.2.11 provides an overview of all other trials in the program, with details of when results for these trials are expected.

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted in June 2022 and subsequently updated in March 2023 to identify all relevant RCT efficacy and safety evidence for tirzepatide and its relevant comparators for weight management to support this appraisal. In total, the SLR and SLR update identified 129 studies meeting the inclusion criteria, of which 40 studies related to tirzepatide (n=2), liraglutide (n=30), and semaglutide (n=8).

Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified two RCTs investigating tirzepatide, Frias *et al.* 2018 and SURMOUNT-1 from the SURMOUNT trial program for tirzepatide in weight management.[3, 88] The Frias *et al.* 2018 study was a Phase 2 trial including 55 patients with T2DM and a BMI of 23–50 kg/m^2 and is therefore not considered relevant to the population considered for this submission (Section B.1.1). No other studies from the SURMOUNT program were identified as part of the clinical SLR. Although the SURMOUNT-2 study has very recently been published as a full-text publication by Garvey *et al.*, the clinical SLR update was conducted prior to this date.[89] The SURMOUNT-3 and -4 results were also not captured in the clinical SLR, since only top-line results are available in the form of a Lilly press-release, also released after the SLR update.[90] A summary of the SURMOUNT-1, -2, -3 and -4 studies is provided in Table 5.

Aligning with the approach taken in TA875 with the STEP-2 study of weight loss with semaglutide in people with T2DM, the SURMOUNT-2 study is not considered within the economic analyses presented in this submission despite the recent availability of a full-text publication and clinical study report (CSR) for this study.[2, 91] Nonetheless, since people with T2DM who require weight management would be eligible for tirzepatide and the SURMOUNT-2 trial also informed the MHRA license, a summary of the efficacy data from SURMOUNT-2 is presented in Appendix M for completeness, and the SURMOUNT-2 CSR is also provided alongside this submission where additional detail can be found.

The rationale for not including SURMOUNT-2 data in the economic model, and not presenting it

in full in Section B.1, is twofold:

- The T2DM indicated was assessed in a separate NICE appraisal. Therefore, many people with T2DM, who meet the additional criteria specified in the forthcoming guidance, will soon have access to the same doses of tirzepatide considered in this appraisal, following its recent recommendation by NICE in positive final draft guidance ID3938.[92]
- In the SURPASS trial programme in T2DM,[93, 94] and in SURMOUNT-2,[89, 95-97] tirzepatide has demonstrated profound effects on HbA1c in patients with T2DM, but these benefits are not fully reflected in the obesity-specific economic model presented in Section B.3, which takes the simplified approach to T2DM accepted by the committee in TA875 to avoid the model being unduly influenced by assumptions made about the complex T2DM treatment pathway.[2]
    - Related to this, the SURMOUNT-2 trial was conducted in a wide and varied population of people with T2DM with respect to concomitant anti-diabetic medication, duration of diabetes, etc. that is not straightforwardly generalisable into current NHS clinical practice for treating T2DM, with respect to NG28.[98] Additionally, it should be noted that the SURMOUNT-2 trial did not include a 5 mg tirzepatide treatment arm.

Given the exclusion of SURMOUNT-2 from the cost-effectiveness analysis and the availability of only top-line results for SURMOUNT-3 & -4 at the time of submission, only SURMOUNT-1 is considered within this submission and both a CSR and a full text publication (Jastreboff *et al.* 2022)[3] are available for this trial.

SURMOUNT-1 was a Phase 3, randomised, placebo-controlled trial which provides evidence for the clinical effectiveness and safety of tirzepatide 5, 10 and 15 mg, each as an adjunct to diet and exercise, for the treatment of overweight and obesity. The population for SURMOUNT-1 was adults with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity (excluding T2DM). Further details of this study are summarised in Table 6.

Table 5. Summary of SURMOUNT studies presented in the submission and appendices

Trial	Study design	Trial population (N)	Key inclusion / exclusion criteria	Interventions	Primary endpoints	Presented in the submission?
SURMOUNT-1 (Tirzepatide for the treatment of obesity in people without T2DM)	A 72-week, phase 3, international, multicentre, double-blind, randomised placebo-controlled trial and an extension period of 2 years for participants with pre-diabetes	Adults with obesity or overweight (with ≥1 weight-related comorbidity) who did not have diabetes mellitus and reported one or more unsuccessful dietary efforts to lose weight (N=2,539)	Inclusion • BMI ≥30 kg/m², or ≥27 kg/m² • Previous diagnosis of at least one of the following: hypertension, dyslipidaemia, OSA, CVD • History of at least one unsuccessful dietary effort to lose weight Exclusion • Diabetes mellitus • Change in body weight greater than 5 kg within 3 months prior to starting study • Family or personal history of MTC, MEN-2, or pancreatitis	• TZP QW 5 mg • TZP QW 10 mg • TZP QW 15 mg • Placebo QW	Percent change from baseline in body weight at Week 72 Percentage of participants who achieve ≥5% body weight reduction at Week 72	Yes; presented in detail through Section B.1
SURMOUNT-2 (Tirzepatide for the treatment of obesity in people with type 2 diabetes)	A 72-week, phase 3, international, multicentre, double-blind, randomised, placebo-controlled trial	Adults with T2DM who have obesity or overweight with at least one self-reported unsuccessful dietary weight loss effort (N=900)	Inclusion • BMI ≥30 kg/m², or ≥27 kg/m² • Previous diagnosis of at least one of the following: hypertension,	• TZP QW 10 mg • TZP QW 15 mg • Placebo QW	Percent change from randomisation in body weight at Week 72 Percentage of participants who achieve ≥5% body weight reduction	Yes; efficacy results are provided in Appendix M.

			dyslipidaemia, OSA, CVD • History of at least one unsuccessful dietary effort to lose weight Exclusion • Diabetes mellitus • Change in body weight greater than 5 kg within 3 months prior to starting study • Family or personal history of MTC, MEN-2, or pancreatitis		from randomisation at Week 72	
SURMOUNT-3 (Tirzepatide for the treatment of obesity in people who have had a prior intensive lifestyle program)	A two-year, phase 3, international, multicentre, double blind, randomised, placebo-controlled trial	Adults without T2DM who have obesity or are overweight (with ≥1 weight-related comorbidity) who have undergone a lifestyle weight loss program (N=800)	Inclusion • Same as SURMOUNT-1 Exclusion • Same as SURMOUNT-1	• MTD of TZP QW (10 mg or 15 mg) • Placebo QW	Percent change from randomisation in body weight at Week 72 Percentage of participants with ≥5% body weight reduction at Week 72	Yes; top-line results provided in the Appendix M. The full results of the SURMOUNT-3 study will be presented at the ObesityWeek conference in October 2023 and submitted for publication in a peer-reviewed journal.
SURMOUNT-4 (Weight maintenance study of tirzepatide for	An 88-week, phase 3, international, multicentre, double-blind, randomised	Adults without T2DM who have obesity or are overweight (with ≥1 weight-related comorbidity) and	Inclusion • Same as SURMOUNT-1 Exclusion	Lead-in phase: • All participants take TZP QW MTD (10 mg or	Percent change from randomisation (week 36) in body weight at week 88	Yes; top-line results provided in Appendix M. The full results of the

the treatment of obesity in people without T2DM)	placebo-controlled trial	who did not have diabetes mellitus (N=750)	• Same as SURMOUNT-1	15 mg) Treatment phase: • MTD TZP QW (10 mg or 15 mg) • Placebo QW		SURMOUNT-4 study will be presented at the European Association for the Study of Diabetes Annual Meeting in October 2023 and submitted for publication in a peer-reviewed journal.

Abbreviations: µiu/ml: micro international units per millilitre; BMI: body mass index; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase 4; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; MEN-2: multiple endocrine neoplasia syndrome type 2; MI: myocardial infarction; MTC: medullary thyroid cancer; MTD: maximum tolerated dose; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; QW: once-weekly; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TSH: thyroid-stimulating hormone; TZP; tirzepatide
Source: Le Roux et al. 2023.[99]

Table 6: Clinical effectiveness evidence for SURMOUNT-1

Study	SURMOUNT-1 (NCT04184622)
Study design	A Phase 3, randomised, placebo-controlled, double-blinded, international, multicentre study
Population	N=2,539

	Adult participants with:
	• obesity, defined as having a BMI ≥30 kg/m^2; or
	• overweight, defined as having a BMI ≥27 kg/m^2 with at least one weight-related comorbidity, including:
	  ○ OSA
	  ○ Hypertension
	  ○ Dyslipidaemia
	  ○ CV disease

Intervention(s)	Tirzepatide 5, 10 and 15 mg as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week)
Comparator(s)	Placebo as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem (outcomes in bold are incorporated into the model base-case)	Measures of weight loss: • **Body weight** • BMI • Waist circumference **Adverse effects of treatment** HRQoL: • IWQOL-Lite-CT • SF-36 • EQ-5D Glycaemic status: • Fasting serum glucose (FSG) • HbA1c (**prediabetes status**)
All other reported outcomes (outcomes in bold are incorporated into the model base-case)	Surrogate endpoints for obesity complications such as T2DM and CV events: • Lipid parameters (**HDL**, **total cholesterol**, triglycerides) • Blood pressure (**SBP**) Fasting insulin

Abbreviations: BMI: body mass index; CV: cardiovascular; EQ-5D: EuroQoL-5 dimensions; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; HRQoL: health-related quality of life; IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite-Clinical Trials Version; OSA: obstructive sleep apnoea; SF-36: Short Form-36; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus; VLDL: very-low-density lipoprotein cholesterol.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The data and trial information presented in the following sections is taken primarily from the CSR, given the more comprehensive reporting of data, though an overview of the trial methodology and the primary and key secondary endpoints is also provided in the Jastreboff (2022) publication.[3] The endpoints most relevant to this appraisal have been presented in Section B.2.6; details on other endpoints recorded in the trials are available in the CSR supplied alongside the submission.

B.2.3.1 Trial design

SURMOUNT-1 is a Phase 3, randomised, placebo-controlled, double-blinded, international, multicentre study designed to assess the efficacy and safety of three once-weekly doses of tirzepatide (5, 10 and 15 mg), compared with placebo, all as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week), in adults with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity (excluding T2DM). The objective of the study was to compare the effect on body weight of tirzepatide 5, 10 and 15 mg once weekly versus placebo as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week) in patients who were overweight or obese.

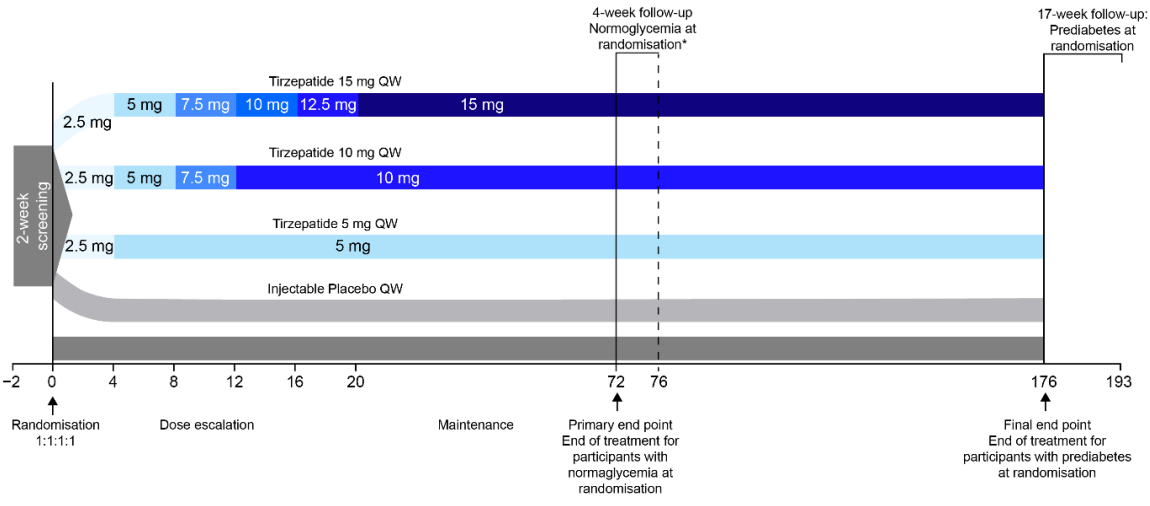
The 72-week, primary study period for SURMOUNT-1 included 3 study periods:

- a 2-week screening period
- a 72-week treatment period
- a 4-week safety follow-up period

In addition, SURMOUNT-1 includes an additional 2-year treatment period followed by a 17-week safety follow-up period for participants with prediabetes at baseline. The 2-year treatment period for participants with prediabetes at baseline is ongoing.

A summary of the trial design of SURMOUNT-1 is presented in Figure 3.

Figure 3. Study design of SURMOUNT-1

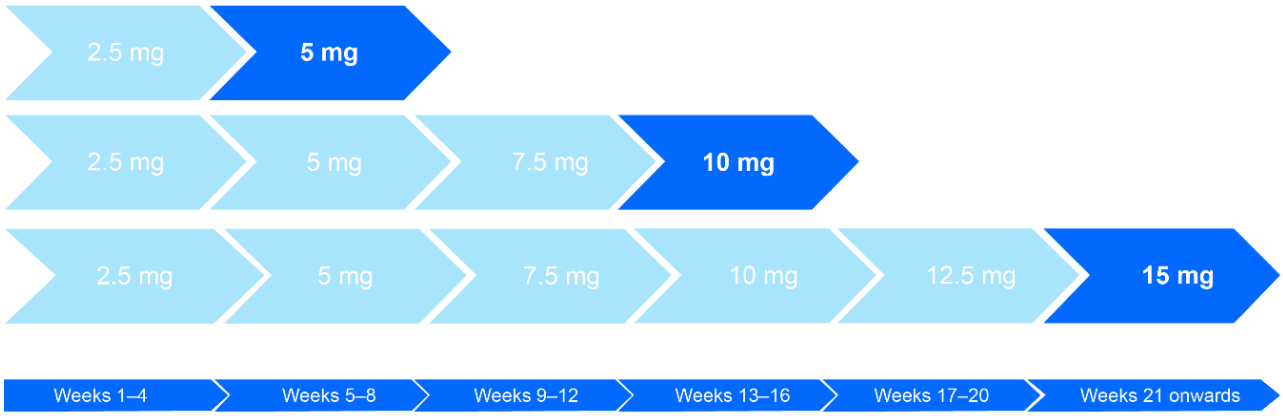


Abbreviations: QW: every week.
Source: SURMOUNT-1 CSR.[100]

B.2.3.1.1 *Dosing algorithm for tirzepatide*

Participants were randomised to either 5 mg, 10 mg or 15 mg once weekly. Tirzepatide dosing algorithms started at 2.5 mg accompanied by dose escalation in 2.5 mg increments every four weeks until the treatment dose was reached. This dose escalation permitted time for development of tolerance to GI effects. The tirzepatide dosing algorithm is summarised in Figure 4 below. Using this dosing algorithm, it takes four weeks to reach a target dose of 5 mg, 12 weeks to reach a target dose of 10 mg and 20 weeks to reach a target dose of 15 mg.

Figure 4: Tirzepatide dosing algorithm in SURMOUNT-1



Footnote: Maintenance doses are shown in bold.
Source: SURMOUNT-1 CSR.[100]

Method of administration

All tirzepatide doses were administered once weekly via SC injection using a pre-filled pen device in the abdomen or thigh if self-administered; a caregiver could administer the injection in the participant's upper arm. There were no restrictions on the time of day each weekly dose of tirzepatide was administered. Participants were advised to administer the injections on the same day and same time each week and were asked to record the actual date and time of all dose administrations.

B.2.3.1.2 *Lifestyle modifications during SURMOUNT-1*

For all participants, lifestyle modification was advised. This consisted of:

- a hypocaloric diet with a 500-calorie deficit that was individually calculated, and
- an increase in physical activity by 150 minutes per week.

During the 72-week study period, all participants consulted with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counselling at Weeks 0, 4, 8 and 12 during dose escalation and then at Week 24 and every 12 weeks thereafter throughout the 72-week trial duration. Participants in the additional 2-year treatment period continued to receive lifestyle management counselling at 3-month intervals.

B.2.3.2 Trial methodology

A summary of the methodology of SURMOUNT-1 is presented in Table 7.

Table 7. Summary of the methodology of SURMOUNT-1

Trial name	SURMOUNT-1
Location	118 centres in 9 countries (Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and the United States, including Puerto Rico)
Trial design	Phase 3, randomised, placebo-controlled, double-blinded, international, multicentre, 72-week study to assess the efficacy and safety of three once-weekly doses of tirzepatide (5, 10 and 15 mg) compared to placebo, all as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week), for adults with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity

Eligibility criteria for participants	**Key eligibility criteria**
	• ≥18 years of age
	• BMI ≥30 kg/m^2, or ≥27 kg/m^2 with at least one weight-related comorbidity, including:
	  ○ Hypertension
	  ○ Dyslipidaemia
	  ○ OSA
	  ○ Cardiovascular disease
	• History of at least one self-reported unsuccessful dietary effort to lose body weight
	Key exclusion criteria
	• Type 1 diabetes mellitus or T2DM
	• Received treatment with medications that may cause weight gain within 3 months prior to randomization
	• Taken medications or remedies intended for weight loss within 3 months prior to randomisation
	• Reported a change in body weight greater than 5 kg within 3 months prior to screening
	• Obesity induced by other endocrinologic disorders, or diagnosed monogenetic or syndromic forms of obesity
	• A history of chronic or acute pancreatitis
	• A family history or personal history of MTC or multiple endocrine neoplasia syndrome type 2
	• A history of significant active or unstable MDD or other severe psychiatric disorders within the last 2 years, or
	• Any lifetime history of a suicide attempt

Method of randomisation	After confirmation of the eligibility criteria, participants were randomised 1:1:1:1 to once-weekly injectable tirzepatide 5 mg, 10 mg, 15 mg, or placebo all as an adjunct to a reduced-calorie diet (500-calorie deficit) and increased physical activity (increased to at least 150 minutes per week). Assignment to treatment group was determined by a computer-generated random sequence using an Interactive Web Response System (IWRS).
Method of blinding	Double-blinding; until the end of the study, treatment assignments remained blinded for the sponsor, investigators, site staff, clinical monitors, and participants. In addition, an external Data Monitoring Committee (DMC) reviewed unblinded safety data.
Method of study drug administration	**Tirzepatide** • Tirzepatide doses of 5 mg, 10 mg, or 15 mg were administered once weekly via SC injection using a pre-filled pen device • The dosing algorithm for tirzepatide is detailed in Section B.2.3.1

	Placebo • Equivalent method of administration to tirzepatide via SC injection using a pen device, as summarised in Section B.2.3.1
Permitted and disallowed concomitant medication	Participants were permitted to use concomitant medications that they required during the study. However, the following exceptions were made: • GLP-1 receptor agonists and DPP-4 inhibitors were not permitted under any circumstances • Metformin was only permitted for participants diagnosed with T2DM during the study • Weight gain- and weight loss-promoting medications were discouraged, although not strictly prohibited
Primary outcomes	**Coprimary endpoints:** • Mean percent change in body weight from baseline to Week 72 for tirzepatide 10 mg and 15 mg • Percentage of study participants who achieve ≥5% body weight reduction from baseline to Week 72 for tirzepatide 10 mg and 15 mg
Secondary and exploratory outcomes	**Key secondary efficacy endpoints (controlled for type 1 error; from baseline to Week 72 unless otherwise specified)** • Mean change in body weight from baseline to Week 20 for pooled tirzepatide 10 mg and 15 mg • Mean percent change in body weight for tirzepatide 5 mg • Percentage of study participants who achieve ≥5% body weight reduction for tirzepatide 5 mg • Percentage of participants who achieve ≥10%, ≥15% and ≥20% body weight reduction for tirzepatide 10 mg and 15 mg • Mean change in waist circumference for tirzepatide 10 mg and 15 mg • Mean change in SF-36v2 acute form Physical Functioning domain score for pooled tirzepatide 10 mg and 15 mg • Mean change in triglycerides, non-HDL cholesterol and HDL cholesterol for pooled tirzepatide 5 mg, 10 mg and 15 mg • Mean change in SBP for pooled tirzepatide 5 mg, 10 mg and 15 mg • Mean change in fasting insulin for pooled tirzepatide 5 mg, 10 mg and 15 mg **Additional secondary efficacy endpoints (from baseline to Week 72 unless otherwise specified)** • Percentage of participants who achieve ≥10% and ≥15% body weight reduction for tirzepatide 5 mg • Mean change in waist circumference for tirzepatide 5 mg • Mean change in SF-36v2 acute form Physical Functioning domain score for tirzepatide 5 mg • Mean change in body weight for tirzepatide 5 mg, 10 mg and 15 mg • Mean change in BMI for tirzepatide 5 mg, 10 mg and 15 mg • Mean change in HbA1c for tirzepatide 5 mg, 10 mg and 15 mg • Mean change in fasting glucose for tirzepatide 5 mg, 10 mg and 15 mg • Mean change in IWQOL-Lite-CT Physical Function composite score for tirzepatide 5 mg, 10 mg and 15 mg • Mean change in DBP for pooled tirzepatide 5 mg, 10 mg and 15 mg • Mean change in LDL-cholesterol, total cholesterol, VLDL-cholesterol, and free fatty acids for pooled tirzepatide 5 mg, 10 mg and 15 mg

	• Population PK and PD parameters
	Exploratory efficacy endpoints
	• Percentage of participants with ≥25% body weight reduction at Week 72
	• Risk difference in proportions for an unconditional treatment effect for participants achieving body weight reduction targets at 72 weeks
	• Percentage of participants with BMI shifts:
	  ○ Percentage achieving a postbaseline BMI <25 kg/m^2
	  ○ Percentage with Class 3 obesity (baseline BMI ≥40 kg/m^2) achieving a postbaseline BMI <25 kg/m^2
	  ○ Percentage with Class 2 obesity (baseline BMI ≥35 and <40 kg/m^2) achieving a postbaseline BMI <25 kg/m^2
	  ○ Percentage with Class 1 obesity (baseline BMI ≥30 and <35 kg/m^2) achieving a postbaseline BMI <25 kg/m^2
	  ○ Percentage with overweight (baseline BMI ≥25 and <30 kg/m^2) achieving a postbaseline BMI <25 kg/m^2
	• Percentage of participants with a change in glycaemic category
	  ○ Prediabetes at baseline to normoglycemia at Week 72
	  ○ Prediabetes at baseline to suspected T2DM at Week 72
	  ○ Normoglycemia at baseline to prediabetes at Week 72
	• Change from baseline in EQ-5D-5L scores at 72 weeks
	• Shifts in PGIS response categories from baseline to postbaseline

Duration of study and follow-up	For participants without prediabetes at baseline, the safety follow-up lasted approximately 4 weeks after the last treatment visit for participants who: • completed the entire treatment period, or • discontinued early and underwent an early-discontinuation visit. For participants with prediabetes at baseline, an additional two-year treatment period is ongoing, which will be followed by a 17-week safety follow-up. During the safety follow-up periods, participants did not and will not receive study drug.
Pre-specified subgroup analyses	• Age group (<65, ≥65 years) • Race • Sex • Ethnicity • Region of enrolment (US, outside the US) • BMI group (<30, ≥30 and <35, ≥35 and <40, ≥40 kg/m^2) • Glycaemic status at randomisation (normoglycemia vs prediabetes

Abbreviations: BMI: body mass index; DBP: diastolic blood pressure; DMC: data monitoring committee; EQ-5D-5L: EuroQoL-5 dimensions 5 level; IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL: low-density lipoprotein; MEN-2 multiple endocrine neoplasia syndrome type 2; MDD: major depressive disorder; MTC: medullary thyroid carcinoma; OSA: obstructive sleep apnoea; PD: pharmacodynamics; PGIS: Patient Global Impression of Status; PK: pharmacokinetics; QW: once weekly; SBP: systolic blood pressure; SF-36v2: Short-Form-36 Health Survey, Version 2, VLDL: very low-density lipoprotein; US: United States.
Source: SURMOUNT-1 CSR.[100]

B.2.3.3 Baseline characteristics of study participants

Overall, demographic and baseline clinical characteristics were comparable across the treatment groups in SURMOUNT-1. Participants had a mean age of 45 years, a mean BMI of 38.0 kg/m^2, and a mean weight of 104.8 kg. In addition, 94.5% of participants had a BMI ≥30.0 kg/m^2, and 67.5% were female. Summaries of the baseline demographic characteristics, baseline clinical

characteristics and baseline comorbidities and certain concomitant therapies are provided in Table 8, Table 9 and Table 10, respectively.

Further details on the specific types of antihypertensive and lipid-lowering therapies used by participants at baseline can be found in the CSR provided alongside this submission.

Table 8. Summary of baseline demographic characteristics of all randomised participants* in SURMOUNT-1

Attribute	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Total (N=2,539)
Age (years), mean ± SD	44.4 ± 12.5	45.6 ± 12.7	44.7 ± 12.4	44.9 ± 12.3	44.9 ± 12.5
Female, n (%)	436 (67.8)	426 (67.6)	427 (67.1)	425 (67.5)	1714 (67.5)
Age Category 1, n (%)					
<65	609 (94.7)	578 (91.7)	605 (95.1)	595 (94.4)	2387 (94.0)
≥65	34 (5.3)	52 (8.3)	31 (4.9)	35 (5.6)	152 (6.0)
Age Category 2, n (%)					
<75	640 (99.5)	629 (99.8)	635 (99.8)	627 (99.5)	2531 (99.7)
≥75	3 (0.5)	1 (0.2)	1 (0.2)	3 (0.5)	8 (0.3)
Country/Region, n (%)					
Argentina	93 (14.5)	90 (14.3)	90 (14.2)	91 (14.4)	364 (14.3)
Brazil	59 (9.2)	59 (9.4)	61 (9.6)	60 (9.5)	239 (9.4)
China	7 (1.1)	9 (1.4)	7 (1.1)	7 (1.1)	30 (1.2)
India	8 (1.2)	9 (1.4)	9 (1.4)	6 (1.0)	32 (1.3)
Japan	33 (5.1)	30 (4.8)	30 (4.7)	31 (4.9)	124 (4.9)
Mexico	108 (16.8)	110 (17.5)	107 (16.8)	108 (17.1)	433 (17.1)
Russian Federation	32 (5.0)	29 (4.6)	30 (4.7)	27 (4.3)	118 (4.6)
Taiwan	15 (2.3)	12 (1.9)	15 (2.4)	16 (2.5)	58 (2.3)
The United States	288 (44.8)	282 (44.8)	287 (45.1)	284 (45.1)	1141 (44.9)
Race, n (%)					
American Indian or Alaska Native	58 (9.0)	56 (8.9)	58 (9.1)	59 (9.4)	231 (9.1)
Asian	71 (11.0)	68 (10.8)	71 (11.2)	66 (10.5)	276 (10.9)
Black or African American	55 (8.6)	48 (7.6)	47 (7.4)	51 (8.1)	201 (7.9)
Multiple	7 (1.1)	9 (1.4)	6 (0.9)	8 (1.3)	30 (1.2)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.5)	9 (0.4)
White	450 (70.0)	447 (71.0)	452 (71.1)	443 (70.3)	1792 (70.6)
Ethnicity, n (%)					
Hispanic or Latino	310 (48.2)	308 (48.9)	297 (46.7)	299 (47.5)	1214 (47.8)
Not Hispanic or Latino	281 (43.7)	276 (43.8)	286 (45.0)	280 (44.4)	1123 (44.2)
Missing	52 (8.1)	46 (7.3)	53 (8.3)	51 (8.1)	202 (8.0)
Education (year), mean ± SD	14.1 ± 4.2	14.0 ± 3.7	14.1 ± 3.8	13.9 ± 4.0	14.0 ± 3.9

Footnotes: 'All randomised participants' were those who were randomly assigned a study treatment (Section B.2.4.3.)
Abbreviations: SD: standard deviation; TZP: tirzepatide
Source: SURMOUNT-1 CSR.[100]

Table 9. Summary baseline clinical characteristics of all randomised participants* in SURMOUNT-1

Attribute	Placebo (N = 643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Total (N=2,539)
Weight (kg), mean ± SD	104.8 ± 21.4	102.9 ± 20.7	105.8 ± 23.3	105.6 ± 22.9	104.8 ± 22.1
Height (cm), mean ± SD	165.6 ± 9.3	165.7 ± 9.0	166.1 ± 9.3	166.1 ± 9.7	165.9 ± 9.3
BMI (kg/m^2), mean ± SD	38.2 ± 6.9	37.4 ± 6.6	38.2 ± 7.0	38.1 ± 6.7	38.0 ± 6.8
BMI Categories, n (%)					
<30	24 (3.7)	38 (6.0)	38 (6.0)	40 (6.3)	140 (5.5)
≥30 to <35	227 (35.3)	241 (38.3)	209 (32.9)	199 (31.6)	876 (34.5)
≥35 to <40	180 (28.0)	174 (27.6)	187 (29.4)	179 (28.4)	720 (28.4)
≥40	212 (33.0)	177 (28.1)	202 (31.8)	212 (33.7)	803 (31.6)
Waist Circumference (cm), mean ± SD	114.0 ± 14.9	113.2 ± 14.3	114.8 ± 15.8	114.4 ± 15.6	114.1 ± 15.2
Prediabetes, n (%)	270 (42.0)	247 (39.2)	262 (41.2)	253 (40.2)	1032 (40.6)
Duration of obesity (year), mean ± SD	14.0 ± 10.7	14.0 ± 10.8	14.7 ± 11.1	14.8 ± 10.8	14.4 ± 10.8
SBP (mmHg), mean ± SD	122.9 ± 12.8	123.6 ± 12.5	123.8 ± 12.8	123.0 ± 12.9	123.3 ± 12.7
DSP (mmHg), mean ± SD	79.6 ± 8.0	79.3 ± 8.1	79.9 ± 8.3	79.3 ± 8.2	79.5 ± 8.2
Pulse rate (bpm), mean ± SD	72.9 ± 9.3	72.3 ± 9.6	71.8 ± 9.6	72.5 ± 10.0	72.4 ± 9.6
Fasting insulin (mIU/L), mean ± SD	14.3 ± 9.9	13.6 ± 10.0	14.1 ± 12.2	14.4 ± 9.3	14.1 ± 10.4
HbA1c (mmol/mol) ± SD	37.4 ± 4.1	37.3 ± 3.96	37.1 ± 4.0	37.2 ± 4.4	37.2 ± 4.1
HbA1c (%) ± SD	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4
Lipid levels (mg/dL), geometric mean (% coefficient of variation)					
Total cholesterol	187.5 (20.5)	187.1 (21.0)	190.6 (19.9)	187.5 (19.9)	188.2 (20.4)
HDL cholesterol	46.6 (27.0)	47.6 (26.3)	47.6 (26.1)	47.6 (25.8)	47.3 (26.3)
LDL cholesterol	109.4 (30.7)	108.7 (30.1)	112.3 (30.3)	109.3 (29.8)	109.9 (30.2)
Triglycerides	130.8 (49.2)	128.7 (51.7)	125.7 (51.1)	128.1 (47.3)	128.3 (49.8)
eGFR (mL/min/1.73 m^2), mean ± SD	98.1 ± 18.3	97.6 ± 17.9	98.3 ± 18.3	98.2 ± 17.7	98.1 ± 18.0
eGFR Categories, n (%)					
≥30 to <45	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	5 (0.2)
≥45 to <60	6 (0.9)	7 (1.1)	10 (1.6)	16 (2.5)	39 (1.5)
≥60 to <90	194 (30.2)	224 (35.6)	184 (28.9)	171 (27.1)	773 (30.4)
≥90	442 (68.7)	398 (63.2)	441 (69.3)	441 (70.0)	1722 (67.8)

Footnotes: *'All randomised participants' were those who were randomly assigned a study treatment (Section B.2.4.3.)
Abbreviations: BMI: body mass index; CKD-EPI: Chronic Kidney Disease-Epidemiology; DSP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SD: standard deviation; TZP: tirzepatide
Source: SURMOUNT-1 CSR.[100]

Table 10. Baseline comorbidities and concomitant medications of all randomised participants* in SURMOUNT-1

Comorbidities†	n (%)				
	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Total (N=2,539)
Hypertension	199 (30.9)	205 (32.5)	208 (32.7)	207 (32.9)	819 (32.3)
Dyslipidaemia	186 (28.9)	201 (31.9)	188 (29.6)	182 (28.9)	757 (29.8)
ASCVD	21 (3.3)	16 (2.5)	20 (3.1)	21 (3.3)	78 (3.1)
PCOS	13 (2.0)	7 (1.1)	13 (2.0)	6 (1.0)	39 (1.5)
OSA	59 (9.2)	41 (6.5)	51 (8.0)	46 (7.3)	197 (7.8)
Osteoarthritis	76 (11.8)	87 (13.8)	86 (13.5)	77 (12.2)	326 (12.8)
Depression	108 (16.8)	119 (18.9)	101 (15.9)	94 (14.9)	422 (16.6)
NAFLD	46 (7.2)	42 (6.7)	44 (6.9)	48 (7.6)	180 (7.1)
Asthma or COPD	78 (12.1)	72 (11.4)	64 (10.1)	53 (8.4)	267 (10.5)
Gout	35 (5.4)	35 (5.6)	34 (5.3)	32 (5.1)	136 (5.4)
Participants using ≥1 Lipid-Lowering Medication	115 (17.9)	116 (18.4)	99 (15.6)	99 (15.7)	429 (16.9)
Participants using ≥1 Antihypertensive Medication	181 (28.1)	196 (31.1)	191 (30.0)	189 (30.0)	757 (29.8)

Footnotes: * 'All randomised participants' were those who were randomly assigned a study treatment (Section B.2.4.3.). † Comorbidities were assessed through review of medical history.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; COPD: chronic obstructive pulmonary disease; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; PCOS: polycystic ovary syndrome; TZP: tirzepatide.
Source: SURMOUNT-1 CSR.[100]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Trial estimands

An estimand is a detailed description of the treatment effect estimated to address a scientific question of interest; more than one estimand can be defined for the same endpoint. In SURMOUNT-1, two estimands were prespecified, which both intended to estimate the tirzepatide treatment effect for all randomised participants. Both estimands are based on the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 (R1) draft addendum on estimands and sensitivity analysis in clinical trials, in which five estimand strategies for estimating the treatment effect are defined. The estimand strategies employed in SURMOUNT-1 are described below.

Both estimands were provided during regulatory submission; the efficacy estimand data were considered the primary source within the submission to the European Medicines Agency (EMA) and therefore the MHRA, while the treatment regimen estimand data were preferred during the submission to the US Food and Drugs Administration (FDA).

B.2.4.1.1 *The efficacy estimand*

Analyses using the efficacy estimand were conducted using the efficacy analysis set (EAS) (Section B.2.4.3) and assessed the average treatment effect of tirzepatide relative to placebo at 72 weeks in the randomised participants had they remained on their randomised treatment for the entire planned 72-week treatment duration. This estimand uses a hypothetical strategy to handle intercurrent events, as defined in (ICH) E9 (R1), and is intended to provide an estimation of the achievable study treatment effect when participants take the treatment as planned.

The efficacy estimand provides a clinically relevant estimate of the average treatment effect of tirzepatide and was considered most appropriate for this submission because it provided the primary source of evidence within both the EMA and MHRA regulatory submissions. This choice of estimand is also aligned with that used and accepted in TA875 (Section B.3.3.1).[2] The efficacy estimand results from SURMOUNT-1 are therefore presented throughout Section B.2.6, and are subsequently used in the NMA analyses, as described in Section B.2.9.

B.2.4.1.2 *The treatment regimen estimand*

Analyses using the treatment regimen estimand were conducted using the full analysis set (FAS) and assessed the average treatment effect of tirzepatide relative to placebo at 72 weeks for the randomised participants regardless of the adherence to treatment. This estimand is intended to give an estimation of the population-level treatment effect comparing tirzepatide vs placebo for all randomized participants regardless of premature study drug discontinuation.

Results from SURMOUNT-1 using the treatment regimen estimand are presented in Appendix M. NMA analyses were also conducted using the treatment regimen estimand, as described in Section B.2.9.4.1, and were subsequently explored in scenario analyses in the economic model (Section B.3.11.3).

B.2.4.2 Statistical methods

Table 11 presents the hypotheses and associated statistical analysis methods adopted in the SURMOUNT-1 study.

Table 11. Statistical methods for the primary analysis of SURMOUNT-1

Hypothetical objective	The alternative hypotheses for the primary objective were to demonstrate that: • Once-weekly **tirzepatide 10 mg** was superior to placebo for percent change in body weight from baseline AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks • Once-weekly **tirzepatide 15 mg** was superior to placebo for percent change in body weight from baseline AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks
Statistical analysis	**Efficacy estimand** The primary analysis related to the efficacy estimand were conducted using the EAS (Section B.2.4.3). Missing values (observations excluded after study discontinuation or not observed) were implicitly handled by using a mixed model for repeated measures (MMRM) under the assumption of missing at random. For MMRM the independent variables of analysis model include treatment group, visit, treatment-by-visit interaction, stratification factors (country/pooled country, sex, and prediabetes status at randomization) as fixed effects, and baseline body weight as a covariate. A logistic regression model with terms of treatment

	group, country/pooled country, sex, and prediabetes status at randomization as fixed effects, and baseline body weight as a covariate, were conducted for binary outcomes. Missing values were imputed by the predicted value from the MMRM model, then the continuous measurements were dichotomized to binary outcomes. **Treatment regimen estimand** The primary analysis related to the treatment regimen estimand were conducted using the FAS (Section B.2.4.3. For analyses related to the treatment regimen estimand, analysis of covariance (ANCOVA) was used for continuous outcomes (e.g., percent weight change) at Week 72 and logistic regression was used for binary outcomes (e.g., achieving 5% weight reduction target) at 72 weeks. Both models included treatment group, country/pooled country, sex, and prediabetes status at randomisation as fixed effects and baseline body weight as a covariate. The analyses were conducted with multiple imputation of missing body weight at 72 weeks and statistical inference over multiple imputation of missing data guided by Rubin (1987).[101] Specifically, for missing data solely due to COVID-19, the missing data were considered as missing at random and imputed using all available non-missing data of the primary outcome measurement from the same treatment arm; for missing data due to other intercurrent events, missing data were imputed based on retrieved dropouts in the same treatment arm, defined as observed primary outcome measurements, from participants in the same treatment group, who had their efficacy assessed after early discontinuation of the study drug. **Type 1 Error rate control strategy for primary and key secondary efficacy analyses** Hypotheses for each type of estimand were tested using 2-sided p-values to control the global type 1 error rate at 0.05 across all primary and key secondary endpoints. The hypotheses related to the endpoints at the end of the additional 2-year follow-up period of the study will not be tested until the final database lock when the additional 2-year follow-up period is complete.
Sample size, power calculation	Approximately 3,429 participants were screened to achieve 2,400 participants randomly assigned to each intervention (600 per group). Participants were randomly assigned in a 1:1:1:1 ratio to tirzepatide 5, 10, 15 mg QW, or placebo. Patient randomisation was stratified based on prediabetes status, country, and sex. The power was assessed based on the following assumptions: • evaluation of superiority of tirzepatide 10 mg and 15 mg to placebo were conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test • a difference of at least 11% mean body weight percentage reduction from randomisation at 72 weeks for tirzepatide 10 mg and/or 15 mg compared with placebo • a common SD of 10% • a dropout rate of 25% Based on these assumptions, randomising 2,400 participants in a 1:1:1:1 ratio to tirzepatide 5 mg, 10 mg, 15 mg, and placebo provides >90% power to demonstrate superiority of tirzepatide 10 mg and/or 15 mg to placebo for percent change in body weight from baseline. The chosen sample size and randomisation ratio also provides >90% power to establish superiority of tirzepatide 10 mg and 15 mg to placebo in term of percentage of participants achieving ≥5% body weight reduction at 72 weeks, conducted in parallel using a Fisher's exact test, each at a 2-sided significance level of 0.025, assuming 25% placebo-treated participants

	and 90% tirzepatide-treated participants achieving the goal and a dropout rate of 25%. Finally, assuming that approximately 60% of the randomised population will have prediabetes, the study sample size also provides >90% power to demonstrate superiority of tirzepatide (all doses combined) over placebo in terms of delaying the onset of diabetes for participants with prediabetes at study entry. This is based on the following assumptions: • 1.6% (corresponding to annual hazard rate of 0.54%) of participants randomised to tirzepatide; • 6% of participants randomised to placebo (corresponding to annual hazard rate of 2.1%) will progress to diabetes during the 3-year period; • 49% of participants will drop out (corresponding to annual drop-out rate of 22%) during the same period; and • the test will be conducted at a 2-sided significance level of 0.05.
Data management, participant withdrawals	Participants who discontinued from study drug permanently continued attending all scheduled study visits to collect all planned efficacy and safety measurements. Participants who were unwilling to attend all scheduled visits and stop the study prior to 72 weeks, returned for a final weight measurement (Visit 99). If participants were unwilling to attend Visit 99, their refusal to attend was documented in the patient medical record. Participants with prediabetes who stopped study drug after 72 weeks returned for a final assessment of weight and glycaemic status (Visit 199). Refusal to attend should be documented in the patient medical record. To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt was made to keep participants in the study irrespective of the following: • adherence to or discontinuation from study drug • adherence to visit schedule • missing assessments • study drug discontinuation due to AE • development of comorbidities • development of clinical outcomes The circumstances listed above were not considered valid reasons for discontinuation from the study. Participants were withdrawn from the study only in the following circumstances: • enrolment in any other clinical study involving an IP or enrolment in any other type of medical research judged not to be scientifically or medically compatible with SURMOUNT-1 • participation in the study needed to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP) • participant requested to be withdrawn from the study and clearly indicated that there will be no further contact of any kind with the site • female participants were withdrawn from the study if the participant became pregnant Participants who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study. A participant was considered lost to follow-up if they repeatedly failed to return for scheduled visits and were unable to be contacted by the study site.

Abbreviations: ANCOVA: analysis of covariance; EAS: efficacy analysis set; FAS: full analysis set; MMRM

REML: restricted maximum likelihood
Source: SURMOUNT-1 CSR.[100] SURMOUNT-1 protocol.[102] Jastreboff (2022);[3]

B.2.4.3 Analysis sets and evaluations

The study analysis populations in SURMOUNT-1 are defined in Table 12 below.

Table 12. Descriptions of analysis populations and data sets

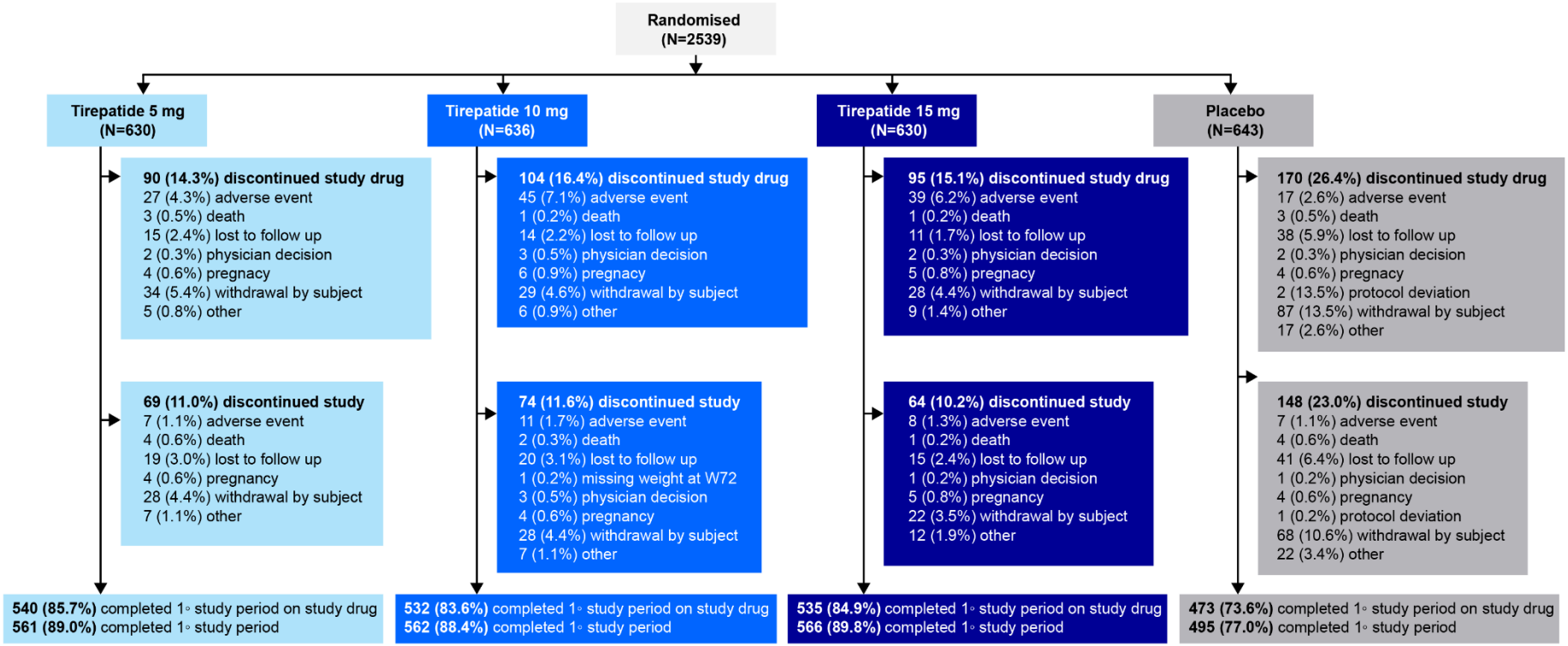
Analysis Population		SURMOUNT-1
Entered Participants	Description	All participants who signed informed consent
	N	3,238
Randomised Participants	Description	All participants who were randomly assigned a study treatment
	N	2,539
Modified intent-to-treat (mITT) population	Description	All randomly assigned participants who took at least 1 dose of study drug. In the event of a treatment error, participants were analysed according to the treatment they were randomised to
	N	2,539
Safety population	Description	Same as the mITT
	N	2,539
FAS	Description	All available data obtained during the treatment period from the mITT population, regardless of adherence to study drug
	N	2,539
EAS*	Description	Data obtained during the treatment period from the mITT population, excluding data after discontinuation of study drug (last dose + 7 days)
	N	2,539
Safety analysis set	Description	All available data obtained during the treatment period plus safety follow-up period 3 from the mITT population, regardless of adherence to study drug
	N	2,539

Footnotes: * The number of participants in the EAS may differ slightly for different measures when the analysis requires baseline value and at least 1 postbaseline value. For this reason, the baseline mean values from EAS and FAS may sometimes be slightly different.
Abbreviations: EAS: efficacy analysis set; FAS: full analysis set; mITT: modified intention-to-treat
Source: SURMOUNT-1 CSR.[100]

B.2.4.4 Participant disposition

In SURMOUNT-1, a total of 2,539 participants were randomised. All participants randomly assigned to treatment received at least 1 dose of study drug. More participants randomised to tirzepatide 5, 10 and 15 mg completed the primary period of the study (88.4% to 89.8% depending on the treatment arm) and study treatment (83.6% to 85.7% depending on the treatment arm) than participants randomised to placebo (77.0% for study, 73.6% for study treatment). The most common reason for study discontinuation and study drug discontinuation was withdrawal by subject (5.8% and 7.0%, respectively). Patient disposition for SURMOUNT-1 through Week 72 is shown in Figure 5.

Figure 5. Participant disposition to Week 72 for SURMOUNT-1



Source: SURMOUNT-1 CSR.[100]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the SURMOUNT-1 trial was conducted using the Cochrane risk of bias assessment tool. Assessment was performed by two reviewers, and any discrepancies were resolved by a third reviewer. The trials identified in the SLR were assessed using the same tool.

A summary of the quality assessment is presented in Table 13; the quality assessments for the relevant trials identified in the SLR are presented in Appendix D.

Table 13. Assessment of quality and risk of bias in the SURMOUNT-1 trial

Criteria	Risk of bias
Was randomisation carried out appropriately?	Yes
	Participants were randomly assigned 1:1:1:1 to the treatment groups. Assignment to treatment group was determined by a computer-generated random sequence using an IWRS.
Was the concealment of treatment allocated adequate?	Yes
	Treatment group assignment was determined by computer-generated random sequence using an IWRS.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
	As stated in Jastreboff 2021 "The demographic and clinical baseline characteristics were generally similar across treatment groups"
Were the care providers, participants and outcomes assessors blind to treatment allocation?	Yes
	Double-blinding
Were there any unexpected imbalanced in drop-outs between groups?	No
	All dropouts accounted for
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
	All outcomes in method section were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
	Appropriate imputation methods were utilised

Source: Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[103]
Abbreviations: CRD: centre for reviews and dissemination; IWRS: interactive web-response system; mITT: modified intention-to-treat.

B.2.6 Clinical effectiveness results of the relevant studies

Brief summary of clinical effectiveness results

- Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for mean percent change in body weight from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority versus placebo, which was evaluated as a key secondary endpoint.
    - In the tirzepatide 10 and 15 mg groups, the mean percent change in body weight from baseline was −21.4% and −22.5%, respectively, compared to −2.4% of the placebo group.
    - In the tirzepatide 5 mg group, the mean percent change in body weight from baseline was −16.0%.
- Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority versus placebo, which was evaluated as a key secondary endpoint.
    - In the tirzepatide 10 and 15 mg groups, 96.2% and 96.3% of participants achieved a body weight reduction of ≥5%, respectively, compared to 27.87% of the placebo group.
    - In the tirzepatide 5 mg group, 89.4% of participants achieved a body weight reduction of ≥5%, respectively.
- Tirzepatide 10 mg and 15 mg were each associated with significantly greater percentages of participants achieving reductions of ≥10%, ≥15%, or ≥20% at Week 72 compared to placebo.
    - In the tirzepatide 10 and 15 mg groups, 85.9% and 90.1% of participants achieved a body weight reduction of ≥10%, respectively, compared to 13.5% of the placebo group.
    - In the tirzepatide 10 and 15 mg groups, 73.6% and 78.2% of participants achieved a body weight reduction of ≥15%, respectively, compared to 6.0% of the placebo group.
    - In the tirzepatide 10 and 15 mg groups, 55.5% and 62.9% of participants achieved a body weight reduction of ≥20%, respectively, compared to 1.3% of the placebo group.

The following sections present the primary and key secondary endpoints for the **efficacy estimand** within the EAS (n=2,539), for reasons outlined in Section B.2.4.1. Results for the treatment-regimen can be found in the CSR provided alongside this submission. It should be noted that for secondary and exploratory endpoints (Section B.2.6.2), the order of presented results does not align with the testing hierarchy outlined in the statistical analysis plan; instead, the sequence of results reflects the data that were considered to be of the greatest relevance to decision-making, and aligning with those specified in the decision problem (Table 1). However, for transparency, all primary and key secondary endpoints are presented in the submission package. Finally, as noted in Table 11, only the primary and key secondary endpoints are controlled for type 1 error; therefore, p-values presented for additional secondary and exploratory endpoints are nominal.

Beyond the endpoints presented in the subsequent sections, the results for the following additional endpoints can be found in Appendix M:

- Mean change in body weight from baseline to Week 20 for pooled tirzepatide 10 mg and 15 mg (key secondary endpoint)
- Mean change in fasting insulin for pooled tirzepatide 5 mg, 10 mg and 15 mg (key secondary endpoint)
- Mean change in SF-36v2 acute form Physical Functioning domain score for pooled tirzepatide 10 mg and 15 mg (key secondary endpoint)
- Mean change in IWQOL-Lite-CT Physical Function composite score for tirzepatide 5 mg, 10 mg and 15 mg (key secondary endpoint)
- Change from baseline in EQ-5D-5L scores at 72 weeks (exploratory endpoint)

B.2.6.1 Primary efficacy endpoints

Percentage change in body weight at Week 72 – *tirzepatide 10 mg and 15 mg each superior to placebo*

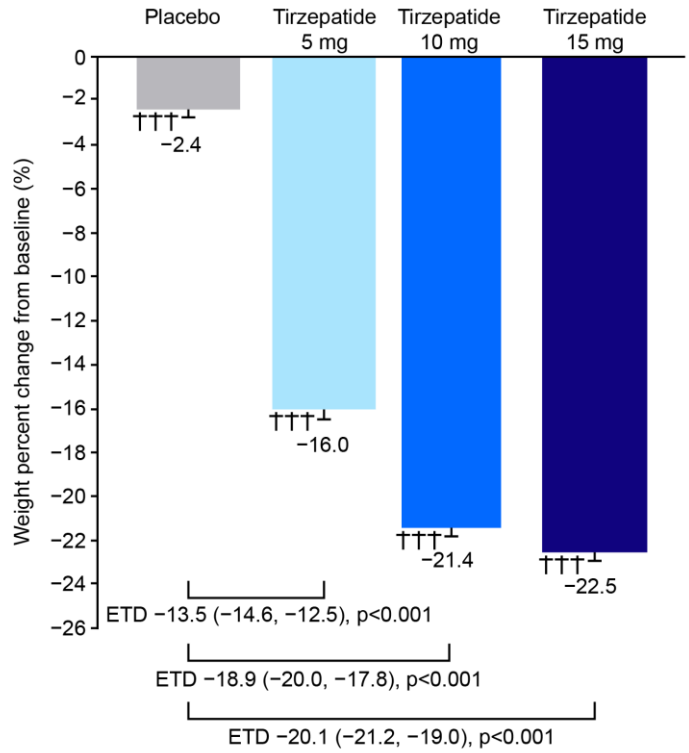
Tirzepatide 10 and 15 mg each achieved superiority compared with placebo for mean percent change in body weight reduction from baseline to 72 weeks, indicating a significantly greater reduction in body weight from baseline in tirzepatide-treated participants relative to those receiving placebo. Tirzepatide 5 mg also achieved superiority compared with placebo for mean percent change in body weight reduction from baseline to 72 weeks, which was a secondary endpoint. A summary of the full results for the percent change in body weight is provided in Table 14 and Figure 6. Figure 7 presents the percent change in body weight over time. Using the efficacy estimand, participants treated with tirzepatide 5, 10, and 15 mg had substantial reductions in body weight from baseline compared with placebo starting at Week 4 until Week 72.

Table 14. Mean percent change from baseline in body weight at Week 72; EAS

Parameters	Placebo (N=643)	TZP 5 mg* (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline (kg)	104.8	102.9	105.9	105.5
Percent change from baseline at 72 weeks (%)	−2.4†††	−16.0†††	−21.4†††	−22.5†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	−13.5*** (−14.6, −12.5)	−18.9*** (−20.0, −17.8)	−20.1*** (−21.2, −19.0)

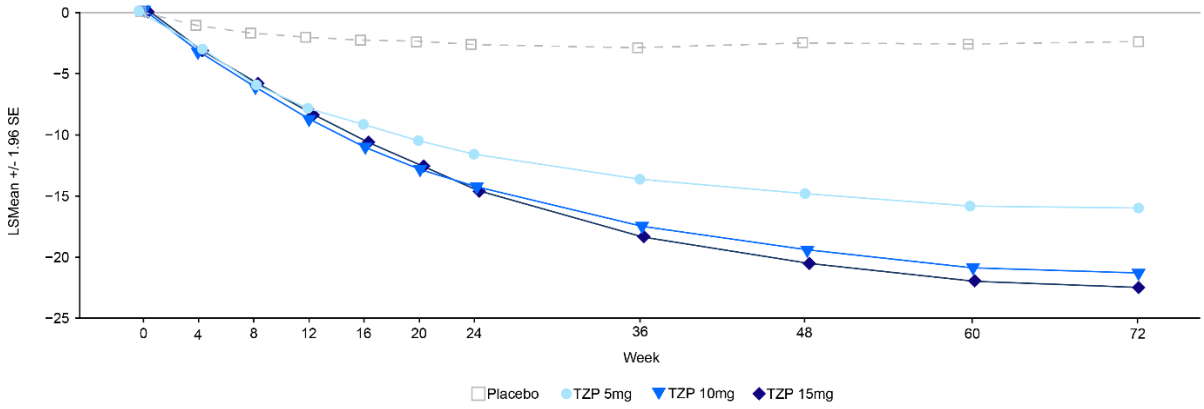
Abbreviations: CI: confidence interval; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: *For the tirzepatide 5 mg group, percent change in body weight at Week 72 is a key secondary objective. Least squares means are shown. MMRM analysis for efficacy estimand.
*** p-Value <0.001 versus placebo for superiority.
††† p-Value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Figure 6. Mean percent change from baseline in body weight at Week 72; EAS



Abbreviations: EAS: efficacy analysis set; ETD: estimated treatment difference; MMRM: mixed model for repeated measures.
Footnotes: Least squares means are shown. MMRM analysis for efficacy estimand. ††† p-Value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Figure 7. Percent change in body weight from baseline to Week 72; EAS

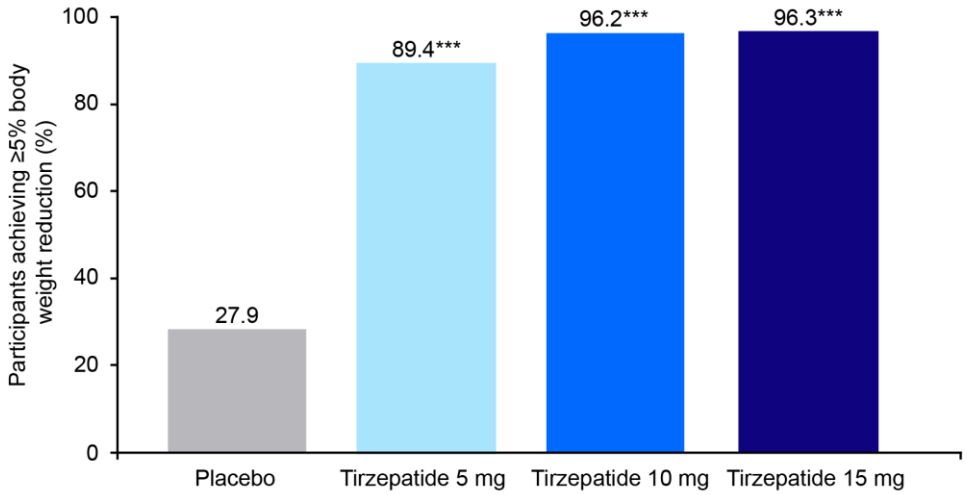


Abbreviations: EAS: efficacy analysis set; LSM: least squares mean; MMRM: mixed model repeated measures; SE: standard error.
Footnotes: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. MMRM model for post-baseline measures: Variable = Baseline + Analysis Country + Sex + Prediabetes Status at Randomization + Treatment + Time + Treatment*Time (Type III sum of squares).
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Percentage of participants with ≥5% body weight reduction – *tirzepatide 10 mg and 15 mg each superior to placebo*

Tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks, which was a key secondary endpoint. A summary of the full results for the percentage of participants with ≥5% body weight reduction is provided in Figure 8.

Figure 8. Percentage of participants achieving ≥5% body weight reduction; EAS



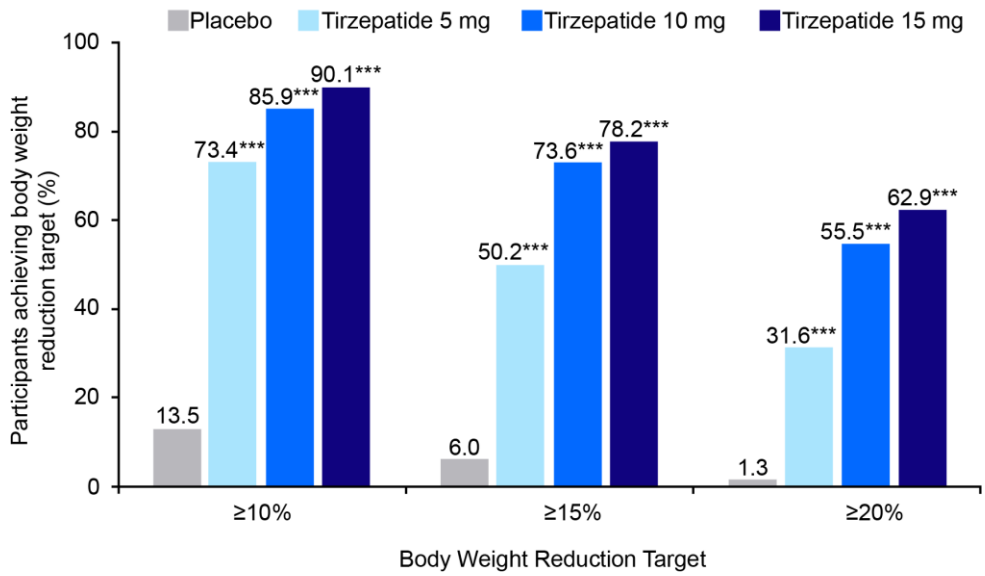
Abbreviations: EAS: efficacy analysis set; MMRM: mixed model for repeated measures.
Footnotes: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand. For the tirzepatide 5 mg group, the percentage of participants achieving ≥5% body weight reduction at Week 72 is a key secondary objective. ***p-value <0.001 versus placebo for superiority.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

B.2.6.2 Secondary and exploratory efficacy endpoints

Percentage of participants with ≥10%, ≥15%, or ≥20% body weight reduction at Week 72 – *tirzepatide 10 mg and 15 mg each superior to placebo*

The percentage of participants with ≥10%, ≥15%, or ≥20% body weight reduction in the tirzepatide 10 and 15 mg groups at Week 72 was investigated as a key secondary endpoint. Tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks. Tirzepatide 5 mg also achieved superiority compared with placebo for the percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction, although it should be noted that the percentage of participants achieving ≥10% or ≥15% body weight reductions at Week 72 was an additional secondary objective, while the percentage of participants achieving ≥20% body weight reduction at Week 72 was an exploratory objective. A summary of the results for the percentage of participants achieving body weight reduction targets at Week 72 is provided in Figure 9.

Figure 9. Percentage of participants achieving body weight reduction of ≥10%, ≥15%, or ≥20% at Week 72; EAS



Abbreviations: EAS: efficacy analysis set; MMRM: mixed model for repeated measures.
Footnotes: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand. For the tirzepatide 5 mg group, the percentage of participants achieving ≥10% or ≥15% body weight reductions at Week 72 is an additional secondary objective and is not controlled for type 1 error. Additionally, ≥20% body weight reduction at Week 72 is an exploratory objective for the tirzepatide 5 mg group.
***p-value <0.001 versus placebo for superiority.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Mean change from baseline in BMI at Week 72 – *tirzepatide 5, 10, and 15 mg each superior to placebo*

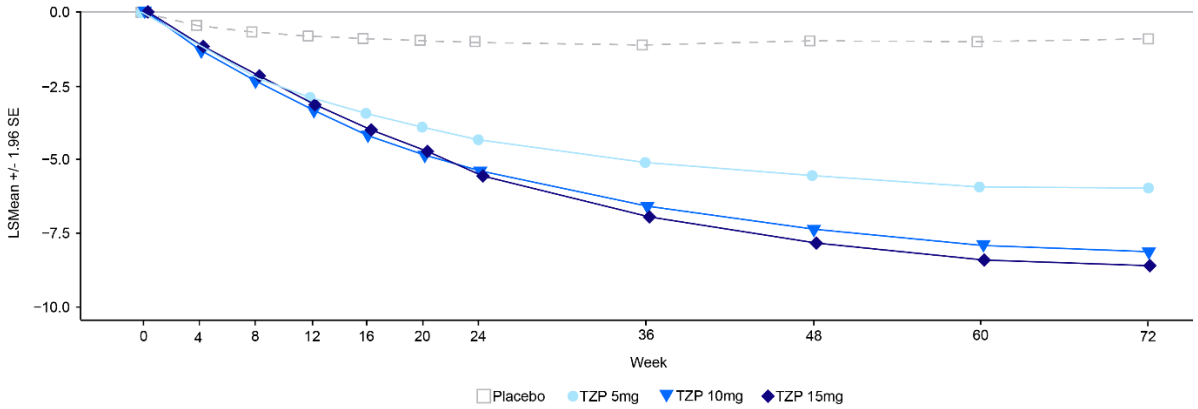
The mean change from baseline BMI at Week 72 for the tirzepatide 5, 10 and 15 mg arms was investigated as an additional secondary endpoint. Tirzepatide 5, 10, and 15 mg each achieved statistically significant mean reductions in BMI compared with placebo from baseline to Week 72. A summary of the full results for the mean change from baseline in BMI at Week 72 is provided Table 15. Figure 10 illustrates the mean change in BMI from baseline to Week 72; participants treated with tirzepatide 5, 10, and 15 mg had substantial reductions in BMI from baseline compared with placebo starting at Week 4 through to Week 72.

Table 15. Mean change in BMI from baseline to 72 Weeks; EAS

Parameters (kg/m²)	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline	38.2	37.4	38.3	38.1
Change from baseline at 72 weeks	−0.9†††	−5.9†††	−8.1†††	−8.6†††
Change difference from placebo at 72 weeks (95% CI)	N/A	−5.1*** (−5.5, −4.6)	−7.2*** (−7.7, −6.8)	−7.7*** (−8.2, −7.3)

Abbreviations: BMI: body mass index; CI: confidence interval; EAS: efficacy analysis set; MMRM: mixed model for repeated measures; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; TZP: tirzepatide.
Footnotes: MMRM analysis for postbaseline measures. Least-squares means are shown.
*** p-value <0.001 versus placebo.
†††p-value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Figure 10. Change from baseline in BMI over time; EAS



Abbreviations: LSM: least squares mean; MMRM: mixed model repeated measures; SE: standard error.
Footnotes: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. MMRM model for post-baseline measures: Variable = Baseline + Analysis Country + Sex + Prediabetes Status at Randomization + Treatment + Time + Treatment*Time (Type III sum of squares).
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Mean change in waist circumference from baseline to Week 72 – *tirzepatide 10 mg and 15 mg each superior to placebo*

Mean change in waist circumference from baseline to Week 72 in the tirzepatide 10 and 15 mg arms was investigated as a key secondary endpoint. Tirzepatide 10 and 15 mg each achieved superiority compared with placebo for mean change reduction in waist circumference at Week 72. Tirzepatide 5 mg also achieved a significantly greater mean change reduction in waist circumference at 72 weeks compared with placebo, which was an additional secondary endpoint (and therefore was not adjusted for multiplicity). A summary of mean change in waist circumference at Week 72 is provided in Table 16.

Table 16. Mean change from baseline in waist circumference at Week 72; EAS

Parameters (cm)	Placebo (N=643)	TZP 5 mg (N=630)*	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline	114.0	113.2	114.9	114.4
Change from baseline at 72 weeks	−3.4†††	−14.6†††	−19.4†††	−19.9†††
Change difference from placebo at 72 weeks (95% CI)	N/A	−11.2*** (−12.3, −10.0)	−16.0*** (−17.2, −14.9)	−16.5*** (−17.7, −15.4)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; N: number of participants who were randomly assigned and received at least 1 dose of study drug; MMRM: mixed model for repeated measures; N/A: not applicable; TZP: tirzepatide.
Footnotes: MMRM analysis. Data shown are least-squares means. *For the tirzepatide 5 mg group, mean change in waist circumference at Week 72 is an additional secondary objective, and therefore not adjusted for multiplicity.
***p-value <0.001 versus placebo for superiority.
†††p-value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Mean change in SBP from baseline to Week 72 – *pooled tirzepatide 5, 10 and 15 mg superior to placebo*

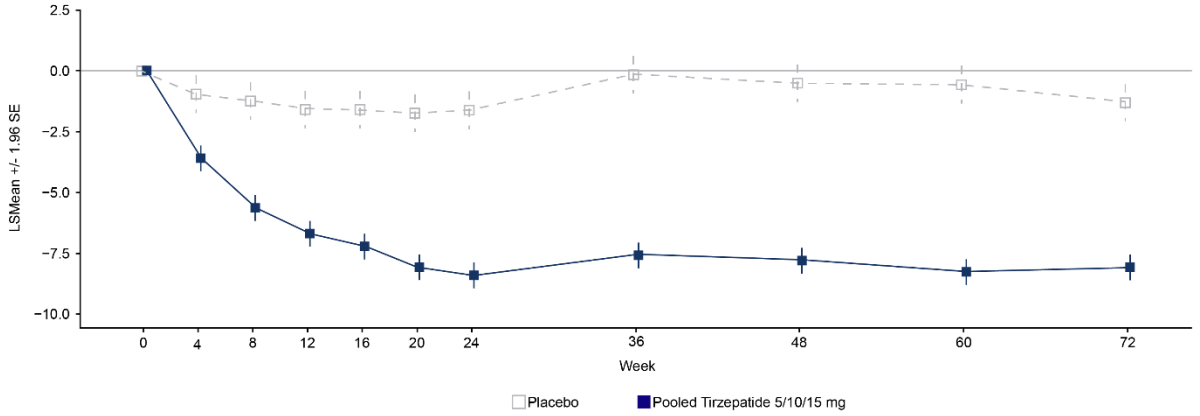
Mean change in SBP for pooled tirzepatide 5 mg, 10 mg and 15 mg was investigated as a key secondary endpoints; all tirzepatide doses were pooled for this endpoint because it was hypothesised was that all 3 tirzepatide doses would improve cardiometabolic parameters in a similar magnitude.[3] Pooled doses of tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo in mean change reduction in SBP at 72 weeks (Table 17). The mean change in SBP over the treatment period is presented in Figure 11.

Table 17. Mean changes in SBP at 72 Weeks; EAS

Parameter (mmHg)	Placebo (N=643)	Pooled TZP 5/10/15 mg (N=1,896)
Baseline	122.8	123.4
Change from baseline at 72 weeks	−1.3††	−8.1†††
Change difference from placebo at 72 weeks (95% CI)	N/A	−6.8*** (−7.9, −5.7)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; MMRM: mixed model for repeated measures; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; SBP: systolic blood pressure; TZP: tirzepatide.
Footnotes: MMRM analysis. Data shown are least-squares means.
***p-value <0.001 versus placebo for superiority.
††p-value <0.01, †††p-value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Figure 11. Change from baseline of sitting systolic blood pressure (mmHg) over time; EAS



Abbreviations: EAS: efficacy analysis set; LSMean: least squares mean; MMRM: mixed model for repeated measures; SE: standard error.
Footnotes: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. MMRM model for post-baseline measures: Variable = Baseline + Analysis Country + Sex + Prediabetes Status at Randomization + Treatment + Time + Treatment*Time (Type III sum of squares).
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Mean change from baseline in triglycerides, non-HDL cholesterol, and HDL cholesterol at Week 72 – *pooled tirzepatide 5, 10 and 15 mg superior to placebo*

Mean change in triglycerides, non-HDL cholesterol and HDL cholesterol for pooled tirzepatide 5, 10 and 15 mg arms was investigated as a key secondary endpoint; similarly to SBP, for the analysis of triglycerides, non-HDL cholesterol, and HDL cholesterol, all tirzepatide doses were pooled because the hypothesis was that all 3 doses would improve lipid levels in a similar

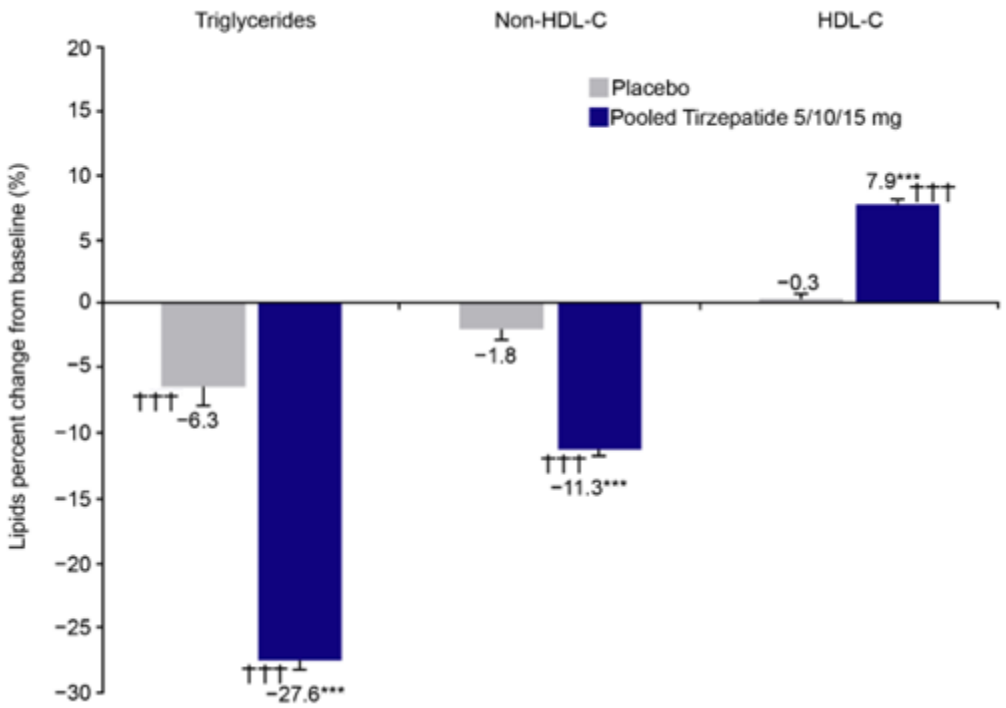
magnitude.[3] Pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo for mean percent reduction in triglycerides and non-HDL cholesterol, and increase in HDL cholesterol (Table 18; Figure 12).

Table 18. Change from baseline in lipid parameters at Week 72; EAS

Parameters	Placebo (N=643)	Pooled TZP 5/10/15 mg (N=1,896)
Triglycerides		
Baseline (mg/dL)	130.5	127.8
Change from baseline at 72 weeks (mg/dL)	−8.1	−35.5
Percent change from baseline at 72 weeks	−6.3†††	−27.6†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	−22.7*** (−25.6, −19.8)
HDL-C		
Baseline (mg/dL)	46.5	47.5
Change from baseline at 72 weeks (mg/dL)	0.1	3.7
Percent change from baseline at 72 weeks (%)	0.3	7.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	7.7*** (5.9, 9.5)
Non-HDL-C		
Baseline (mg/dL)	137.2	138.2
Change difference from baseline at 72 weeks (mg/dL)	−2.5	−15.6
Percent change from baseline at 72 weeks (%)	−1.8	−11.3†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	−9.7*** (−11.7, −7.7)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; HDL-C: high density lipoprotein cholesterol; N/A: not applicable; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: MMRM analysis. Data shown are estimated means. Log transformations were applied to raw data for lipid parameters.
***p-value <0.001 versus placebo for superiority.
†††p-value <0.001 versus baseline.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

Figure 12. Percent change from baseline in triglycerides, HDL-C, and non-HDL-C at Week 72; EAS



Abbreviations: EAS: efficacy analysis set; HDL-C: high-density lipoprotein cholesterol; MMRM: mixed model for repeated measures.
Footnotes: MMRM analysis. Data presented are the estimated means ± standard errors.
***p-value <0.001 versus placebo for superiority.
†††p-value<0.001 versus baseline.
Source: SURMOUNT-1 CSR.[100]

Mean change in HbA1c from baseline to 72 weeks – *tirzepatide 5, 10 and 15 mg each superior to placebo*

Mean change in HbA1c for tirzepatide 5, 10 and 15 mg was investigated as an additional secondary endpoint. At Week 72, tirzepatide 5, 10, and 15 mg each resulted in statistically significant mean reductions in HbA1c from baseline compared with placebo at Week 72, as detailed in

Table 19.

Table 19. Mean change in HbA1c from baseline to 72 Weeks; EAS

Parameters	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline (%)	5.6	5.6	5.6	5.6
Baseline (mmol/mol)	37.4	37.2	37.1	37.1
Change from baseline at 72 Weeks (%)	−0.1†††	−0.4†††	−0.5†††	−0.5†††
Change from baseline at 72 Weeks (mmol/mol)	−0.8†††	−4.4†††	−5.3†††	−5.6†††
Change difference from placebo at 72 Weeks (95% CI) (%)	N/A	−0.3*** (−0.4, −0.3)	−0.4*** (−0.5, −0.4)	-0.4*** (−0.5, −0.4)
Change difference from placebo at 72 Weeks (95% CI) (mmol/mol)		−3.6*** (−4.0, −3.2)	-4.6*** (−4.9, −4.2)	-4.8*** (−5.2, −4.5)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; HbA1c: glycated haemoglobin; MMRM; mixed model for repeated measures; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; TZP: tirzepatide.
Footnotes: MMRM analysis. Least-squares means are shown.
***p-Value <0.001 versus placebo.
†††p-Value <0.001 versus baseline.
Source: SURMOUNT-1 CSR.[100]

Percentage of participants with a change in glycaemic category – *tirzepatide 5, 10 and 15 mg each result in improvements in glycaemic status at Week 72*

The percentage of participants with a change in glycaemic category was investigated as an exploratory endpoint. Table 20 presents the change in glycaemic category from baseline to Week 72. Of the participants with prediabetes at baseline, a greater proportion in the tirzepatide arms reverted to normoglycaemia at 72 weeks, compared to those with prediabetes at baseline in the placebo arm. In addition, a smaller proportion of participants in the tirzepatide arms with prediabetes at baseline had suspected T2DM at Week 72 compared to the placebo arm. Finally, a smaller proportion in the tirzepatide arms with normoglycaemia at baseline has prediabetes or suspected T2DM at Week 72 compared with the placebo arm, indicating that tirzepatide 5, 10 and 15 mg each provide greater improvements in glycaemic control compared with placebo alone.

Table 20. Glycaemic status from baseline to 72 weeks

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				
		Normoglycemia N (%)	Prediabetes N (%)	Suspected T2DM N (%)	Undetermined N (%)	Total N (%)
Placebo (N=643)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 5 mg (N=630)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=636)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=630)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HbA1c: glycated haemoglobin; N: number of participants in the population in the specified treatment group; n: number of participants in the specified category; OGTT: 2-hour oral glucose tolerance test; TZP: tirzepatide; T2DM: type 2 diabetes mellitus.
Footnotes: Percentage values refer to the total patients in each treatment arm. Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT was counted in 'Suspected T2DM'. 'Suspected T2DM' was adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT was counted in 'Undetermined'.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01; Dated: 14th July 2023)

Mean change in fasting serum glucose (FSG) at Week 72 – *tirzepatide 5, 10 and 15 mg superior to placebo*

Mean change in FSG at Week 72 for tirzepatide 5, 10 and 15 mg was investigated as a secondary efficacy endpoint. At Week 72, tirzepatide 5, 10, and 15 mg each resulted in statistically significant mean reductions in FSG compared with placebo. A summary of mean change in fasting insulin from baseline to Week 72 is presented in Table 21.

Table 21. Mean changes in FSG from baseline to Week 72; EAS

Parameters	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline (mg/dL)	95.8	95.4	95.5	95.2
Baseline (mmol/L)	5.3	5.3	5.3	5.3
Change from baseline at 72 weeks (mg/dL)	0.9	–7.7†††	–9.7†††	–10.6†††
Change from baseline at 72 weeks (mmol/L)	0.1	–0.4 †††	–0.5†††	–0.6†††
Change difference from placebo at 72 Weeks (95% CI) (mg/dL)	–8.6*** (–10.0, –7.2)	–10.6*** (–12.0, –9.2)	–11.4*** (–12.8, –10.0)	–8.6*** (–10.0, –7.2)
Change difference from placebo at 72 Weeks (95% CI) (mmol/L)	0.5*** (–0.6, –0.4)	–0.6*** (–0.7, –0.5)	–0.6*** (–0.7, –0.6)	0.5*** (–0.6, –0.4)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; FSG: fasting serum glucose; MMRM = mixed model for repeated measures; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; TZP: tirzepatide.
Footnotes: MMRM analysis for postbaseline measures. Shown are least-squares means.
***p-value <0.001 versus placebo for superiority.
†††p-value <0.001 versus baseline.
Source: SURMOUNT-1 CSR.[100]

B.2.7 Subgroup analysis

This section presents the relevant post-hoc subgroup analyses for the SURMOUNT-1 trial that are used in the model. All the efficacy data presented below were derived using the efficacy estimand. Equivalent data for the treatment regimen estimand are presented in Appendix E.

- The SURMOUNT-1 post-hoc subgroup data presented below for the BMI ≥30 kg/m^2 and at least one weight-related comorbidity (67% of the EAS; Table 22) and BMI ≥35 kg/m^2 plus prediabetes plus high CVD risk subgroups (21% of the EAS; Table 23) were used in the NMA subgroup analyses (Section B.2.9) since indirect treatment comparisons were required in these populations.
- The SURMOUNT-1 post-hoc subgroup data presented below for the BMI ≥30 kg/m^2 (94% of the EAS; Table 24) and BMI ≥35 kg/m^2 (60% of the EAS; Table 25) subgroups (both irrespective of comorbidities) were used directly in the model, since no indirect treatment comparisons were required in the these populations (diet and exercise is the only comparator in these populations).

The results from the SURMOUNT-1 prespecified subgroup analyses for both estimands, which aimed to assess potential treatment effect modifiers affecting the change from baseline in body weight, are presented in Appendix E. Overall, analyses of the percentage change in body weight and the percentage of participants achieving ≤5% weight loss at Week 72 were generally consistent with the primary results of the SURMOUNT-1 trial, with the treatment difference

favouring all three doses of tirzepatide compared with placebo in the majority of subgroups.

B.2.7.1 BMI ≥30 kg/m^2 with at least one comorbidity

The results of the subgroup analysis for the expected eligible population relative to the efficacy results of the EAS are presented in Table 22. Overall, the results of this subgroup analyses for the subgroup of people with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity were consistent with those of the EAS.

Table 22. Key efficacy endpoints for the subgroup of people with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity

	BMI ≥30 kg/m^2 with ≥1 comorbidity (N=1,705)				EAS (N=2,539)			
	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]	Placebo [redacted]	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Placebo (N=643)
Change from baseline to Week 72								
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−16.0 (0.4)	−21.4 (0.4)	−22.5 (0.4)	−2.4 (0.4)
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	7.0 (0.8)	8.6 (0.8)	8.2 (0.8)	0.2 (0.7)
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−4.9 (0.6)	−5.6 (0.6)	−7.4 (0.6)	−1.1 (0.7)
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]	−7.0 (0.5)	−8.2 (0.5)	−7.6 (0.5)	−1.2 (0.5)

Abbreviations: BMI: body mass index; HDL: high-density lipoprotein; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure; TZP: tirzepatide.
Footnotes: † As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.
Source: Jastreboff 2022; Eli Lilly Data on File, 2023[3]

B.2.7.2 BMI ≥35 kg/m^2 with prediabetes and high CV risk

The results of the subgroup analyses for the population with a BMI of ≥35 kg/m^2 with prediabetes and a high CV risk relative to the efficacy results of the EAS are presented in Table 23. Overall, the results of the efficacy analyses for the subgroup of people with a BMI of ≥35 kg/m^2 with prediabetes and high CV risk were consistent with those of the EAS.

Table 23. Key efficacy endpoints for the subgroup of people with a BMI of ≥35 kg/m^2 with prediabetes and high CV risk

	BMI ≥35 kg/m^2 with prediabetes and high CV risk (n=545)				EAS population (n=2,539)			
	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]	Placebo [redacted]	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Placebo (N=643)
Change from baseline to Week 72								
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−16.0 (0.4)	−21.4 (0.4)	−22.5 (0.4)	−2.4 (0.4)
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	7.0 (0.8)	8.6 (0.8)	8.2 (0.8)	0.2 (0.7)
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−4.9 (0.6)	−5.6 (0.6)	−7.4 (0.6)	−1.1 (0.7)
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]	−7.0 (0.5)	−8.2 (0.5)	−7.6 (0.5)	−1.2 (0.5)

Abbreviations: BMI: body mass index; CV: cardiovascular; HDL: high-density lipoprotein; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure.
Footnotes: † As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.
Source: Jastreboff 2022; Eli Lilly Data on File, 2023[3]

B.2.7.3 BMI ≥30 mg/kg^2 (irrespective of comorbidities)

The results of the subgroup analysis for the population of people with a BMI of ≥30 mg/kg^2 are presented in Table 22. Overall, the results of this subgroup analyses for the subgroup of people with a BMI of ≥30 mg/kg^2 were consistent with those of the EAS.

Table 24. Key efficacy endpoints for the subgroup of people with a BMI of ≥30 mg/kg^2

	BMI ≥30 mg/kg^2 with ≥1 comorbidity (N=2,399)				EAS (N=2,539)			
	TZP 5 mg [redacted]	TZP 10 mg ([redacted]	TZP 15 mg ([redacted])	Placebo [redacted])	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Placebo (N=643)
Change from baseline to Week 72								
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−16.0 (0.4)	−21.4 (0.4)	−22.5 (0.4)	−2.4 (0.4)
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	7.0 (0.8)	8.6 (0.8)	8.2 (0.8)	0.2 (0.7)
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−4.9 (0.6)	−5.6 (0.6)	−7.4 (0.6)	−1.1 (0.7)
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]	−7.0 (0.5)	−8.2 (0.5)	−7.6 (0.5)	−1.2 (0.5)

Abbreviations: BMI: body mass index; HDL: high-density lipoprotein; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure; TZP: tirzepatide.
Footnotes:†As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.
Source: Jastreboff 2022; Eli Lilly Data on File, 2023[3]

B.2.7.4 BMI ≥35 kg/m^2 (irrespective of comorbidities)

Table 25 presents the results of the subgroup analyses for the population of people with a BMI of ≥35 kg/m^2. Overall, these results were consistent with those of the EAS.

Table 25. Key efficacy endpoints for the subgroup of people with a BMI of ≥35 kg/m^2

	BMI ≥35 kg/m^2 (n=1,523)				EAS population (n=2,539)			
	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]	Placebo [redacted]	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Placebo (N=643)
Change from baseline to Week 72								
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−16.0 (0.4)	−21.4 (0.4)	−22.5 (0.4)	−2.4 (0.4)
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	7.0 (0.8)	8.6 (0.8)	8.2 (0.8)	0.2 (0.7)
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]	−4.9 (0.6)	−5.6 (0.6)	−7.4 (0.6)	−1.1 (0.7)
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]	−7.0 (0.5)	−8.2 (0.5)	−7.6 (0.5)	−1.2 (0.5)

Abbreviations: BMI: body mass index; HDL: high-density lipoprotein; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure.
Footnotes:. † As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.
Source: Jastreboff 2022; Eli Lilly Data on File, 2023[3]

B.2.8 Meta-analysis

All efficacy data supporting the use of tirzepatide for the treatment of adults with a BMI≥30 kg/m^2 and at least one weight-related comorbidity were provided by the SURMOUNT-1 trial. As such, no efficacy meta-analyses were required for this submission; however, an NMA was conducted and is presented below in Section B.2.9.

B.2.9 Indirect and mixed treatment comparisons

- While a reduced calorie diet and increased physical exercise represents one of the key comparators used in NHS clinical practice, no direct head-to-head evidence is available for the other relevant comparators for tirzepatide; therefore, an NMA was conducted to assess the relative efficacy of tirzepatide versus SC semaglutide 2.4 mg and liraglutide 3.0 mg in the populations considered in the economic analysis.

Methods and study inclusion

- The NMA was based on evidence from the RCTs identified in the clinical SLR presented in Section B.2.1. Of the 118 studies included in the SLR, studies were assessed for their eligibility to be included the NMA in order to construct a homogenous network of studies; this culminated in a total of 6 studies being included in the analyses
    - The main reason for exclusion of studies was due to studies with intervention not of interest, studies with different populations of interest and studies without timepoints of interest
- NMA analyses included CfB in weight (%), CfB in HDL, CfB in SBP and CfB in total cholesterol; these endpoints are used to inform risk equations in the economic model
- An NMA was conducted using the efficacy estimand for use in the model base case. NMA analyses were conducted both for the whole SURMOUNT-1 trial population (BMI ≥30 kg/m^2, or overweight BMI ≥27 kg/m^2 with at least one weight-related comorbidity) and for the populations considered in the economic model for whom indirect treatment comparisons were required (BMI ≥30 kg/m^2 with one weight-related comorbidity [base case population] and BMI ≥35 kg/m^2 with prediabetes and a high CVD risk).
    - An NMA was not relevant for the BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2 subgroups (each irrespective of comorbidities) given that the only comparator in these subpopulations is a reduced calorie diet and increased physical activity (Section B.3.2.3.2), and head-to-head evidence for this comparison is available from SURMOUNT-1 post-hoc analyses (Section B.2.7.3).
- An NMA using the treatment regimen estimand was also conducted for use in the economic model scenario analyses.
- In order to ensure that the most appropriate model was selected for each analysis, four models were used for each analysis and their fit assessed. These models were fixed effect (FE) and random effect (RE) models, and FE and RE models with an adjustment for baseline risk
    - When RE model fail to converge or model fit of FE and RE models were similar based on deviance information criterion (DIC) and deviance statistics, FE models were chosen for ease of interpretation.[87]

Results

- Based on the efficacy estimand analyses in the population with a BMI ≥30 kg/m^2 with one weight-related comorbidity, all three doses of tirzepatide had a statistically superior CfB in weight (%) compared to placebo, and the 10 mg and 15 mg doses of tirzepatide also demonstrated statistically superior weight loss compared to semaglutide
- For CfB HDL, all three doses of tirzepatide were statistically superior to both placebo and semaglutide.
- For CfB total cholesterol, all three doses of tirzepatide were statistically superior compared to placebo. The 15 mg dose of tirzepatide also had a numerically superior decrease in total cholesterol compared to semaglutide.
- For CfB in SBP, all three doses of tirzepatide had a statistically superior decrease in SBP compared to placebo. The 10 mg and 15 mg doses of tirzepatide also had a numerically

superior decrease in SBP compared to semaglutide.

- The efficacy estimand analyses results in the whole trial population were congruent with the comparative efficacy findings for diet and exercise and semaglutide in the base case population.
- In the while trial population and BMI ≥35 kg/m^2 with prediabetes and high CVD risk subpopulation, all three doses of tirzepatide were numerically or statistically superior to liraglutide for all endpoints.
- Additional analyses using the treatment regimen estimand were also conducted; these were largely consistent with the efficacy estimand analyses that informed the model base case.

Conclusions

- The NMA provides robust results that are generalisable to UK clinical practice. A rigorous assessment of feasibility was conducted and limited concerns with regards to inconsistency and heterogeneity were identified all six studies included in the NMA. In addition, results of the sensitivity analyses demonstrate the robustness of the results of the main analyses.
- In the base case population and other relevant populations considered in this appraisal, the NMA provides strong evidence for the clinical effectiveness of tirzepatide relative to its comparators, given that all three doses of tirzepatide consistently show a substantial improvement in CfB in weight (%) when compared to both diet and exercise and semaglutide. These results support the SURMOUNT-1 trial in the conclusion that tirzepatide presents a clinically effective alternative to existing treatments for obesity.

As detailed in the previous sections, the SURMOUNT-1 trial provided direct head-to-head evidence on the efficacy and safety of tirzepatide versus placebo, both as an adjunct to a reduced calorie diet and increased physical exercise. While a reduced calorie diet and increased physical exercise represents one of the key comparators used in NHS clinical practice, no direct head-to-head evidence is available for the other relevant comparators for tirzepatide; therefore, an NMA was conducted to assess the relative efficacy of tirzepatide versus SC semaglutide 2.4 mg and liraglutide 3.0 mg in the populations considered in the economic analysis (Section B.3.2.1):

- The base case population: BMI ≥30 kg/m^2 and at least one weight-related comorbidity, which considers diet and exercise and semaglutide as comparators
- The relevant subpopulations for whom indirect treatment comparisons were required: BMI ≥35 kg/m^2 plus prediabetes plus high cardiovascular risk, which considers diet and exercise, semaglutide and liraglutide as comparators

The relative efficacy and safety of tirzepatide versus semaglutide and liraglutide were also assessed in the full trial population from SURMOUNT-1 (BMI ≥30 kg/m^2, or overweight BMI ≥27 kg/m^2 with at least one weight-related comorbidity). However, it should be noted that the NMA analyses in the full population is not used in the economic model, given that direct head-to-head evidence is available for the relevant comparator (a reduced calorie diet and increased physical activity) in this population from SURMOUNT-1. Similarly, an NMA was not relevant for the BMI ≥35 kg/m^2 and 30 kg/m^2 (both irrespective of comorbidities) subgroups, given that the only comparator in these subpopulations is a reduced calorie diet and increased physical activity (Section B.3.2.3.2), and head-to-head evidence for this comparison is available from SURMOUNT-1 post-hoc analyses (Section B.2.7.3).

The following sections summarise the findings of the feasibility assessment (Section B.2.9.3), the analyses methods (Section B.2.9.4), results from analyses informing the cost-effectiveness model (Section B.2.9.5), and a discussion of the results (Section B.2.9.5).

Overall, this NMA provides robust results on the comparative efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg versus relevant comparators within patients with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity, and should be considered generalisable to the use of tirzepatide as a more efficacious option than the current standard of care for obesity management for these patients.

B.2.9.1 Identification of comparator studies

This NMA was based on evidence from the RCTs identified in the clinical SLR which was conducted in June 2022 and updated in March 2023 to identify all relevant RCTs in patients with obesity; see Section B.2.1 and Appendix D for further details of the SLR. Of the 129 studies included in the SLR and SLR updates, a total of 6 were eligible for inclusion in the network. Further details of the studies included in the NMA as well as those that were excluded alongside the reasons for their exclusion are provided in Section B.2.9.3. The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool and responses were consolidated. Assessment was performed by two reviewers, and any discrepancies were resolved by a third reviewer. The risk of bias assessment for all studies identified by the SLR included in the NMA is presented in Appendix D.

B.2.9.2 Interventions

The interventions and dosages of interest for the NMA are listed in Table 26. For the comparators (semaglutide and liraglutide), the dosages approved by the MHRA were selected.

Table 26. Interventions of interest for the NMA

Intervention	Dose
Tirzepatide	5 mg QW
	10 mg QW
	15 mg QW
Semaglutide[104]	2.4 mg QW
Liraglutide[105]	3.0 mg QD

Abbreviations: QD, every day; QW, every week; NMA, network meta-analysis.

B.2.9.3 Feasibility assessment

On completion of the SLR based on the June 2022 searches, the feasibility of conducting an NMA was assessed. In particular, the feasibility assessment considered identification of treatment effect modifiers (TEMs), eligibility and heterogeneity, interventions, the analysis time window, study design and baseline characteristics, outcome definitions, estimands, and outcome availability.

B.2.9.3.1 *Identification of treatment effect modifying variables*

Since an NMA estimates relative treatment effects, TEM variables are required to be balanced across studies for an NMA to be appropriate. As such, relevant baseline characteristics considered to be TEM variables were identified based on available literature and SURMOUNT-1 subgroup results.

Specifically, based on an individual patient-level indirect treatment comparison (ITC) of liraglutide and semaglutide, the semaglutide obesity NICE technology appraisal (TA875) noted that sex, baseline HbA1c and weight were considered to be treatment effect modifiers.[2] Moreover, weight

may be measured by BMI or weight in kilograms and is expected to be correlated with waist circumference.

Comorbidities such as dyslipidaemia, hypertension and cardiovascular disease were also mentioned as potential effect modifiers by TA875.[2] T2DM may be treatment effect modifying based on the results of SURMOUNT-2 vs SURMOUNT-1, as well as STEP-2 vs STEP-1.[3, 89, 93, 97] Race/ethnicity and age were not considered to be treatment effect modifying, based on the conclusions of TA875, and SURMOUNT-1 subgroup data for tirzepatide versus placebo.[2, 100]

Finally, based on clinical opinion the following were also considered to be potential treatment effect modifiers: OSA, background therapy (principally diet and exercise), concomitant medication and physical functional as measured by component of HRQoL questionnaires such as SF-36 and IWQOL-Lite-CT.

Each of the above characteristics were evaluated for studies included in the NMA. Patient baseline characteristics for the eligible studies were assessed for heterogeneity, and specific attention was given to characteristics considered to be TEM.

B.2.9.3.2 *Eligibility assessment*

As part of the feasibility assessment, studies were assessed for their eligibility to be included in the NMA. This eligibility assessment was conducted to construct a homogenous network of studies with similar patient populations, study designs, reported timepoints, reported outcomes and patient baseline characteristics, to generate robust comparative estimates of tirzepatide versus semaglutide and liraglutide.

An explanation of each Stage (1–6) of the eligibility assessment process is provided below, and Figure 13 summarises the number of studies excluded from the records identified in the SLR (Stage 1) based on these assessments of feasibility (Stages 2–5). This culminated in 6 studies being included in the NMA (Stage 6). A list of studies excluded at each stage is included in Appendix D.

Stage 1: 118 unique studies were identified by the SLR and were assessed for their eligibility to be included in the NMA.

Stage 2: Only studies identified in the SLR reporting on tirzepatide, liraglutide and semaglutide were considered for inclusion in networks, given that these are the key comparators specified in the decision problem for which there is no direct head-to-head evidence versus tirzepatide. Although studies reporting on orlistat (amongst other treatments licenced by the FDA and EMA) were included in the SLR, these were excluded from networks as orlistat is not considered to be a relevant comparator to tirzepatide (Section B.1.1). Studies were also excluded where patients received treatments in conjunction with cognitive behavioural therapy (CBT) or intensive behavioural therapy (IBT). Included studies were assumed to be equivalent in terms of background therapy (placebo treatments, such as diet, exercise, and lifestyle interventions, see Section B.2.9.3.4), meaning they could be included in the networks via a common placebo arm.

Stage 3: Studies were required to have a sufficiently similar patient population to that of SURMOUNT-1 in terms of TEM variables. To align with SURMOUNT-1, comparator studies were excluded if the patient population all had T2DM, had comorbidities which would adversely impact weight loss, or included patients with BMI from 27–30 kg/m^2 without at least one weight-related comorbidity. To reduce heterogeneity in baseline BMI between studies, studies with a high BMI

eligibility threshold (≥32 kg/m^2) were excluded (thresholds for included studies were either BMI ≥30 kg/m^2 [O'Neil, 2018]; or BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 and ≥1 weight-related comorbidity [all other studies]).

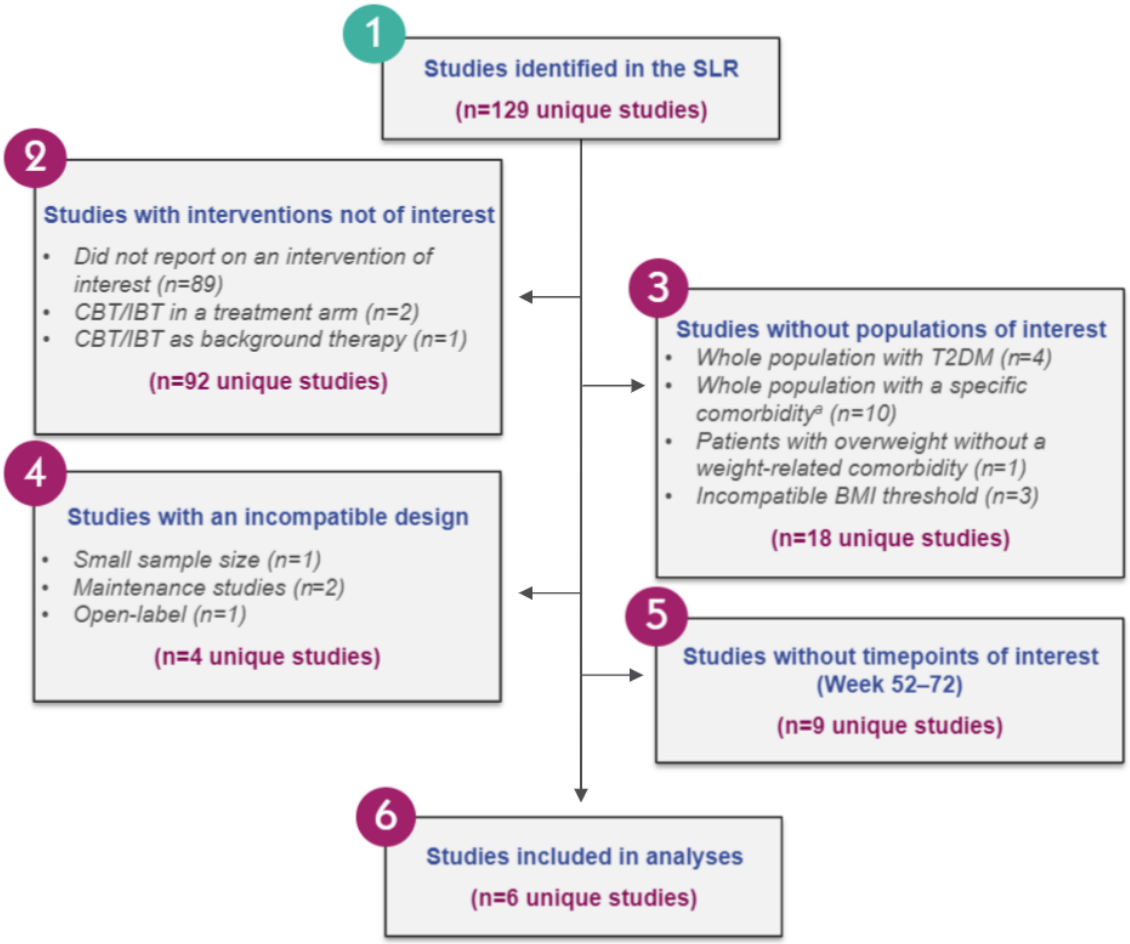
Stage 4: Study designs were also assessed and those not deemed to be comparable to the SURMOUNT-1 trial were excluded. These were studies with a small sample size (<30 patients per arm), maintenance studies, or studies which had an open-label extension phase during which participants, investigators, sponsor and analysts were unblinded.

Stage 5: Studies with a treatment duration of less than 52 weeks or not reporting at timepoints of interest (between Week 52 and Week 72, see Section B.2.9.3.3) were excluded.

Stage 6: 6 studies were included in the analyses, as detailed in Section B.2.9.3.4.

Finally, heterogeneity of study design, patient baseline characteristics and placebo response were assessed for the remaining studies; no further studies were excluded during the feasibility assessment due to concerns with heterogeneity in TEMs and placebo response.

Figure 13. PRISMA diagram for study inclusion as assessed during the feasibility assessment



Footnotes: [*] The specific comorbidities were binge eating disorder, COPD, gastrectomy, gastric bypass, heart failure, knee osteoarthritis, NAFLD, psychosis and schizophrenia.
Abbreviations: BMI, body mass index; CBT, cognitive behavioural therapy; COPD, chronic obstructive pulmonary disorder; IBT, intensive behavioural therapy; NAFLD: non-alcoholic fatty liver disease; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review; T2DM, type 2 diabetes mellitus.

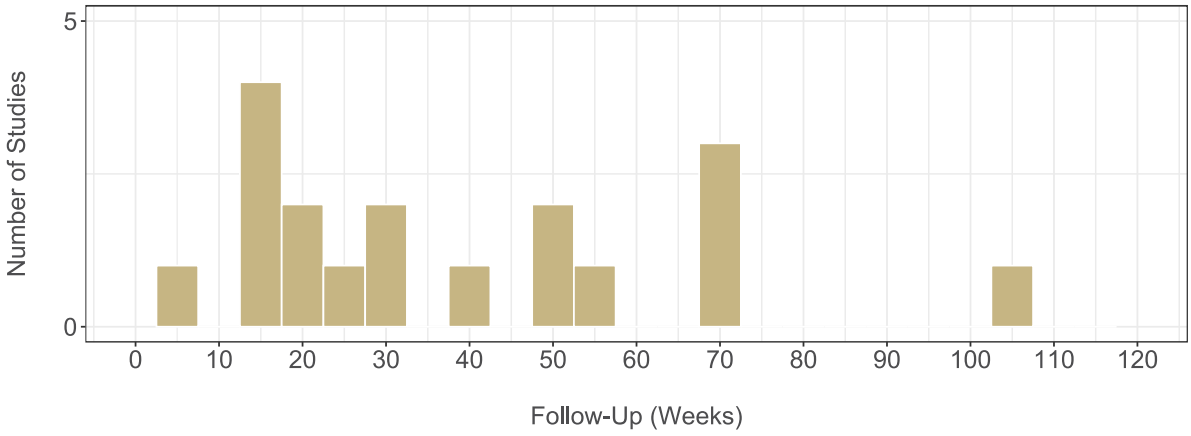
B.2.9.3.3 *Analysis timepoints*

During the feasibility assessment, the timepoints reported by each study were summarised for both efficacy and safety outcomes, as shown in Figure 14 and Figure 15, respectively. As part of the feasibility assessment, and based on data availability, the timepoint of interest for all analyses was identified to be 52–72 weeks from baseline, where baseline was defined as the initiation of treatment, and where all timepoints in this window were assumed to be equivalent. Studies not reporting within this time window were excluded from the NMA.

The justification for the timepoint of interest is that physicians or decision-makers considering different treatments would assess efficacy and safety at the primary endpoints of the relevant trials. This is the time at which all patients have been receiving the full treatment dose for at least 52 weeks. As such, the primary endpoints of the relevant trials were appropriate for a comparison of both efficacy and safety of treatments across trials.

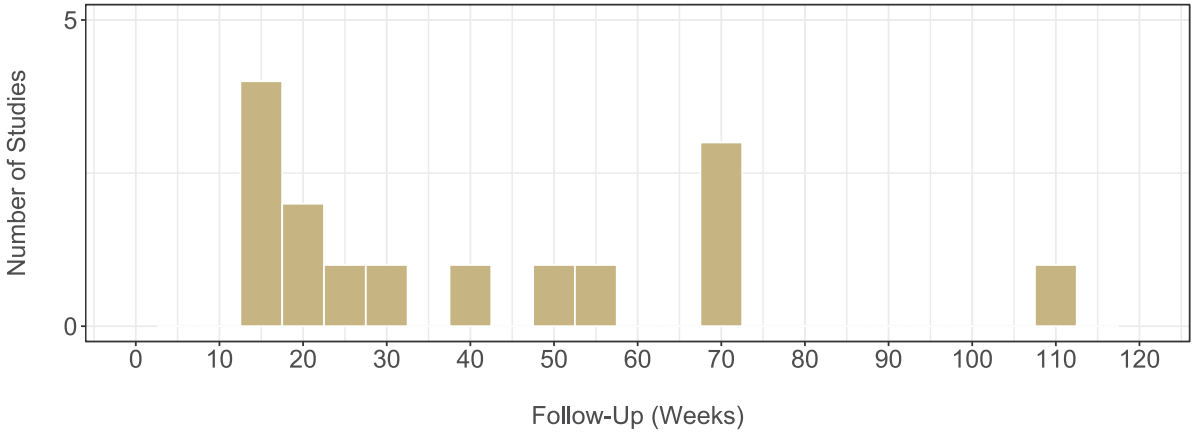
All trials eligible for the NMA had a primary endpoint between Week 52 and Week 72. From each trial, only the primary timepoint was used for each trial as data input, as these were considered equivalent across trials.

Figure 14. Reported timepoints for efficacy outcomes



Footnotes: 19 unique studies were eligible to include in this plot, which comprises the 13 studies excluded at Stage 5 of the eligibility assessment, and the six studies included in analyses.

Figure 15. Reported timepoints for safety outcomes



Footnote: 19 unique studies were eligible to include in this plot, which comprises the 13 studies excluded at Stage 5 of the eligibility assessment, and the six studies included in analyses.

B.2.9.3.4 *Summary of included studies*

Study-level characteristics

Studies included in the analyses were deemed to be comparable in terms of their study design; all studies included in the analyses were RCTs, and most were two-arm trials (4/6), though STEP 8 was a three-arm trial and SURMOUNT-1 was a four-arm trial. Most studies (5/6) were double-blind, though STEP 8 (comparing two active treatments) was double-blind between the active treatments and the matched placebo, but not between the active treatment groups due to differences in dosing. Most studies (5/6) were multinational, with STEP 8 being a single-country study. Reported sample sizes varied considerably (range: 239–4,435 patients). Studies were published between 2015–2022. The interventions and eligible populations for each study are detailed in Table 27.

Table 27. Interventions and eligible populations of included studies

Study	Intervention(s)	Eligible Population
O'Neil et al. 2018[106]	• Liraglutide 3.0 mg QD • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m² and ≥1 previous unsuccessful nonsurgical weight-loss attempt
SCALE Obesity and Prediabetes[80]	• Liraglutide 3.0 mg QD • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with hypertension or dyslipidaemia
STEP 1[12]	• Semaglutide 2.4 mg QW • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥1 treated or untreated weight-related comorbidity (hypertension, dyslipidaemia, OSA, or CVD) and ≥1 self-reported unsuccessful dietary weight loss effort
STEP 5[107]	• Semaglutide 2.4 mg QW • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m², or BMI ≥27 kg/m² with ≥1 weight-related comorbidity (hypertension, dyslipidaemia, OSA or CVD)
STEP 8[108]	• Semaglutide 2.4 mg QW • Liraglutide 3.0 mg QD • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥1 treated or untreated weight-related comorbidity (hypertension, dyslipidaemia, OSA, or CVD) and ≥1 self-reported unsuccessful dietary weight loss effort
SURMOUNT-1[3]	• Tirzepatide 5 mg QW • Tirzepatide 10 mg QW • Tirzepatide 15 mg QW • Placebo	• Aged ≥18 years without diabetes • BMI ≥30 kg/m^2, or a BMI ≥27 kg/m^2 and ≥1 weight-related comorbidity (hypertension, dyslipidaemia, OSA, or CVD), and ≥1 self-reported unsuccessful dietary weight loss effort

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; OSA, obstructive sleep apnoea; QD, every day; QW, every week.

Risk of bias

The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool.[109] Important aspects of risk of bias in clinical trials are not normally reported in conference

abstracts due to text restrictions and therefore these data sources were not assessed.

The risk of bias assessment of the full-text publications showed that overall, few studies were assessed as having a high risk of bias in any of the categories under investigation, although several were classified as unclear. This was mostly due to lack of information and was for the most part related to the method of randomisation, allocation concealment, and patient drop-outs. As the majority of studies were classified as low risk with regard to method of randomisation and selective reporting, the overall risk of bias among the studies included in the SLR may be considered manageable, as they are unlikely to be due to underlying methodological weakness.

Patient baseline characteristics

Heterogeneity in patient baseline characteristics was also assessed for the studies included in the analyses. Based on eligibility criteria, and despite some minor deviations in baseline characteristics, studies included in the analysis were deemed to be sufficiently comparable for analysis with respect to TEM variables.

Patient baseline characteristics for the whole trial population are summarised in Table 28 and also presented in Figure 16 to Figure 23. No plot has been included for T2DM as no patients in the included studies had T2DM at baseline. Baseline characteristics for each of the subgroups considered in the NMA were not available for comparator studies; however, given there were limited concerns with respect to TEMs between whole trial populations, it was assumed that subgroups would also be sufficiently comparable with respect to TEM variables.

Table 28. Descriptive statistics of patient characteristics across studies for the whole trial population

Study Name	Sample Size	Age, Mean (SD)	Female, %	Race/Ethnicity*, %							Waist Circumference (cm), Mean (SD)	Body Weight (kg), Mean (SD)	BMI, Mean (SD)	HbA1c %, Mean (SD)	T2DM, %	OSA, %	SF-36, Mean (SD)
				American Indian or Alaska Native	Asian	Black or African American	White	Native Hawaiian or other Pacific Islander	Other	Hispanic							
O'Neil, 2018	239	47.3 (12.3)	65	-	-	7.9	73.2	-	3.1	-	118.1 (15.1)	111.8 (24.1)	39.5 (7)	5.5 (0.4)	0	-	-
SCALE Obesity and Prediabetes	4974	45.1 (12.1)	78.4	0.3	3.7	9.5	85	-	1.5	10.6	114.8 (14.4)	106.2 (21.5)	38.3 (6.4)	5.6 (0.4)	0	-	-
STEP 1	1961	46.3 (12.7)	74.1	-	13.3	5.7	75.1	-	5.9	12	114.7 (14.7)	105.3 (21.9)	37.9 (6.6)	5.7 (0.3)	0	11.7	50.9 (7.2)
STEP 5	304	47.4 (11)	77.6	1	0.7	4	93.1	-	1.3	12.8	115.8 (14.9)	106.1 (22)	38.6 (7)	5.7 (0.4)	0	16.8	-
STEP 8	338	49.1 (13.2)	78.4	-	3.8	18.9	73.7	-	3.5	11.5	113.3 (15.6)	104.5 (23.9)	37.5 (6.9)	5.5 (0.3)	0	18.1	-
SURMOUNT-1	2539	44.9 (12.5)	67.5	9.1	10.9	7.9	70.6	0.3	1.2	47.8	114.1 (15.2)	104.8 (22.1)	38 (6.8)	5.6 (0.4)	0	7.8	49.6 (7.8)

Footnotes: The whole trial population definition was comparable between studies: O'Neil, 2018 defines ITT as all participants who were randomly assigned and all available in-trial data; SCALE Obesity and Prediabetes defines ITT as all patients who underwent randomisation and received at least one dose of a study drug and had at least one assessment after baseline; STEP 1 defines ITT as all randomly assigned participants; STEP 5 and STEP 8 define ITT as all randomly assigned participants regardless of treatment adherence or rescue intervention. * In most studies, patients could report on more than one race or ethnicity category, meaning that the total reported percentages add to greater than 100%.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; ITT, intention to treat; OSA, obstructive sleep apnoea; SF, short-form health survey; SD, standard deviation;T2DM, type 2 diabetes mellitus.

Figure 16. Heterogeneity assessment: age at baseline

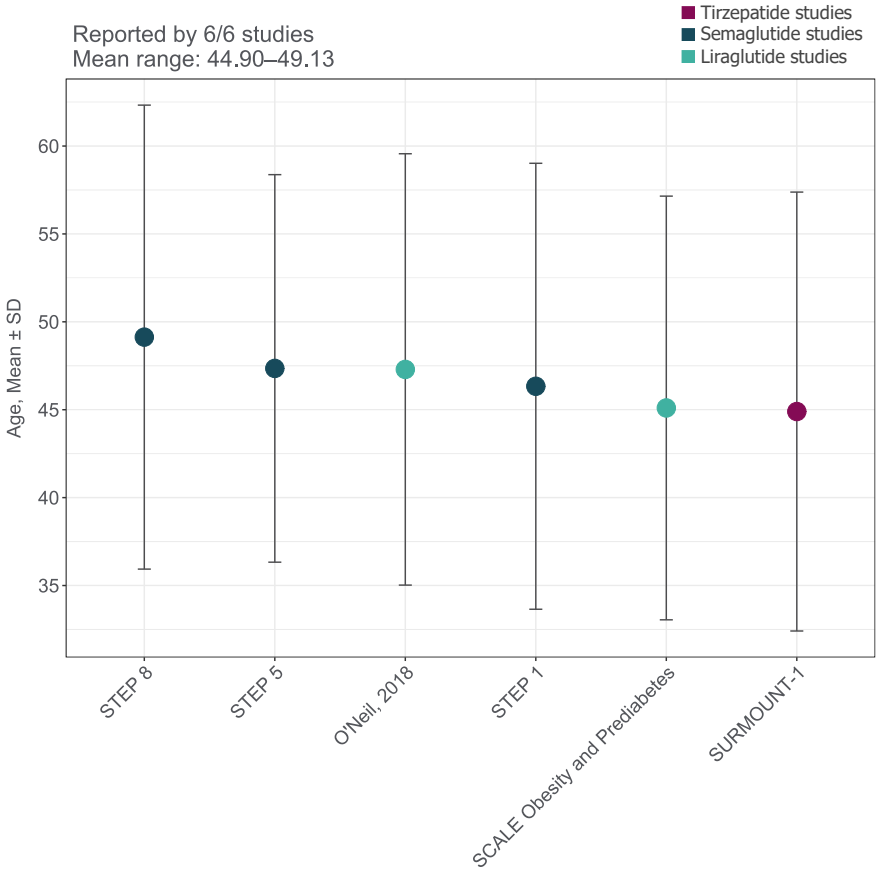


Figure 17. Heterogeneity assessment: sex

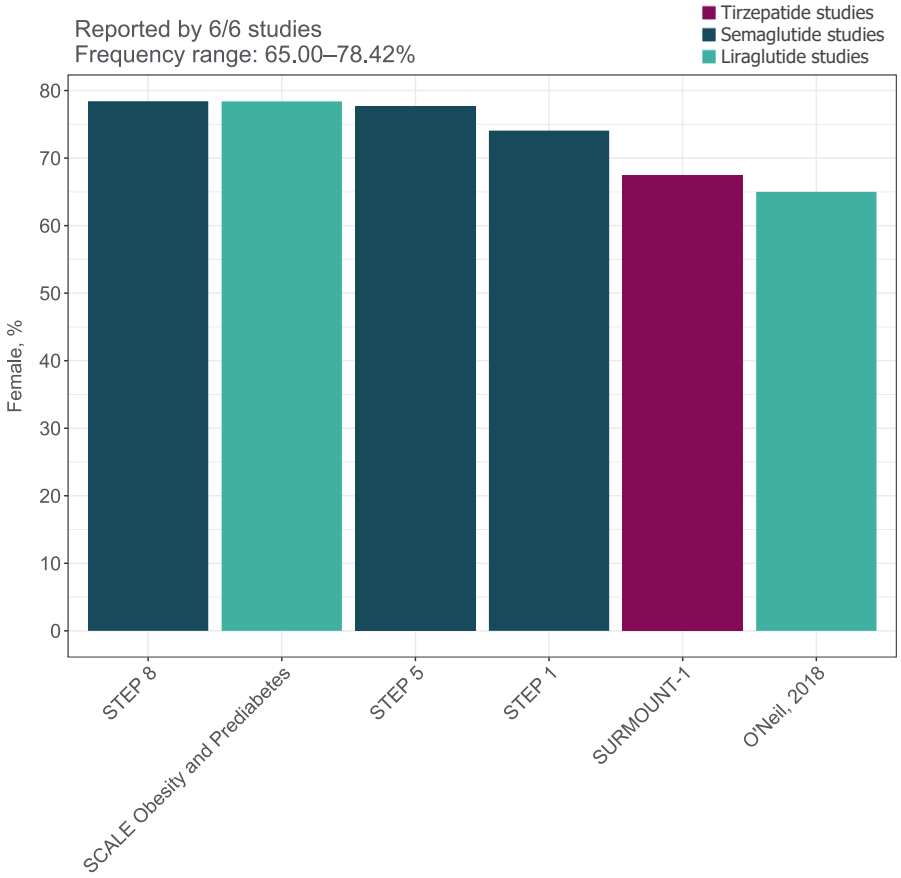


Figure 18. Heterogeneity assessment: waist circumference at baseline

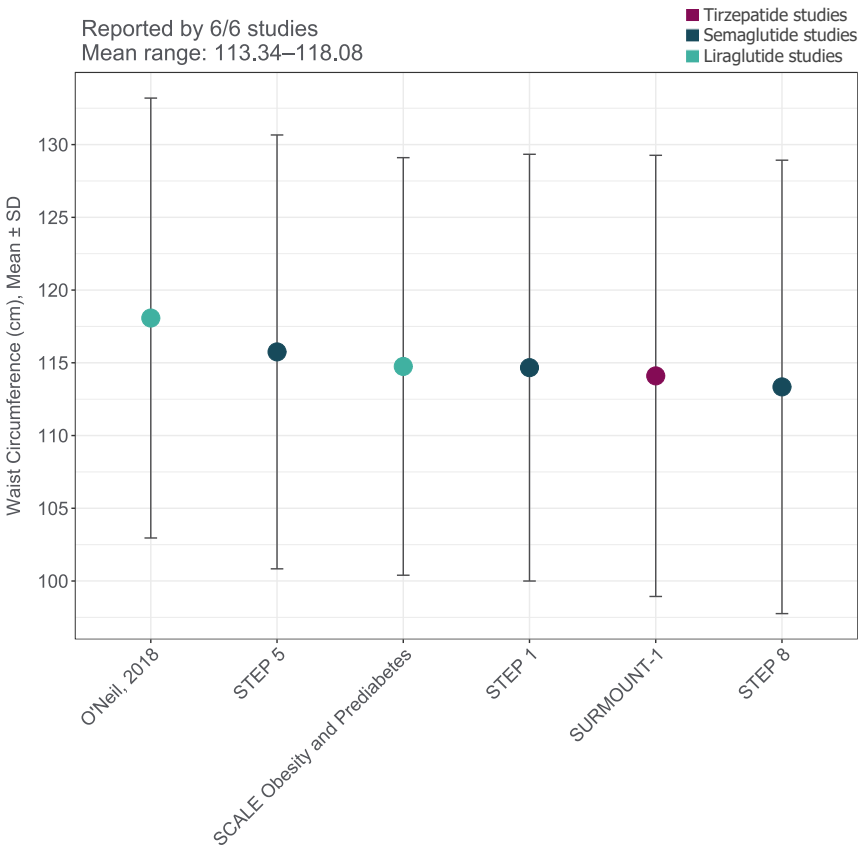


Figure 19. Heterogeneity assessment: Body weight at baseline

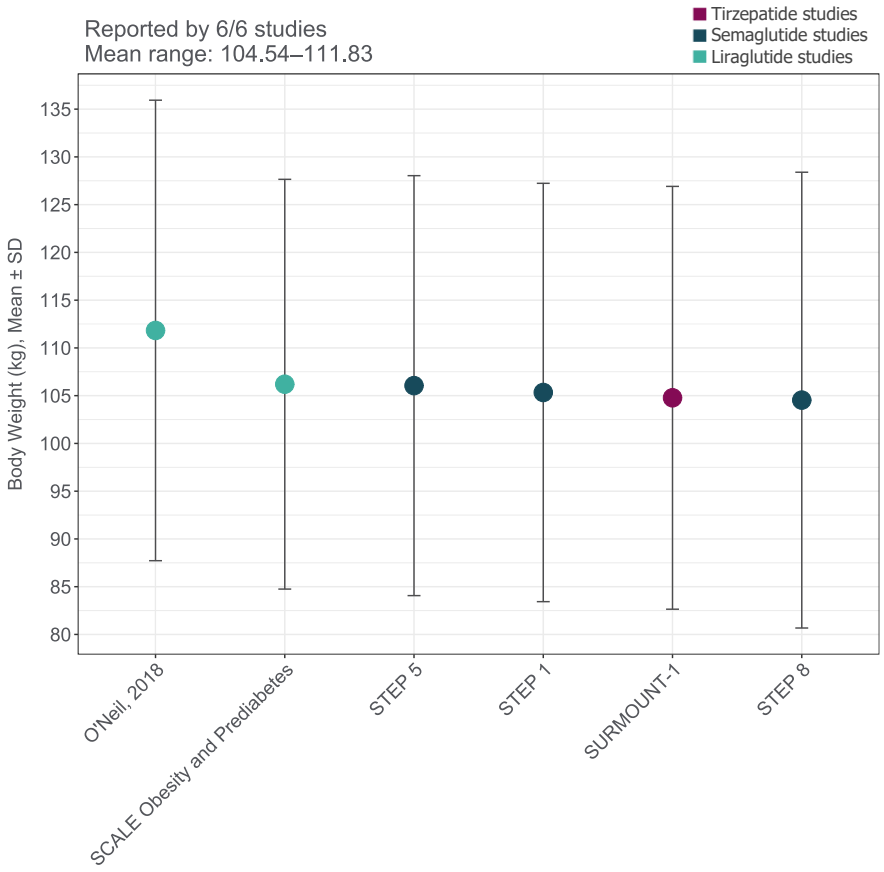


Figure 20. Heterogeneity assessment: BMI at baseline

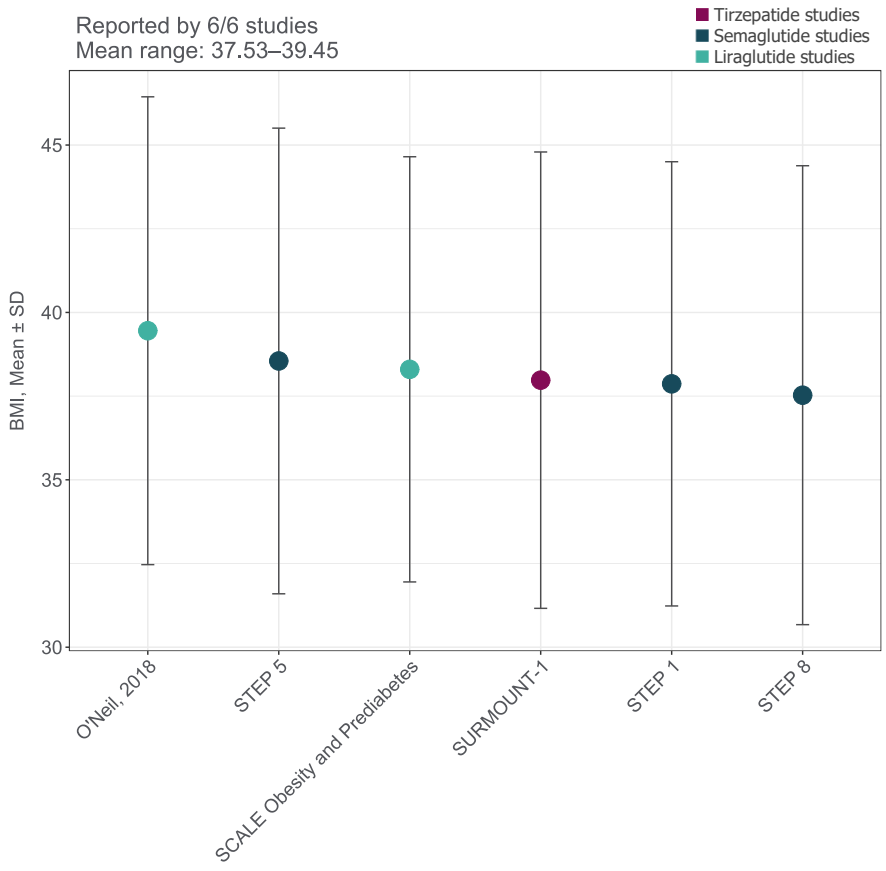


Figure 21. Heterogeneity assessment: HbA1c at baseline

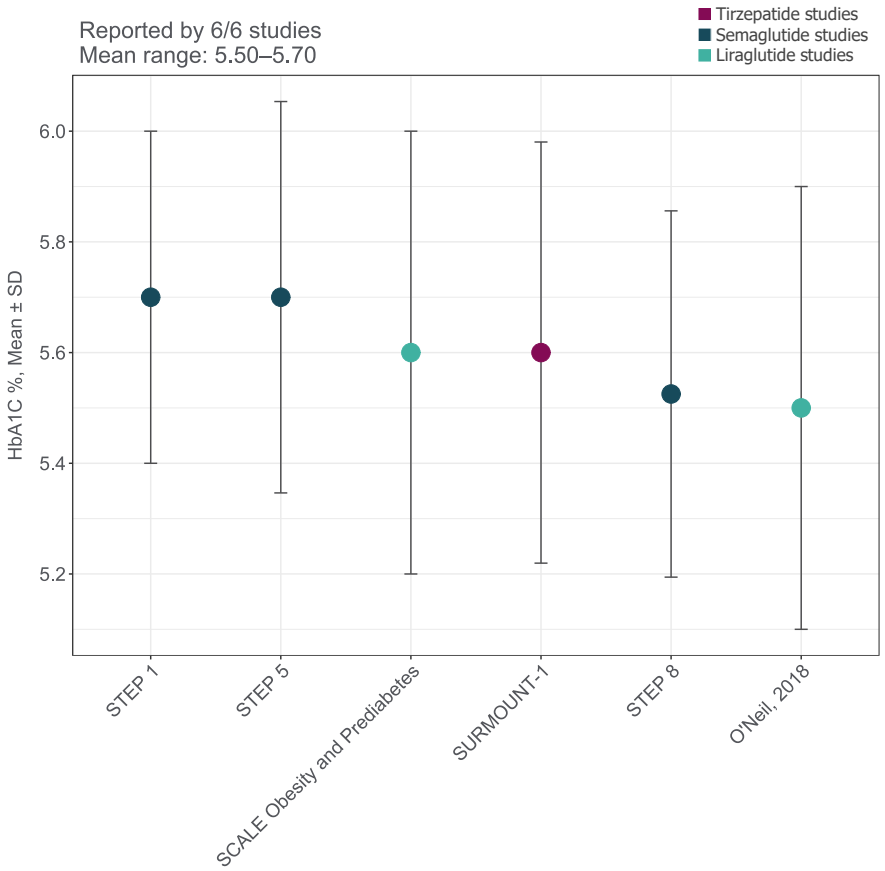


Figure 22. Heterogeneity assessment: OSA at baseline

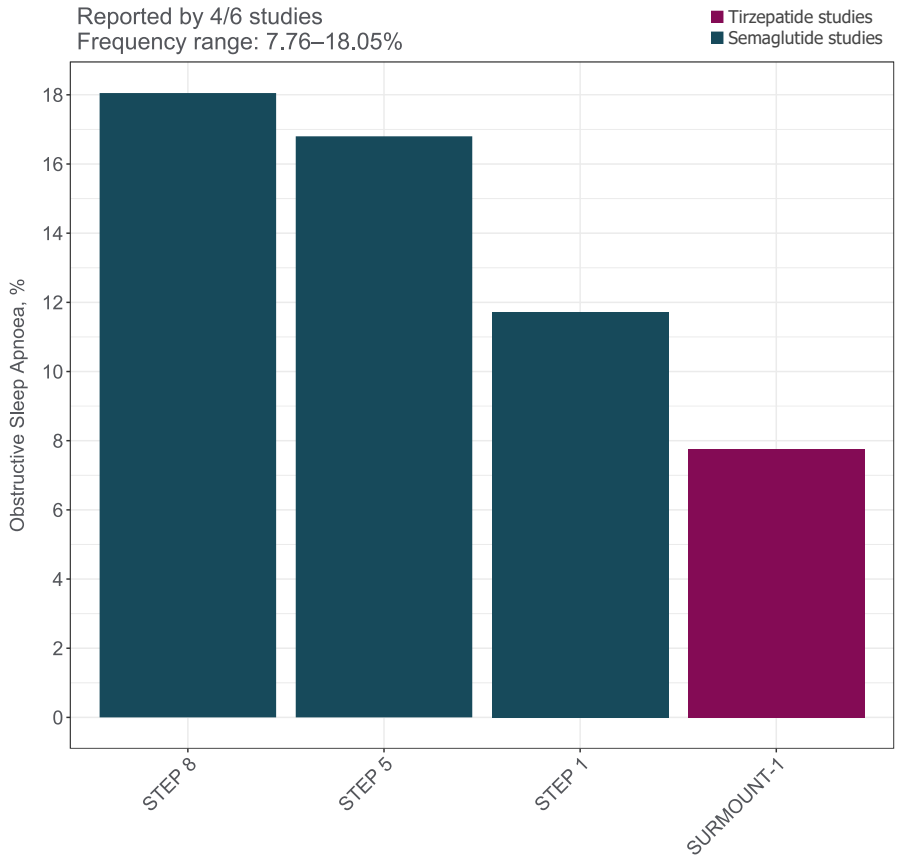
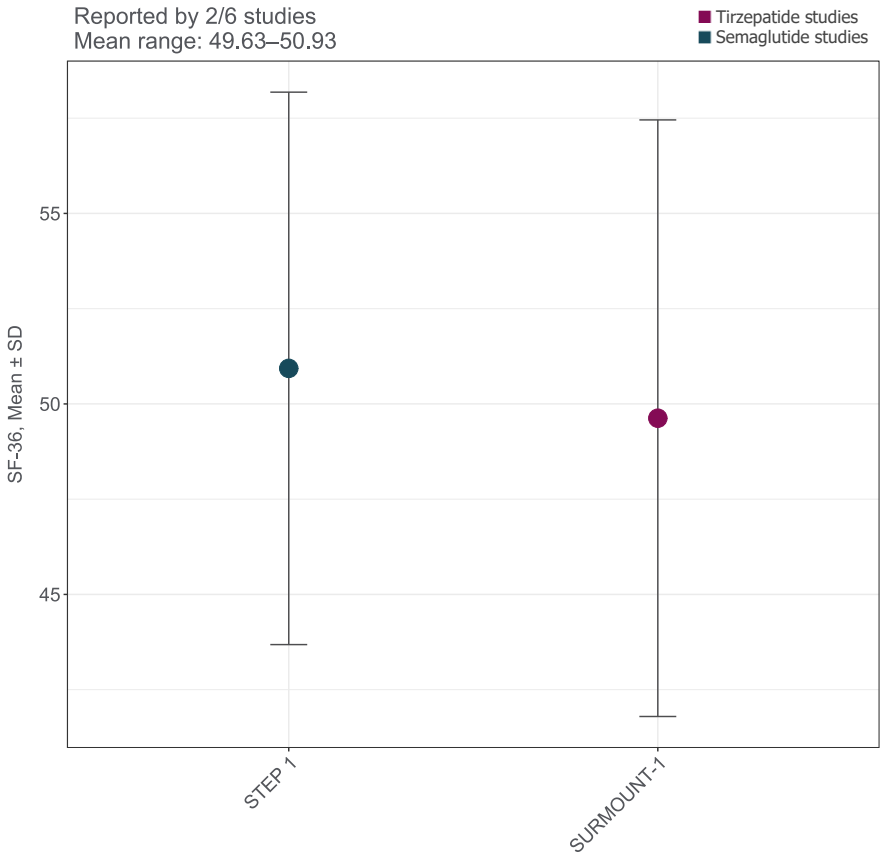


Figure 23. Heterogeneity assessment: SF-36 score at baseline



Comparability of background therapy (diet and exercise)

The heterogeneity of the background therapies of each included study was assessed to ensure that placebo arms were comparable and therefore suitable as a connecting node between tirzepatide and the comparators of interest, semaglutide and liraglutide. Table 29 presents the details of background therapy received in each study. For the purposes of the analyses, specifications of placebo (principally diet and exercise) were considered comparable across studies.

Table 29. Background therapies of included studies

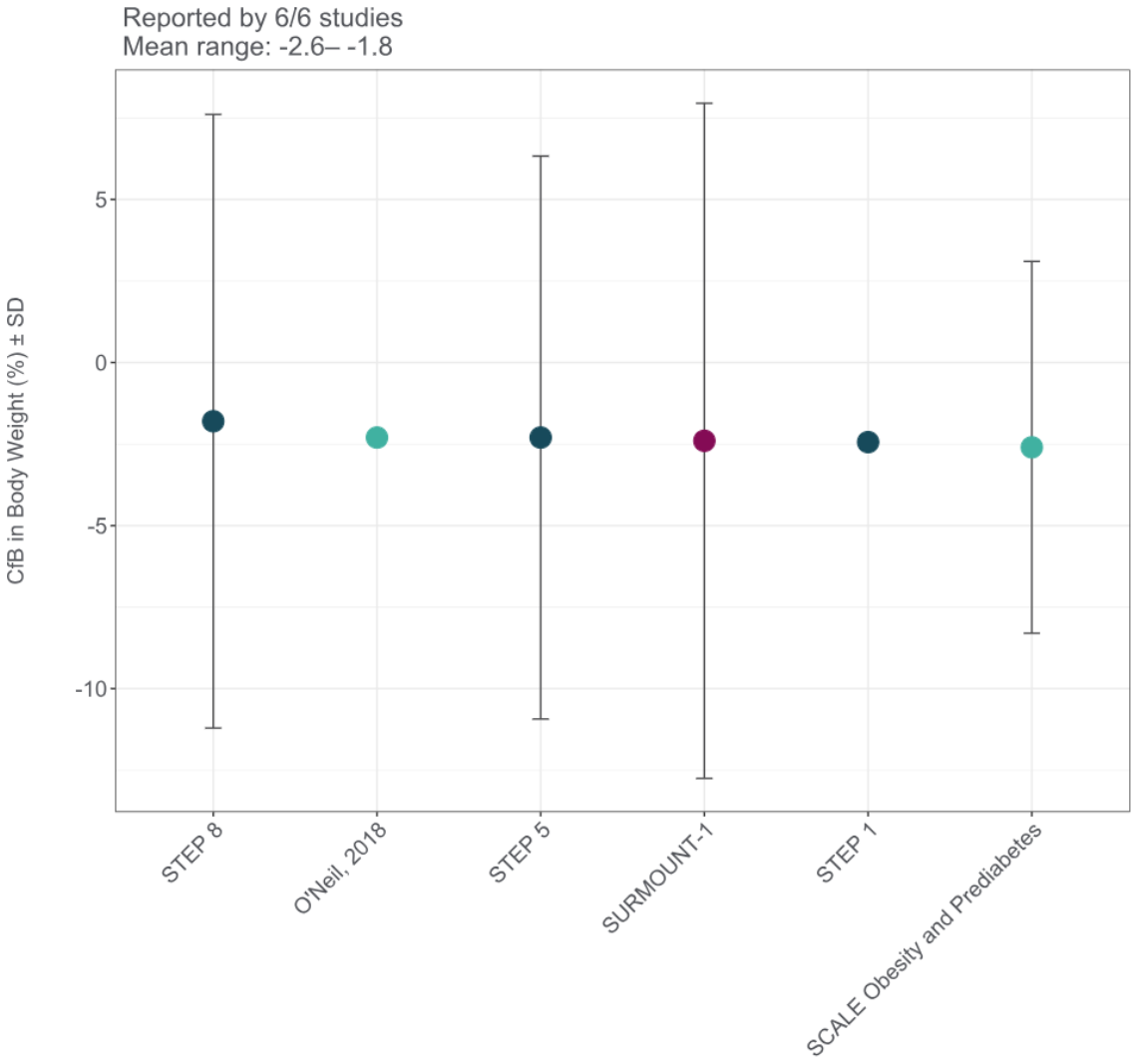
Study Name	Background Therapy	Summary
O'Neil, 2018[106]	**Diet:** estimated energy requirements minus 500 kcal/day; maintenance diet without energy deficit recommended to participants whose BMI declined to ≤22 **Exercise:** physical activity counselling based on participant capability, recommended ≥150 min/week without specifying exercise intensity **Other:** NA	Diet + Exercise
SCALE Obesity and Prediabetes[80]	**Diet:** 30% of energy from fat, 20% from protein and 50% from carbs, estimated energy requirements minus 500 kcal/day; 3-day food diary was dispensed for completion every second month **Exercise:** pedometers provided **Other:** individual or group standardised dietary and exercise counselling; 3-day food diary for completion every 2 months	Diet + Exercise + Lifestyle Intervention
STEP 1[12]	**Diet:** estimated energy requirements minus 500 kcal/day **Exercise:** 150 minutes/week of physical activity, such as walking, encouraged **Other:** individual dietary and exercise counselling every 4 weeks	Diet + Exercise + Lifestyle Intervention
STEP 5[107]	**Diet:** estimated energy requirements minus 500 kcal/day **Exercise:** 150 minutes/week of physical activity, such as walking, encouraged **Other:** individual dietary counselling every 4 weeks	Diet + Exercise
STEP 8[108]	**Diet:** estimated energy requirements minus 500 kcal/day **Exercise:** ≥150 minutes/week **Other:** NA	Diet + Exercise
SURMOUNT-1[3]	**Diet:** estimated energy requirements minus 500 kcal/day; balanced meals **Exercise:** ≥150 minutes/week **Other:** regular lifestyle counselling sessions	Diet + Exercise + Lifestyle Intervention

Abbreviations: BMI, body mass index; kcal, kilocalories; NA, not applicable.

To further assess differences in the effect of placebo across studies, CfB in body weight (a key outcome) was inspected for each of the placebo arms in the whole trial and the base case population across the studies to be included in the analyses. The CfB in body weight results across trial for placebo arms provides an indication regarding the similarity of trial populations, placebo treatments and background therapies and therefore the suitability of treating all placebo arms as a single node in the network for this key outcome. Figure 24 shows the CfB in body weight (%) for the placebo arms for all 6 studies in the whole trial population at the primary

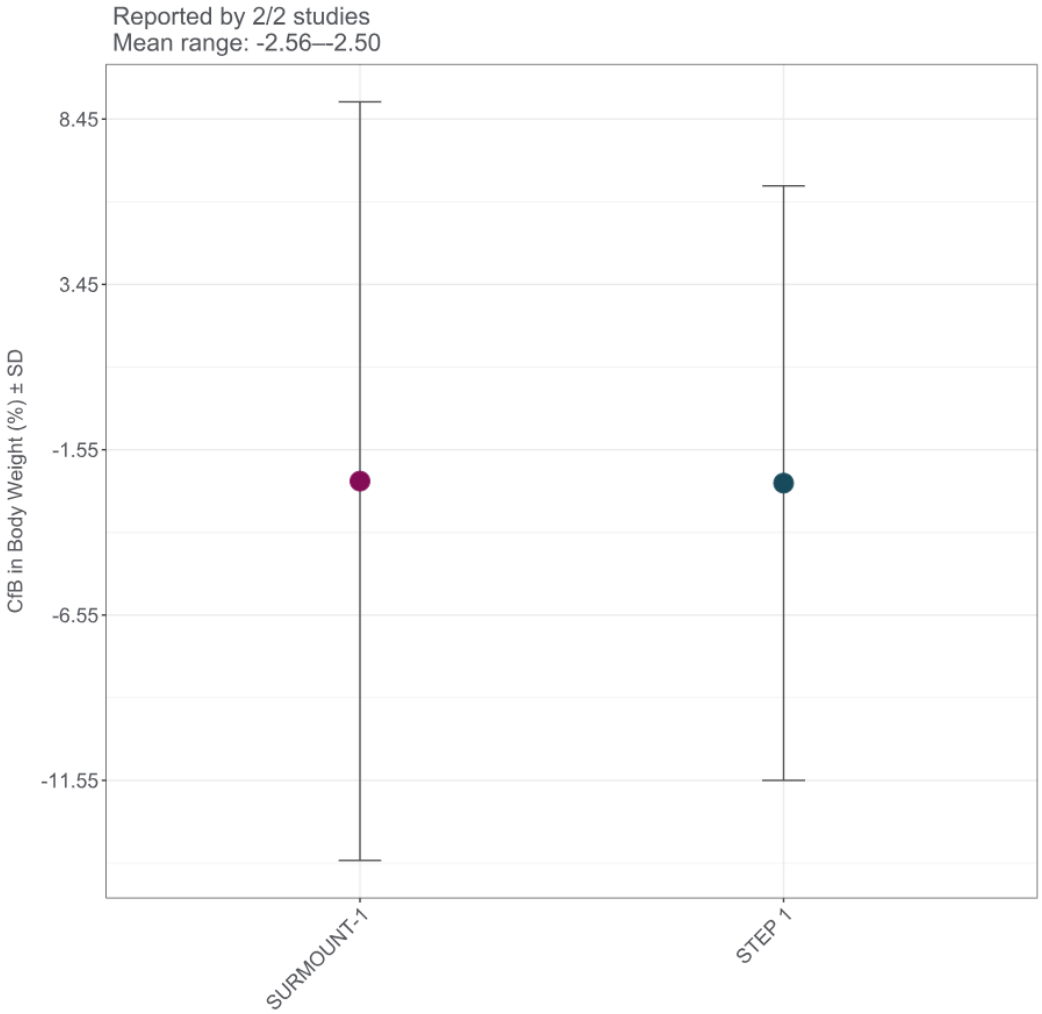
endpoint for each study (between Weeks 52 and 72). Figure 25 shows the CfB in body weight (%) for the placebo arms for the BMI ≥30kg/m^2 with at least one weight-related comorbidity subgroup at the primary endpoint for each study (between Weeks 52 and 72). The results for the placebo arm were similar across trials both in the whole trial and the base case populations, with a mean CfB in body weight between 0 kg and −5 kg. However, as noted in Section B.2.9.4.3, heterogeneity in placebo response was also assessed statistically for each outcome of interest.

Figure 24. Placebo response: CfB in body weight (whole trial population; efficacy estimand)



Abbreviations: CfB, change from baseline; SD, standard deviation.

Figure 25. Placebo response (BMI ≥30kg/m^2 with at least one weight-related comorbidity; efficacy estimand)



Abbreviations: CfB, change from baseline; SD, standard deviation.

B.2.9.3.5 *Outcome definitions*

Based on the requirements for the cost-effectiveness analysis and the risk equations selected (Section B.3.3.2), four outcomes were considered to be of interest for the NMA. These outcomes were CfB body weight (%), CfB SBP, CfB HDL and CfB total cholesterol. These outcomes were reviewed across trial to determine if they were comparable to the definition used in SURMOUNT-1. The SURMOUNT-1 outcome definitions for each outcome of interest are noted in Table 30.

CfB SBP was reported in terms of absolute change across all studies and was therefore comparable for all studies; CfB body weight (%) was also consistently reported in terms of percentage/ratio change and was therefore comparable for all studies. CfB HDL and total cholesterol were reported as a mixture of absolute change, percentage change or ratio change. For these outcomes, SURMOUNT-1 reported the percentage change, and percentage change and ratio change were considered comparable. However, the required data to calculate the absolute change was not available for any of the studies reporting percentage/ratio change and it was determined that absolute change could not be converted to percentage change, as the mean of the percentage change for each individual is not equivalent to the percentage difference between the baseline and endpoint means.

Table 30. Outcomes considered in the NMA

Variable	Type	Absolute or Percentage Change
Weight CfB, %	Continuous	Percentage change
HDL CfB	Continuous	Percentage change
Total Cholesterol CfB	Continuous	Percentage change
CfB in SBP	Continuous	Absolute change

Abbreviations: CfB, change from baseline; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NMA, network meta-analysis; SBP, systolic blood pressure.

B.2.9.3.6 *Estimands*

Estimands, where reported, were assessed to ensure homogeneity of reported outcomes across studies. The two most commonly reported estimands were:

- **Treatment regimen estimand**: results regardless of adherence to randomised treatment
- **Efficacy estimand**: results if all patients remained on the randomised treatment for the entire study period

Studies in which the estimands were not formally defined as treatment regimen or efficacy estimands were considered comparable with the treatment regimen estimand if observations after treatment discontinuation were included, and comparable with the efficacy estimand if observations after treatment discontinuation were not included.

It was determined for this analysis that on-treatment and trial product estimands were comparable with the efficacy estimand of SURMOUNT-1, whilst the treatment policy estimand was considered to be comparable with the treatment regimen estimand of SURMOUNT-1 (Table 31). Further explanation of the estimands employed in SURMOUNT-1 is provided in Section B.2.4.1.

Given that the efficacy estimand was considered more appropriate for use in the economic model and aligned with the approach in TA875 (Section B.3.3.1), an NMA was conducted using the efficacy estimand for the whole trial population and the subgroups of interest for use in the model. However, an NMA using the treatment regimen estimand was also conducted for use in cost-effectiveness model (CEM) scenario analyses.

Since the concept of estimands is relatively new, the SCALE study (liraglutide) did not report an estimand comparable to the efficacy estimand for all outcomes. For CfB weight (%), patients were asked to return at Week 56 even if they withdrew, so it was assumed that the analysis for this outcome was most similar to the treatment regimen estimand. For all other outcomes (CfB SBP, CfB HDL and CfB total cholesterol), it is not specified whether measurements were taken at Week 56 if patients withdrew early.[80] Therefore, for the analyses of these outcomes (CfB SBP, CfB HDL and CfB total cholesterol), the definition of estimand did not align with treatment regimen, and is closer to an efficacy estimand, assuming that adherence rates were high. As such, for the analysis of CfB in weight in the whole trial population and the BMI ≥35 kg/m^2 with prediabetes and high CVD risk subgroup, an estimand more closely aligning with treatment regimen was utilised for SCALE in the efficacy estimand and treatment regimen estimand NMAs. Additionally, the treatment regimen and efficacy estimand NMA of CfB SBP, CfB HDL and CfB total cholesterol used an estimand for SCALE that didn't include patients that withdrew early.

While this may have introduced some heterogeneity from SCALE in the CfB in weight efficacy estimand network, and in the CfB SBP, CfB HDL and CfB total cholesterol treatment regimen and efficacy estimand networks, this was considered a more appropriate approach than excluding this study from the networks entirely.

Table 31. Estimand definitions

Study	Estimand Comparable to Treatment regimen Estimand	Estimand Comparable to Efficacy Estimand
O'Neil, 2018	**Treatment policy estimand:** All participants who were randomly assigned treatment, irrespective of adherence	**On-treatment:** Observed changes are without imputation and used either all available data at week 52 (in-trial) or only data from those still on treatment
SCALE Obesity and Prediabetes	**Available data for CfB in weight:** All randomised participants who received at least one dose of a study drug and had at least one assessment after baseline; patients who withdrew early were asked to return at Week 56 for measurements of their weight and AEs.	**Available data for CfB SBP, CfB HDL and CfB total cholesterol:** All randomised participants who received at least one dose of a study drug and had at least one assessment after baseline.
STEP 1	**Treatment policy estimand:** All randomised participants, regardless of treatment discontinuation or use of a rescue intervention	**Trial product estimand:** All randomised participants assuming they all remained on trial product for the trial duration without use of a rescue intervention
STEP 5		
STEP 8		
SURMOUNT-1	**Treatment regimen estimand:** All randomised participants regardless of adherence to treatment	**Efficacy estimand:** All randomised participants who remained on their randomised treatment for the entire planned 72-week treatment duration

B.2.9.3.7 *Outcome availability*

Table 32 to Table 34 present the availability of each outcome for the whole trial population and subpopulation in each study eligible for analysis.

Table 32. Studies reporting outcomes included in the CEM for the whole trial population

Trial	CfB Weight %	CfB HDL	CfB Total Cholesterol	CfB SBP
O'Neil, 2018	Y	Y	Y	Y
SCALE Obesity and Prediabetes	Y	Y	Y	Y
STEP 1	Y	Y	Y	Y
STEP 5	Y	N	N	Y
STEP 8	Y	Y	Y	Y
SURMOUNT-1	Y	Y	Y	Y
Total	6	5	5	6

Abbreviations: CEM: cost effectiveness model; CfB, change from baseline.

Table 33. Studies reporting outcomes included in the CEM for the base case population

Trial	CfB Weight %	CfB HDL	CfB Total Cholesterol	CfB SBP
O'Neil, 2018	N	N	N	N
SCALE Obesity and Prediabetes	N	N	N	N
STEP 1	Y	Y	Y	Y
STEP 5	N	N	N	N
STEP 8	N	N	N	N
SURMOUNT-1	Y	Y	Y	Y
Total	2	2	2	2

Abbreviations: CEM: cost effectiveness model; CfB, change from baseline.

Table 34. Studies reporting outcomes included in the model for the BMI ≥35 kg/m^2 with prediabetes and high CV risk

Trial	CfB Weight %	CfB HDL	CfB Total Cholesterol	CfB SBP
O'Neil, 2018	N	N	N	N
SCALE Obesity and Prediabetes	Y	Y	Y	Y
STEP 1	Y	N	Y	Y
STEP 5	N	N	N	N
STEP 8	N	N	N	N
SURMOUNT-1	Y	Y	Y	Y
Total	3	2	3	3

Abbreviations: BMI: body mass index; CEM: cost effectiveness model; CfB, change from baseline.

B.2.9.3.8 *Summary*

On completion of the clinical SLR, strict eligibility criteria were applied in order to identify a homogenous set of studies reporting on treatments that were connected to tirzepatide via placebo, with semaglutide and liraglutide (the comparators of interest). Characteristics considered to be TEM were identified, and heterogeneity was considered for each of these TEMs. Eligibility criteria for interventions, populations, study design and timepoint were applied, resulting in six studies being included in the NMA. Overall, there was relative homogeneity in the summary statistics of TEMs across studies, allowing for the NMA to be conducted without population-adjustment methods. Outcome definitions and estimands were compared, and analyses were deemed to be feasible for all outcomes required for the economic analysis.

B.2.9.4 Methodology

Bayesian methods were used to conduct all NMA analyses. All analyses were conducted using the software OpenBUGS version 3.2.3, using the statistical software R version 4.2.1, through the R package *R2OpenBUGS*.[110-112] The OpenBUGS code can be found in Appendix D.

B.2.9.4.1 *Analyses presented*

The analyses presented in the submission are summarised below. Further details on data cleaning, model and parameter specification, results output and model selection are provided in further detail in the later sections.

Efficacy estimand analyses

Whole trial analyses

Analyses for the whole trial population (BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with at least one weight-related comorbidity) using the efficacy estimand were conducted on networks including studies that reported on tirzepatide, liraglutide and semaglutide. Results from these analyses are not used in the economic model, since the only comparator in this population is diet and exercise. However, they are provided for transparency and to allow comparison with the subgroup analyses.

Subgroup analyses

Analyses were also conducted for each subpopulation considered in the economic analyses for whom indirect treatment comparisons were required, including:

- BMI ≥30 kg/m^2 with at least one weight-related comorbidity. This analysis informs the model base case
- BMI ≥35 kg/m^2 with prediabetes and a high CVD risk. This analysis informs the BMI ≥35 kg/m^2 with prediabetes and a high CVD risk subpopulation considered in the economic analysis

As noted previously, NMA were not relevant for the BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2 (both irrespective of comorbidities) subgroups, given that the given that the only comparator in these subpopulations is a reduced calorie diet and increased physical activity (Section B.3.2.3.2), and head-to-head evidence for this comparison is available directly from SURMOUNT-1 post-hoc analyses (Section B.2.7.3; Appendix E).

Treatment regimen analyses

Analyses were conducted using the treatment regimen estimands. These analyses were conducted for the endpoints included in the model for both the whole trial population and each of the subpopulations listed above, for use in scenario analyses in the economic model.

B.2.9.4.2 *Data cleaning and preparation*

Input data files were prepared using arm-level data as input for each NMA.

For all outcomes, means and standard errors (SEs) were used as input. Where the mean and SE were not reported by a study, these were calculated as below:

- If the mean was missing and the median was available, the mean was approximated by the median
- If CfB mean or median estimates were missing, these were calculated as the difference between the mean outcome and the mean at baseline, or the median outcome and median at baseline if mean values were not available

- If the SE was missing and the standard deviation (SD) was available: the SE was obtained from the SD by dividing the SD by the square root of the sample size (N)
- If the SE and SD were missing but 95% CI were available: the SE was obtained from the 95% CI using the following formula:

$$SE = \frac{Upper\ CI - Lower\ CI}{2 \times 1.96}$$

- If the SE, SD, and 95% CI were missing and the interquartile range (IQR) was available: the SD was obtained from the IQR using the following formula, where $Q1$ is the lower quartile and $Q3$ the upper quartile and σ is the SD:

$$\sigma = \frac{(Q3 - Q1)}{2 \times 0.6745}$$

- If the SE, SD, 95% CI and IQR were all missing: the uncertainty associated with the mean was unknown and was imputed. In the absence of a standard approach in the Cochrane guidelines, for each network for which one or more studies have no information on variability (this was the case in a minority of networks), missing SDs were imputed as described below, with SEs then derived from the imputed SDs.[113] SDs were imputed as the pooled SD (σ_{pooled}) from k studies in the network that did report on variability, where for study i, σ_i is its SD and n_i is its sample size:

$$\sigma_{\text{pooled}} = \sqrt{\frac{(n_1 - 1){\sigma_1}^2 + (n_2 - 1){\sigma_2}^2 + \cdots + (n_k - 1){\sigma_k}^2}{n_1 + n_2 + \cdots + n_k - k}}$$

- In networks where outcomes were measured by percentage CfB, some studies reported this as a ratio, from which percentage changes were approximated by multiplying the ratio by 100 and subsequently subtracting 100 (e.g. a ratio of 0.97 was be converted as 0.97 * 100 – 100 = -3%). The SE of the percentage change was ted by multiplying the SE of the ratio by 100
- No studies in any network use the geometric mean to report a CfB. Therefore, it was not necessary to approximate mean CfB using the geometric mean in any network

B.2.9.4.3 *Model specification*

For all outcomes considered (CfB body weight (%), CfB SBP, CfB HDL and CfB total cholesterol) a normal distribution with an identity link was specified, as recommended in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 (p. 25–26) for an NMA of continuous CfB outcomes.[114] The model for CfB outcome ${y^{\Delta}}_{\{s,k\}}$ with CfB variance $var\left({y^{\Delta}}_{\{s,k\}}\right)$ for study *s*, and treatment arm *k*, is described as follows:

$${y^{\Delta}}_{\{s,k\}} \sim N\left(\nu_{\{s,k\}}, var\left({y^{\Delta}}_{\{s,k\}}\right)\right),$$

and

$$\nu_{\{s,k\}} = \mu_{\{s\}} + \delta_{\{s,k\}},$$

where $\mu_{\{s\}}$ is the estimated mean outcome in the baseline arm of trial s and $\delta_{\{s,k\}}$ is specified as $d_{t_{\{s,k\}}} - d_{t_{\{s,1\}}}$ for fixed effect models, and as $\delta_{\{s,k\}} \sim N(d_{t_{\{s,k\}}} - d_{t_{\{s,1\}}}, \tau^2)$ for random effect models,

with τ^2 the between-study heterogeneity variance. Assessment of model fit and the choice of model is described in Section B.2.9.4.10.

Adjustment for baseline risk

Baseline risk was adjusted for via meta-regression as described in NICE DSU TSD 3 (p. 42–46).[115] A plot of placebo response (baseline risk) for CfB in body weight (kg) did not identify any difference in this regard amongst the studies (Section B.2.9.3.4). Additionally, to adjust for baseline risk, the following was specified in the linear predictor:

$$\nu_{\{s,k\}} = \mu_{\{s\}} + \delta_{\{s,k\}} + \beta(\mu_{\{s\}} - \bar{\mu})$$

where $\mu_{\{s\}}$ is the study-level baseline risk, $\bar{\mu}$ the overall network baseline risk and β the interaction for baseline risk with treatment, assumed to be the same across all treatments. Fixed and random effects models were fitted, with assessment of model fit and the choice of model described in Section B.2.9.4.10.

Multi-arm adjustment

Multi-arm adjustment was incorporated in all random effects models described above to account for multi-arm correlations, following the approach outlined in NICE DSU TSD 2 (p. 35–38).[114]

B.2.9.4.4 *Assessment of heterogeneity*

A thorough assessment of heterogeneity in study design, patient baseline characteristics and placebo response was conducted for the included studies. All studies included in the analyses were deemed to have comparable characteristics (Section B.2.9.3).

The posterior between-study SD was produced from random effects models for each analysis in order to provide a measure of statistical heterogeneity. In addition, pairwise meta-analyses to assess statistical heterogeneity (via I squared) were conducted, although it should be noted that I squared was not calculated for outcomes where only one study informed each comparator (Appendix D). Overall, results from the I squared analyses indicate limited heterogeneity in the networks where this analysis could be conducted; however, the wide 95% CIs mean this conclusion is subject to some uncertainty.

B.2.9.4.5 *Assessment of inconsistency*

For networks which include STEP 8, direct evidence between semaglutide versus liraglutide was included in the NMA, which may have introduced inconsistency between direct and indirect evidence for semaglutide versus liraglutide. As recommended in NICE DSU TSD 4, unrelated mean effect models which do not assume consistency within networks were fitted for each primary analysis network which contained STEP 8, to assess whether there was inconsistency.[116] When STEP 8 did not feature in the networks, there was no possibility of inconsistency as the networks were star shaped in such instances (i.e. comparisons of comparators were connected only via placebo).

B.2.9.4.6 *Simulation parameters*

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in OpenBUGS, version 3.2.3 (revision 1012).[110] For each analysis, three chains

with different sets of initial values were used and an initial 20,000 iterations were run as a burn-in period to achieve convergence. The burn-in was then discarded and the analysis results based on a further 60,000 iterations per chain with a thinning factor of 1 for a total of 180,000 iterations. Further iterations were conducted if required, and Monte Carlo SEs were checked to ensure sufficient accuracy.[117]

B.2.9.4.7 *Prior distributions*

Vague priors

Vague priors were specified for all basic model parameters (with the Uniform distribution for variance parameters, and Normal distributions otherwise), with prior distribution parameters (e.g. upper limit of the Uniform distributions) modified according to scale of the outcome. The initial prior distributions used for each model are listed in Table 35. The variance of the Normal distributions and upper limit of the Uniform distribution were modified where appropriate for each specific outcome.

Table 35. Initial prior distributions used for model parameters

Parameter	Chain 1
μ	Normal(0,100)
δ	Normal(0,100)
τ	Uniform(0,20)

Informative priors

For outcomes where RE and baseline risk RE models were fitted and there was evidence that the between-study standard deviation τ had not updated after drawing Markov chain Monte Carlo samples (i.e. the posterior distribution of τ also remained uniformly distributed), informative priors for τ were used. Informative priors for τ were specified based on the approach described by Turner *et al.*, i.e., $\tau^2 \sim lognormal(-2.56, 1.74^2)$. [118]

B.2.9.4.8 *Assessment of convergence*

Convergence was assessed using history trace plots, smoothed Kernel posterior density plots and Brook–Gelman–Rubin (BGR) diagnostic plots.

History trace plots of the parameters of interest display the evolution of the variables against iteration number and are a good tool to assess for non-convergence in the simulation. The plots must show all the characteristics of a random series: no trend over iteration number, values well dispersed in space and which do not remain localised as iteration number increases.

The smoothed Kernel density plots were inspected to ensure that the posterior density functions of each parameter of interest were approximately globally unimodal and symmetric. This was use to confirm whether convergence towards a sensible posterior distribution had been achieved. In particular, convergence of the posterior distribution of the between-study SD was checked for all random effect models.

Auto-correlation plots were used to assess the dependence between successive iterations of the Markov chains and Monte Carlo standard errors were checked to ensure sufficient information had been sampled. In particular, it was ensured that Monte Carlo SEs were less than 5% of the

standard deviations of the basic model parameters.

The BGR diagnostic plots were used to assess the within-chain and between-chain variability. Once the chains converged, the variability was assessed to ensure it was approximately equal to one and was stable across iterations.

B.2.9.4.9 *Results output*

Relative treatment effects were produced for all outcomes using the posterior median of mean differences. 95% credible intervals (CrIs) were produced, and the strength of association determined whether or not the CrIs included the value of no effect (0 for mean differences, 1 for ORs).

Relative treatment effects and 95% CrIs for all comparable treatments are presented in league tables for each outcome. Forest plots were also generated for each comparator versus each dose of tirzepatide, and versus placebo. Ranking parameters were also generated, including probability best, median rank, mean Surface Under the Cumulative Ranking Curve (SUCRA) value, and SUCRA plots. SUCRA plots are provided in a separate document alongside this submission.[119]

Absolute treatment effects were also produced for all outcomes, using the placebo arm of SURMOUNT-1 as the reference treatment. For each outcome, the mean CfB of each treatment was generated. Absolute treatment effects and 95% CrIs are presented in table format.

B.2.9.4.10 *Model selection*

In order to ensure that the most appropriate model was selected for each analysis, several models were used for each analysis and their fit assessed. These models were FE and RE models, and FE and RE models with an adjustment for baseline risk (Section B.2.9.4.3). A corresponding inconsistency model was fitted according to which of the above four consistency models was preferred (Section B.2.9.4.5).

All five models were fitted for the whole trial population analyses (both for the efficacy and treatment regimen estimand). For subgroup analyses, inconsistency models were not required as STEP 8 did not feature in these networks, so four models were fitted.

The selection process to determine the most appropriate model for each outcome per analysis is described below.

Fixed versus random effects

Both FE and RE models were fitted for all analyses. The deviance information criterion (DIC), total residual deviance and effective number of parameters were generated and compared between the two models. When model fit of FE and RE models were similar based on DIC and residual deviance statistics, FE models were chosen for ease of interpretation.[87]

With versus without adjustment for baseline risk

The baseline risk model was selected over the standard model if it had a better fit. This assessment was informed by whether an interaction existed between the baseline risk and treatment effect, as indicated by the CrI for the interaction effect estimate. A comparison of the DIC, total residual deviances and between-study SDs between models also informed this

assessment.

Consistency versus inconsistency model

In networks where an inconsistency was possible (i.e. where at least one loop existed in the network), an inconsistency model was also fitted. The DIC, total residual deviance and between-study SD were generated and compared versus the favoured consistency model. Arm-specific residual deviances were also assessed between the two models in order to identify any potential inconsistency.

B.2.9.5 Results

For concision, only the NMA results informing the model base case and the whole trial population results are presented in the following sections. A summary of the analysis results presented elsewhere in the submission package is provided in Table 36. Convergence plots of each NMA informing the CEM base case are provided alongside the submission.[120]

As noted in Section B.2.9.4.10, where model fit of FE and RE models were similar, FE models were chosen for use in the economic model.

Table 36. Summary of NMA results presented in the submission

Analyses	Location
Analyses for BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity – FE results (efficacy estimand)	Section B.2.9.5.1
Analyses for the whole trial population – FE results (efficacy estimand)	Section B.2.9.5.2
Analyses for BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity – RE results (efficacy estimand)	Appendix D
Analyses for the whole trial population – RE results (efficacy estimand)	Appendix D
Analyses for BMI ≥35 kg/m^2 with prediabetes and a high CVD risk – FE and RE results (efficacy estimand)	Appendix D
Analyses for BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity – FE and RE results (treatment regimen estimand)	Appendix D
Analyses for the whole trial population – FE and RE results (treatment regimen estimand)	Appendix D
Analyses for BMI ≥35 kg/m^2 with prediabetes and a high CVD risk – FE and RE results (treatment regimen estimand)	Appendix D

Abbreviations: CVD: cardiovascular disease; FE: fixed effects; RE: random effects.

An explanation of how to interpret the results for continuous outcomes is given in Appendix D.

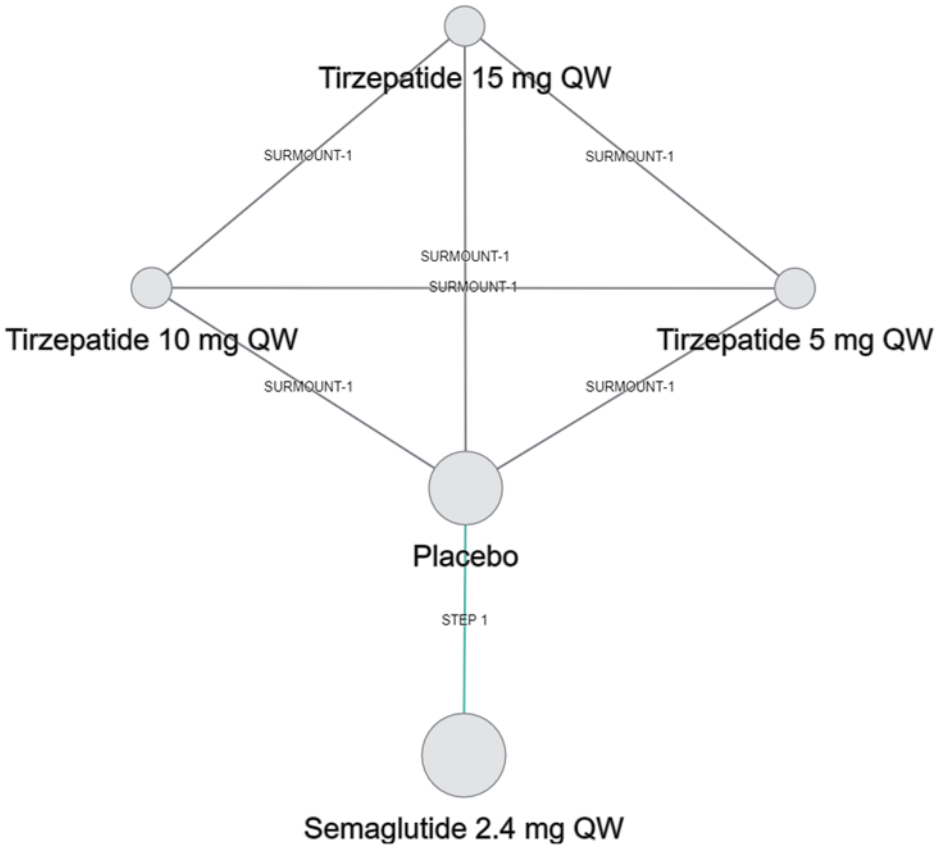
B.2.9.5.1 *Efficacy estimand analysis for BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity – FE results (base-case results)*

The following section presents the analysis results for patients with a BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, which include the results of model fitting, a description of which model was selected, and the posterior treatment effect estimates and their associated 95% CrIs for the chosen model in the form of league tables and forest plots. As noted above, these results inform the model base case.

CfB in weight (%)

An NMA of CfB in weight (%) was conducted for the analysis network presented in Figure 26. The model statistics are shown in Table 37, and the mean differences in treatment effect and 95% CrIs are presented in Table 38 and Figure 27.

Figure 26. Analysis network: BMI ≥30 kg/m2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in weight (%)



Footnotes: Teal indicates two-arm trials; grey indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: BMI, body mass index; CfB, change from baseline; QW, every week.

Table 37. Model fit statistics: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in weight (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RE BR InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 6 data points in this network.
Abbreviations: BR, baseline risk; BMI, body mass index; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; InfoPrior, informative prior; pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC or residual deviance between the unadjusted FE and RE models, the unadjusted FE model was selected as the favoured model. The RE informative prior model results are presented in the Appendix D.4.2.1.

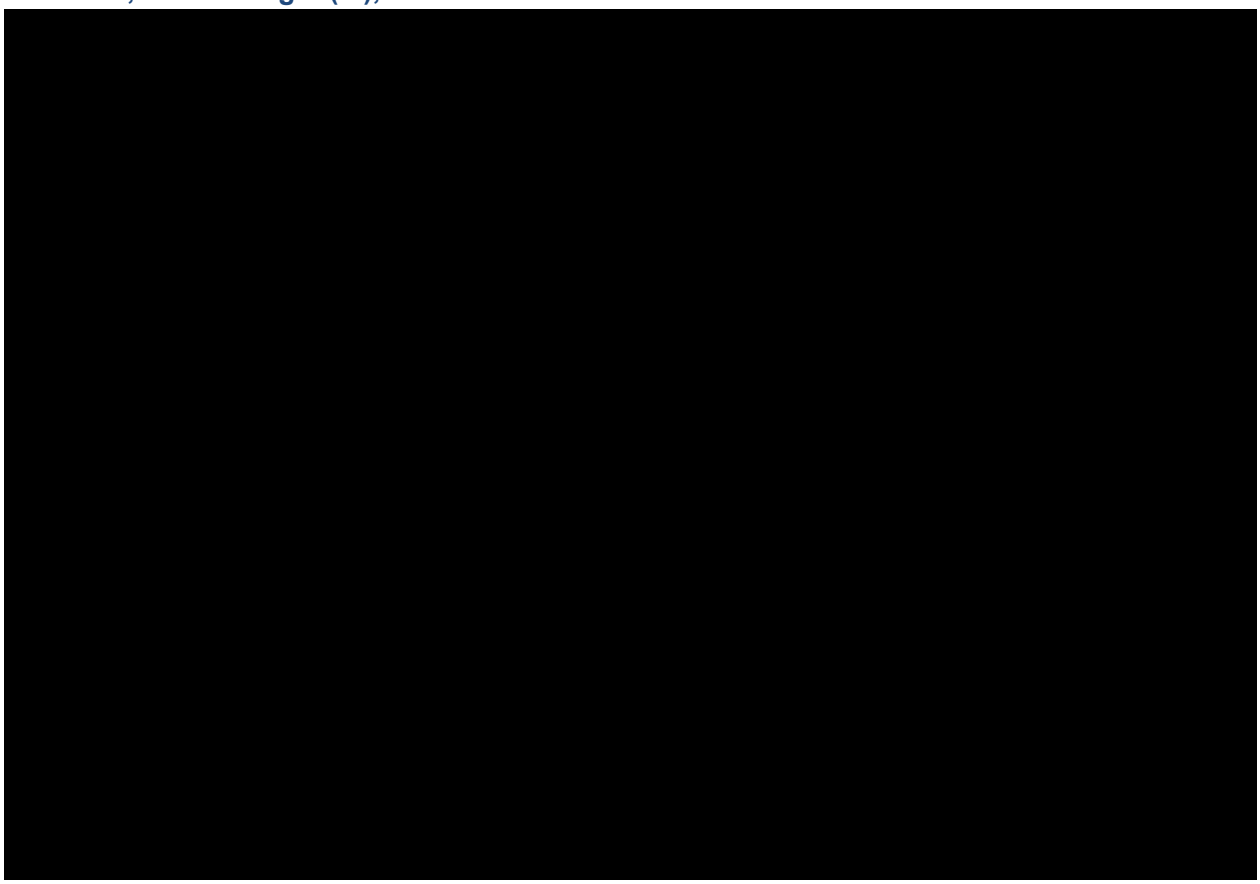
The FE unadjusted model results are presented in Table 38 and Figure 27. All three doses of tirzepatide had a statistically superior decrease in weight (negative CfB in weight [%]) compared to placebo. The 10 mg and 15 mg doses of tirzepatide had a statistically superior weight loss compared to semaglutide. The 15 mg dose of tirzepatide had the greatest absolute CfB in weight (%) of all the interventions (Table 38).

Table 38. League table: mean difference (95% CrI), BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in weight (%), FE model

		Comparator					Absolute CfB in Weight (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QW, every week.

Figure 27. Forest plot: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in weight (%), FE model



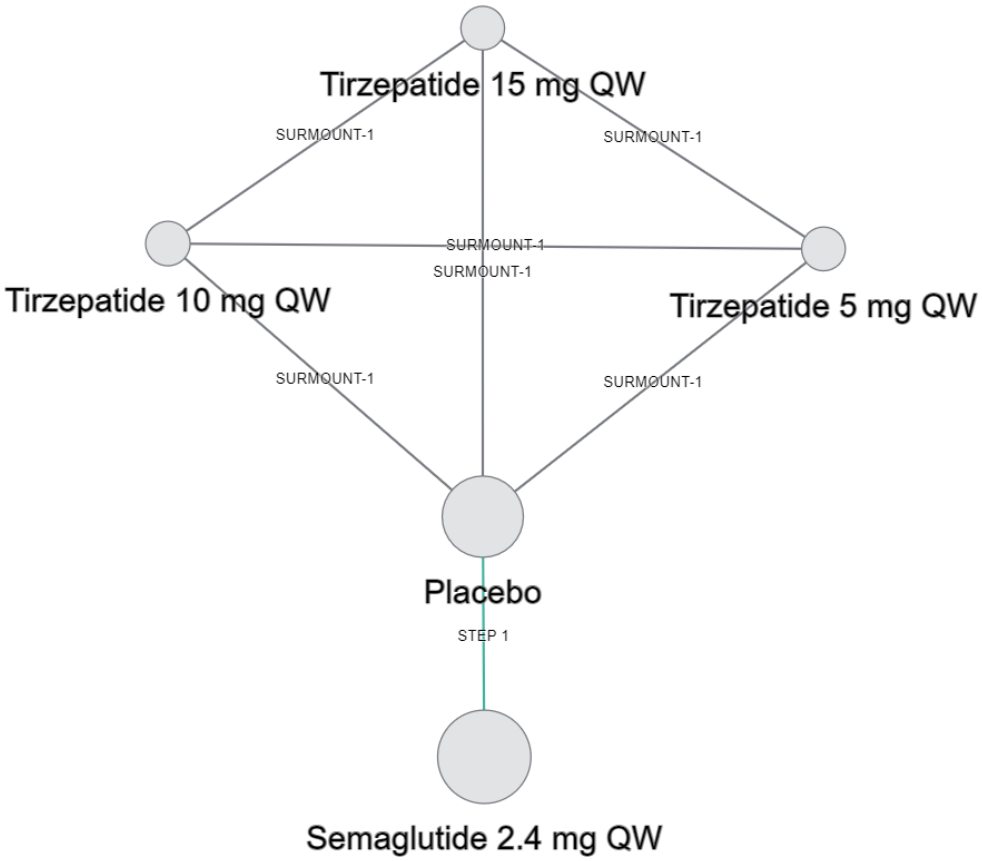
Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QW, every week.

CfB in HDL (%)

An NMA of CfB in HDL (%) was conducted for the analysis network presented in Figure 28. The model statistics are shown in

Table 39, and the mean differences in treatment effect and 95% CrIs are presented in Table 40 and Figure 29.

Figure 28. Analysis network: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in HDL (%)



Footnotes: **Teal** indicates two-arm trials; **grey** indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: BMI, body mass index; CfB, change from baseline; HDL, high density lipoprotein; QW, every week.

Table 39. Model fit statistics: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in HDL (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 6 data points in this network; assessment for inconsistency was conducted only for the preferred model (i.e. the FE unadjusted model).
Abbreviations: BR, baseline risk; BMI, body mass index; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; HDL, high density lipoprotein; InfoPrior, informative prior; pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC or residual deviance between the unadjusted FE and RE models, the unadjusted FE model was selected as the favoured model. The RE informative prior model results are presented in the Appendix Section D.4.2.1.

The FE unadjusted model results are presented in Table 40 and Figure 29. Estimated absolute CfB in HDL (%) is also presented in Table 40. All three doses of tirzepatide had a statistically superior increase in HDL (positive CfB in HDL [%]) compared to placebo semaglutide. The 15 mg dose of tirzepatide had the greatest absolute CfB in HDL (%) of all the interventions (Table 40).

Table 40. League table: mean difference (95% CrI), BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in HDL (%), FE model

		Comparator					Absolute CfB in HDL (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; HDL, high density lipoprotein; QW, every week.

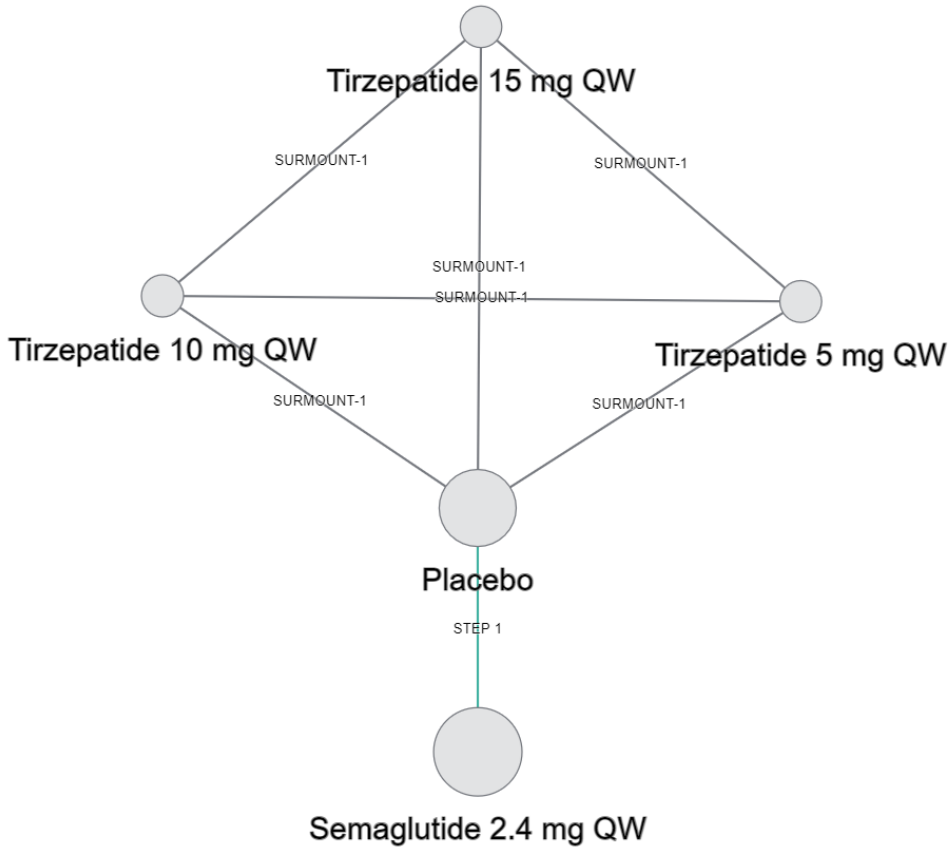
Figure 29. Forest plot: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in HDL (%), FE model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; HDL, high density lipoprotein; QW, every week.

CfB in total cholesterol (%)

An NMA of CfB in total cholesterol (%) was conducted for the analysis network presented in Figure 30. The model statistics are shown in Table 41, and the mean differences in treatment effect and 95% CrIs are presented in Table 42 and Figure 31.

Figure 30. Analysis network: BMI ≥30 kg/m² with ≥1 weight-related comorbidity, efficacy estimand, CfB in total cholesterol (%)



Footnotes: Teal indicates two-arm trials; grey indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: BMI, body mass index; CfB, change from baseline; QW, every week.

Table 41. Model fit statistics: BMI ≥30 kg/m² with ≥1 weight-related comorbidity, efficacy estimand, CfB in total cholesterol (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 6 data points in this network.
Abbreviations: BR, baseline risk; BMI, body mass index; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; InfoPrior, informative prior; pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC or residual deviance between the unadjusted FE and RE models, the unadjusted FE model was selected as the favoured model. The RE informative prior model results are presented in the Appendix D.4.2.1.

The FE unadjusted model results are presented in Table 42 and Figure 31. Estimated absolute CfB in total cholesterol (%) is also presented in Table 42. All three doses of tirzepatide had a statistically superior decrease in total cholesterol (negative CfB in total cholesterol [%]) compared to placebo. The 15 mg dose of tirzepatide had a numerically superior decrease in total cholesterol compared to semaglutide. The 15 mg dose of tirzepatide had the greatest absolute CfB in total cholesterol (%) of all the interventions (Table 42).

Table 42. League table: mean difference (95% CrI), BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in total cholesterol (%), FE model

		Comparator					Absolute CfB in Total Cholesterol (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QW, every week.

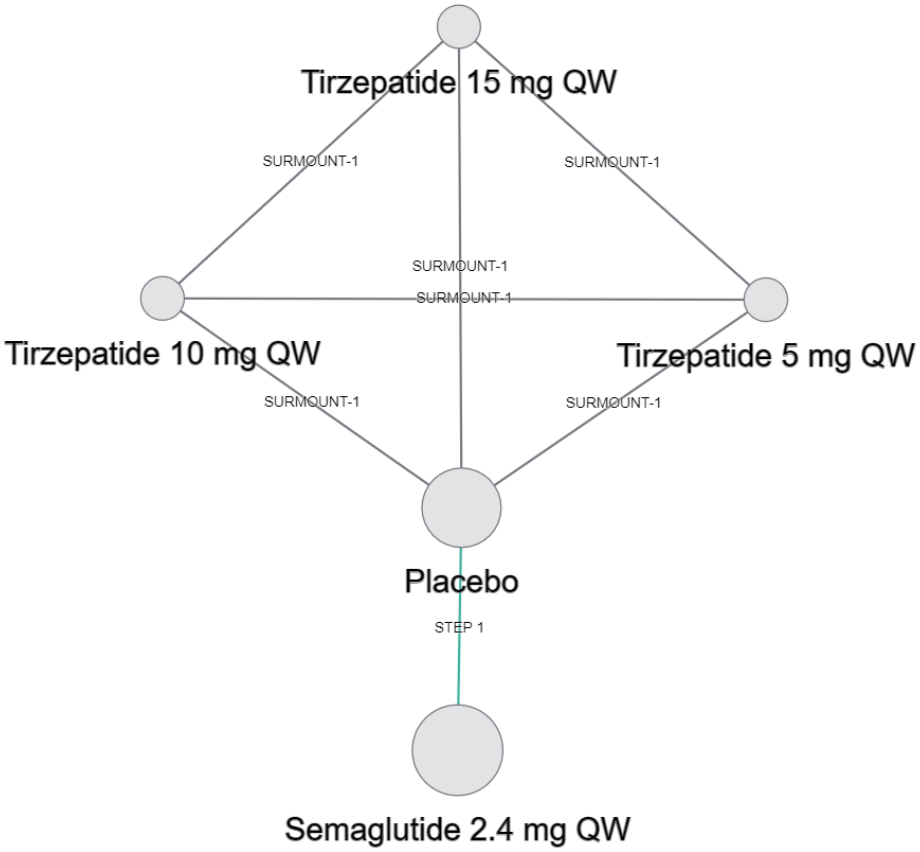
Figure 31. Forest plot: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in total cholesterol (%), FE model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; QD, everyday; QW, every week; RE, random effects.

CfB in SBP (mmHg)

An NMA of CfB in SBP (mmHg) was conducted for the analysis network presented in Figure 32. The model statistics are shown in Table 43, and the mean differences in treatment effect and 95% CrIs are presented in Table 44 and Figure 33.

Figure 32. Analysis network: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in SBP (mmHg)



Footnotes: Teal indicates two-arm trials; grey indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: BMI, body mass index; CfB, change from baseline; QW, every week; SBP, systolic blood pressure.

Table 43. Model fit statistics: BMI ≥30 kg/m2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in SBP (mmHg)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR InfoPrior model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 6 data points in this network.
Abbreviations: BR, baseline risk; BMI, body mass index; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; InfoPrior, informative prior; pD, effective number of parameters; RE, random effects; SBP, systolic blood pressure; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC or residual deviance between the unadjusted FE and RE models, the unadjusted FE model was selected as the favoured model. The RE informative prior model results are presented in the Appendix D.4.2.1.

The FE model results are presented in Table 44 and Figure 33. Estimated absolute CfB in SBP (mmHg) is also presented in Table 44. All three doses of tirzepatide had a statistically superior decrease in SBP (negative CfB in SBP [mmHg]) compared to placebo. The 10 mg and 15 mg doses of tirzepatide had a numerically superior decrease in SBP compared to semaglutide. The 10 mg dose of tirzepatide had the greatest absolute CfB in SBP (mmHg) of all the interventions (Table 44).

Table 44. League table: mean difference (95% CrI), BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in SBP (mmHg), FE model

		Comparator					Absolute CfB in SBP (mmHg)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects: QW, every week; SBP, systolic blood pressure.

Figure 33. Forest plot: BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity, efficacy estimand, CfB in SBP (mmHg), FE model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.

Abbreviations: BMI, body mass index; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QW, every week; SBP, systolic blood pressure.

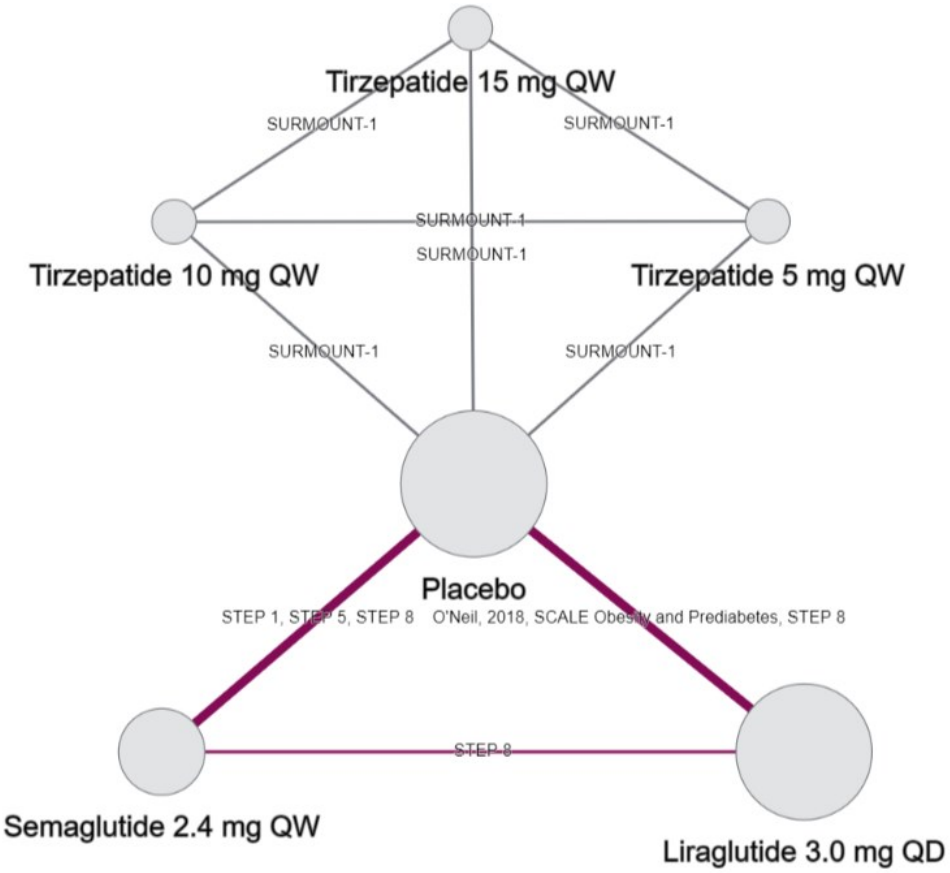
B.2.9.5.2 *Analysis for the whole trial population – FE results*

The following section presents the results of the analyses for the whole trial population, which include the results of model fitting, a description of which model was selected, and the posterior treatment effect estimates and their associated 95% CrIs for the chosen model in the form of league tables and forest plots.

CfB in weight (%)

An NMA of CfB in weight (%) was conducted for the analysis network presented in Figure 34. The model statistics are shown in Table 45, and the mean differences in treatment effect and 95% CrIs are presented in Table 46 and Figure 35.

Figure 34. Analysis network: whole trial population, efficacy estimand, CfB in weight (%)



Footnotes: Teal indicates two-arm trials; grey indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: CfB, change from baseline; QD, everyday; QW, every week.

Table 45. Model fit statistics: whole trial population, efficacy estimand, CfB in weight (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inconsistency model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

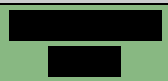
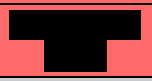
Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 15 data points in this network; assessment for inconsistency was conducted only for the preferred model (i.e. the FE unadjusted model).
Abbreviations: BR, baseline risk; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC or residual deviance between the unadjusted

FE and RE models, the unadjusted FE model was selected as the favoured model. There was no evidence of inconsistency within the network, as the DIC of the inconsistency model was similar to the FE unadjusted model. The unadjusted RE model results are presented in the Appendix D.4.3.

The FE unadjusted model results are presented in Table 46 and Figure 35. All three doses of tirzepatide had a statistically superior weight loss (negative CfB in weight [%]) compared to liraglutide and placebo. The 10 mg and 15 mg doses of tirzepatide had a statistically superior weight loss compared to semaglutide, while the 5 mg dose of tirzepatide had a numerically inferior weight loss compared to semaglutide. The 15 mg dose of tirzepatide had the greatest absolute CfB in weight (%) of all the interventions.

Table 46. League table: mean difference (95% CrI), whole trial population, efficacy estimand, CfB in weight (%), FE unadjusted model

		Comparator						Absolute CfB in Weight (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Liraglutide 3.0 mg QD	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW							
	Tirzepatide 10 mg QW							
	Tirzepatide 15 mg QW							
	Liraglutide 3.0 mg QD							
	Semaglutide 2.4 mg QW							
	Placebo							

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week.

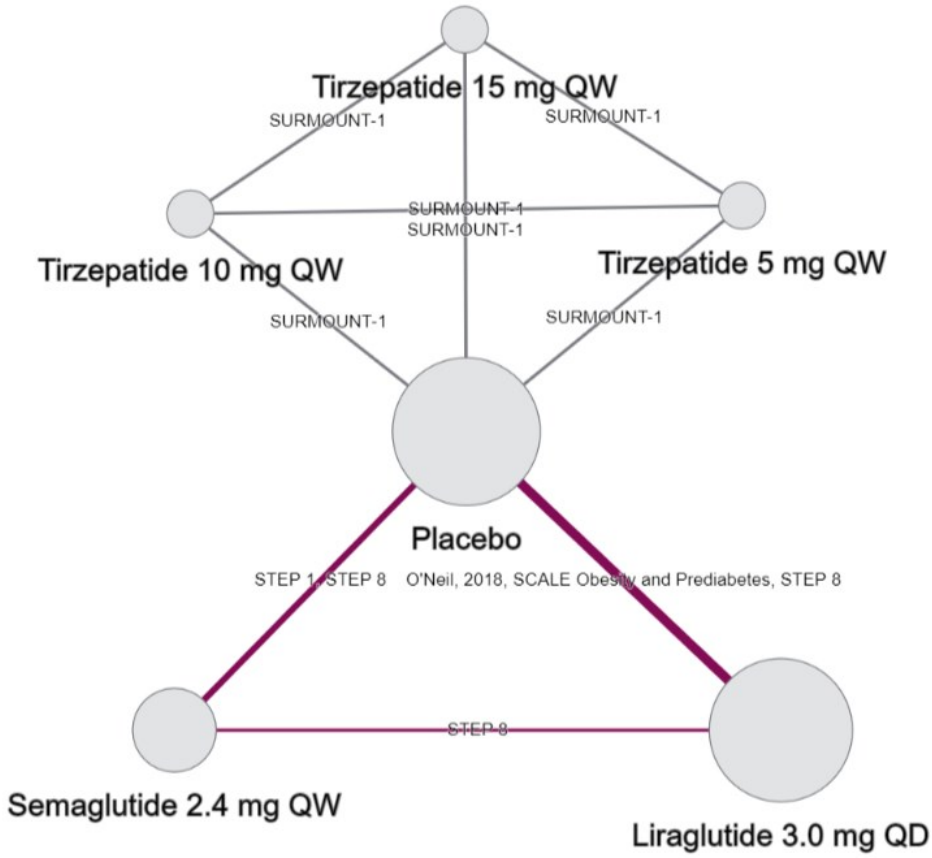
Figure 35. Forest plot: whole trial population efficacy estimand, CfB in weight (%), FE unadjusted model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week.

CfB in HDL (%)

An NMA of CfB in HDL (%) was conducted for the analysis network presented in Figure 36. The model statistics are shown in Table 47, and the mean differences in treatment effect and 95% CrIs are presented in Table 48 and Figure 37.

Figure 36. Analysis network: whole trial population, efficacy estimand, CfB in HDL (%)



Footnotes: Purple indicates three-arm trials; **grey** indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: CfB, change from baseline; HDL, high-density lipoprotein; QD, everyday; QW, every week.

Table 47. Model fit statistics: whole trial population efficacy estimand, CfB in HDL (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inconsistency model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 13 data points in this network; assessment for inconsistency was conducted only for the preferred model (i.e. the FE unadjusted model).
Abbreviations: BR, baseline risk; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects,

HDL, high density lipoprotein; pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC between the unadjusted FE and RE models, and comparable residual deviances for both models, the unadjusted FE model was selected as the favoured model. There was no evidence of inconsistency within the network, as the DIC of the inconsistency model was similar to the FE unadjusted model. The unadjusted RE model results are presented in the Appendix D.4.3.

The FE unadjusted model results are presented in Table 48 and Figure 37. All three doses of tirzepatide had a statistically superior increase in HDL (positive CfB in HDL [%]) compared to placebo, liraglutide and semaglutide. The 10 mg dose of tirzepatide had the greatest absolute CfB in HDL of all the interventions (Table 48).

Table 48. League table: mean difference (95% CrI), whole trial population efficacy estimand, CfB in HDL (%), FE unadjusted model

		Comparator						Absolute CfB in HDL (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Liraglutide 3.0 mg QD	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Liraglutide 3.0 mg QD	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; HDL, high density lipoprotein; QD, everyday; QW, every week.

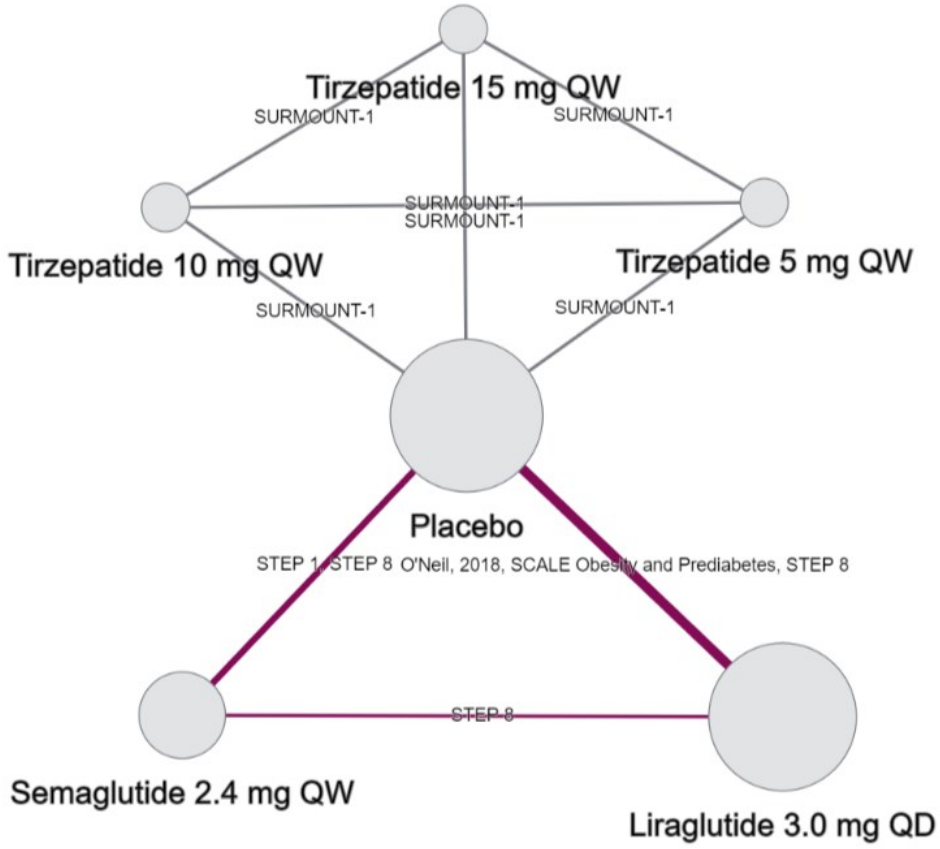
Figure 37. Forest plot: whole trial population efficacy estimand, CfB in HDL (%), FE unadjusted model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; HDL, high density lipoprotein; QD, everyday; QW, every week.

CfB in total cholesterol (%)

An NMA of CfB in total cholesterol (%) was conducted for the analysis network presented in Figure 38. The model statistics are shown in Table 49, and the mean differences in treatment effect and 95% CrIs are presented in Table 50 and Figure 39.

Figure 38. whole trial population efficacy estimand analyses network: CfB in total cholesterol (%)



Footnotes: Purple indicates three-arm trials; **grey** indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: CfB, change from baseline; QD, everyday; QW, every week.

Table 49. Model fit statistics: whole trial population efficacy estimand, CfB in total cholesterol (%)

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between–Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inconsistency model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 13 data points in this network; assessment for inconsistency was conducted only for the preferred model (i.e. the FE unadjusted model).

Abbreviations: BR, baseline risk; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects, pD, effective number of parameters; RE, random effects; SD, standard deviation.

The unadjusted models were favoured over the models adjusting for baseline risk, as the 95% CrI for the interaction between baseline risk and treatment effect included the value 0 of no interaction. With no substantial difference in DIC between the unadjusted FE and RE models (<5 points),[121] and despite a lower residual deviance for the unadjusted RE model, the unadjusted FE model was selected as the favoured model for consistency with the other endpoints, although it should be noted these data were not used in the economic model base case. There was no evidence of inconsistency within the network, as the DIC of the inconsistency model was similar to the FE unadjusted model. The unadjusted RE model results are presented in the Appendix D.4.3.

The FE unadjusted model results are presented in Table 50 and Figure 39. All doses of tirzepatide had a numerically superior decrease in total cholesterol (negative CfB in total cholesterol [%]) compared to placebo and liraglutide. The 15 mg dose of tirzepatide had a numerically superior decrease in total cholesterol compared to semaglutide, whilst the 5 and 10 mg dose of tirzepatide had a numerically inferior increase in total cholesterol compared to semaglutide. The 15 mg dose of tirzepatide had the greatest absolute CfB in total cholesterol of all the interventions (Table 50).

Table 50. League table: mean difference (95% CrI), whole trial population efficacy estimand, CfB in total cholesterol (%), FE unadjusted model

		Comparator						Absolute CfB in total cholesterol (%)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Liraglutide 3.0 mg QD	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Liraglutide 3.0 mg QD	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week.

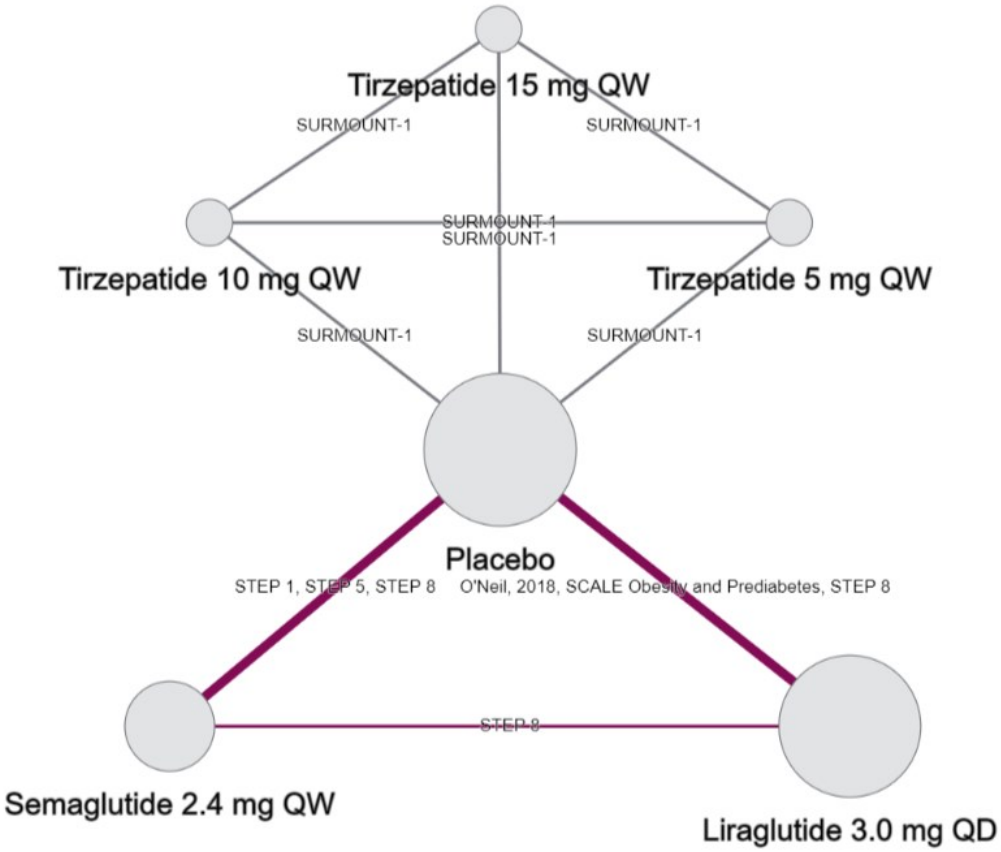
Figure 39. Forest plot: whole trial population efficacy estimand, CfB in total cholesterol (%), FE unadjusted model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week.

CfB in SBP (mmHg)

An NMA of CfB in SBP (mmHg) was conducted for the analysis network presented in Figure 40. The model statistics are shown in Table 51, and the mean differences in treatment effect and 95% CrIs are presented in Table 52 and Figure 41.

Figure 40. whole trial population efficacy estimand analyses network: CfB in SBP (mmHg)



Footnotes: Purple indicates three-arm trials; **grey** indicates four-arm trials; node size indicates the number of patients receiving each intervention; edge width indicates the number of trials informing a given comparison.
Abbreviations: CfB, change from baseline; QD, everyday; QW, every week; SBP, systolic blood pressure.

Table 51. Model fit statistics: whole trial population efficacy estimand, CfB in SBP (mmHg)

Model Type	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE unadjusted model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE BR model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inconsistency model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Bold text indicates the selected model; residual deviance is to be interpreted with reference to 15 data points in this network; assessment for inconsistency was conducted only for the preferred model (i.e. the FE BR model).
Abbreviations: BR, baseline risk; CfB, change from baseline; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; pD, effective number of parameters; RE, random effects; SBP, systolic blood pressure; SD, standard deviation.

The FE model adjusting for baseline risk was selected as the favoured model as the 95% CrI for the interaction between baseline risk and treatment effect did not contain the value of 0. With no substantial difference in DIC or residual deviance between the adjusted FE and RE models (<3 points), the adjusted FE model was selected as the favoured model. The adjusted RE model results are presented in the Appendix D.4.3.

The FE model adjusting for baseline risk results are presented in Table 52 and Figure 41. All three doses of tirzepatide had a numerically superior reduction in SBP (negative CfB in SBP [mmHg]) compared to placebo and liraglutide. The 10 mg dose of tirzepatide had a statistically superior reduction in SBP compared to semaglutide and the 15 mg dose of tirzepatide had a numerically superior reduction in SBP compared to semaglutide, whilst the 5 mg dose of tirzepatide had a numerically inferior reduction in SBP compared to semaglutide. The 10 mg dose of tirzepatide had the greatest absolute CfB in SBP of all the interventions (Table 52).

Table 52. League table: mean difference (95% CrI), whole trial population efficacy estimand, CfB in SBP (mmHg), FE BR model

		Comparator						Absolute CfB in SBP (mmHg)
		Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Liraglutide 3.0 mg QD	Semaglutide 2.4 mg QW	Placebo	
Reference	Tirzepatide 5 mg QW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 10 mg QW	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tirzepatide 15 mg QW	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Liraglutide 3.0 mg QD	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
	Semaglutide 2.4 mg QW	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Footnotes: League table showing how each comparator treatment (columns) performed versus each reference treatment (rows); the final column shows the absolute treatment effect of each reference treatment (rows); results are given as the posterior median of mean differences and 95% CrIs; dark green indicates where the comparator is statistically superior compared to the reference; light green indicates where the comparator is numerically superior compared to the reference; dark red indicates where the comparator is statistically inferior compared to the reference; light red indicates where the comparator is numerically inferior compared to the reference.
Abbreviations: BR: baseline risk; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week; SBP, systolic blood pressure.

Figure 41. Forest plot: whole trial population efficacy estimand, CfB in SBP (mmHg), FE BR model

Footnotes: Forest plot showing how each comparator treatment (right) performed versus each reference treatment (left); results are given as the posterior median of mean differences and 95% CrIs.
Abbreviations: BR: baseline risk; CfB, change from baseline; CrI, credible interval; FE, fixed effects; QD, everyday; QW, every week; SBP, systolic blood pressure

B.2.9.6 Discussion and conclusions

B.2.9.6.1 *Summary of findings*

This NMA was informed by a recently conducted, methodologically robust SLR of clinical efficacy and safety data in obesity and overweight. In total, 129 studies were included in the clinical SLR (original and update), which were evaluated for their suitability to include in an NMA. A rigorous assessment of feasibility for key efficacy and safety outcomes of interest was conducted. Eligibility and homogeneity were assessed based on reported interventions, compatibility of patient populations, study design, reported timepoints, estimands, and outcome definitions. This assessment resulted in the identification of six studies suitable for inclusion in the NMA. All six studies were considered to be homogenous with respect to TEMs, study design, patient populations, reported outcomes, comparability of placebo arms and reporting timepoints, implying that an NMA was an appropriate methodology for this comparative synthesis.

Overall, in the BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity population, all three doses of tirzepatide showed statistically superior decreased in CfB weight compared to placebo, and the 10 mg and 15 mg doses of tirzepatide also demonstrated statistically superior weight loss compared to semaglutide. Consistent with the findings from SURMOUNT-1, the 15 mg dose of tirzepatide had the greatest absolute CfB in weight of all the interventions. Regarding CfB HDL, all three doses of tirzepatide also demonstrated statistically superior improvements in HDL compared to both placebo and semaglutide.

Consistent with the CfB weight results, the 15 mg dose of tirzepatide had the greatest absolute CfB in HDL of all the interventions. For CfB total cholesterol, all three doses of tirzepatide had a statistically superior decrease in total cholesterol compared to placebo. In the comparison versus semaglutide, the 15 mg dose of tirzepatide had a numerically superior decrease in total cholesterol compared to semaglutide, and tirzepatide 15 mg also demonstrated the greatest absolute improvement in total cholesterol of all the interventions. Finally, for SBP, all three doses of tirzepatide showed a statistically superior improvement versus placebo, and the 10 mg and 15 mg doses were also numerically superior to semaglutide. Overall, the 10 mg dose of tirzepatide had the greatest absolute CfB in SBP of all the interventions.

Additional populations and treatment regimen NMA results

Comparing the whole trial population and the BMI ≥35 kg/m^2, prediabetes and high risk for CVD population to the BMI ≥30 kg/m^2 with one weight-related comorbidity subgroup summarised above, results were generally similar. For the whole trial population, tirzepatide 15 mg demonstrated numerical or statistical superiority compared with semaglutide and placebo across all outcomes, consistent with the BMI ≥30 with at least one weight-related comorbidity population. In addition, the degree of superiority (numerical or statistical) observed for tirzepatide 15 mg versus placebo and semaglutide was aligned between these populations for all outcomes. However, the 15 mg tirzepatide dose demonstrated slightly lesser numerical improvements compared to placebo and semaglutide in CfB weight (%), CfB in HDL and CfB total cholesterol compared to the BMI ≥30 with at least one weight-related comorbidity population. In contrast, the whole trial population demonstrated numerically greater improvements in CfB SBP compared to the BMI ≥30 with at least one weight-related comorbidity population.

In the BMI ≥35 kg/m^2 prediabetes and high CVD subgroup, tirzepatide demonstrated numerical or statistical superiority versus placebo for all outcomes; however, unlike the base case population, tirzepatide 15 mg was numerically inferior compared to semaglutide for CfB HDL and CfB SBP. In contrast, for CfB weight (%) and CfB HDL, there was a numerically greater improvement versus semaglutide in the BMI ≥35 kg/m^2 prediabetes and high CVD subgroup compared to the base case population.

The treatment regimen estimand analyses found similar results compared to analyses of the efficacy estimand, though generally slightly less favourable, as would be expected. In the base case population (BMI ≥30 kg/m^2 with one weight-related comorbidity) for the outcomes where comparator data was reported to sufficient granularity (CfB weight, CfB SBP) there was the same statistical interpretation: for CfB weight, tirzepatide 15 was statistically superior to both semaglutide and placebo, whilst for CfB SBP, tirzepatide 15 was statistically superior to placebo but numerically superior to semaglutide.

Overall, the additional NMA results show the robustness of the NMA analyses to decisions made regarding the choice of subpopulations and demonstrate the consistent pattern of statistical interpretation between the efficacy estimand and treatment-regimen estimand.

B.2.9.6.2 *Strengths and Limitations*

Limitations of the NMA include that the SLR on which the NMA was based was restricted to publications written in English; hence, relevant publications in other languages may have been excluded. Furthermore, the SLR did not cover documentation from health technology assessment (HTA) bodies; additional data relevant to the NICE submission were identified from targeted searches of NICE TAs conducted separately to the SLR, but it is possible that relevant data from other HTA documents were missed. While the SLR identified many studies reporting on comparators of interest, the vast majority of

studies identified from the SLR were ultimately excluded from the NMA as they reported on treatments not considered to be relevant for the analysis, which resulted in a small, but robust, evidence base of only six studies used to inform the NMA. As a result, the networks of studies formed for each outcome included only between one to three studies reporting for each comparator of interest, with even fewer studies being included for the subgroups as results were not reported across all BMI subgroups for all comparators.

Strengths of the NMA include that the NMA was conducted based on a robust SLR conducted according to Cochrane standards, thereby identifying RCTs assessing the efficacy and safety of tirzepatide or key comparators, meaning that evidence informing the analysis was systematically identified and extracted. In addition, NICE technology appraisals (TAs) were searched for outcomes or BMI threshold subgroups not included in the publications identified through the SLR. As all included studies were randomised trials, within-trial bias was reduced, and randomisation was expected to be preserved in the analysis. Data extracted during the SLR included a range of study characteristics, patient baseline characteristics, and outcomes, allowing a comprehensive feasibility assessment to be conducted, and a range of clinically-relevant efficacy and safety outcomes to be considered for analyses.

A systematic feasibility assessment was conducted to ensure that studies informing the NMA were comparable in terms of study design, patient populations and the reported outcomes. In addition, both TEMs and the comparability of placebo arms and reporting timepoints were assessed and considered. The studies included in the NMA included the pivotal studies for all comparators of interest and were considered generally homogenous in terms of the patient population, and were considered to be largely aligned with eligibility criteria for SURMOUNT-1.

Robust NMA analyses were conducted, with the methodology used in line with key methodological guidance documents (in particular, NICE DSU TSDs 2, 3 and 4).[114-116] Multiple models were independently fitted for each outcome, allowing for an assessment to determine the most appropriate model for each outcome. Fixed effects models were fitted as well as random effect models, and models adjusting for baseline risk were also fitted, to account for potential differences in placebo response rates across studies, and the most appropriate model selected for each outcome.

B.2.9.7 Conclusions

In conclusion, the NMA described above provides strong evidence for the clinical effectiveness of tirzepatide relative to its comparators. In the base case population, all three doses also show a statistically significant improvement in all endpoints compared to placebo. All three doses of tirzepatide also demonstrated statistical superiority compared to semaglutide for CfB HDL. For CfB weight (%), tirzepatide 10 and 15 mg demonstrated statistical superiority over semaglutide, and the 15 mg tirzepatide also demonstrated numerical improvements versus semaglutide for CfB total cholesterol and CfB SBP. These results support the SURMOUNT-1 trial in the conclusion that tirzepatide presents a clinically effective alternative to existing treatments for obesity.

B.2.10 Adverse reactions

Summary of adverse events

- The SURMOUNT-1 trial demonstrated that tirzepatide 5, 10 and 15 mg have an acceptable safety profile, with gastrointestinal (GI) events (including nausea, diarrhoea and constipation) representing the most common treatment-emergent adverse events (TEAEs).
    - Most GI TEAEs were transient, mild to moderate in severity, and occurred primarily during the dose-escalation period.
- A total of 137 (5.4%) participants permanently discontinued from study drug due to an AE, including 21 (3.3%) participants in the placebo group and 30 (4.8%), 46 (7.2%), and 40 (6.3%) participants in the tirzepatide 5, 10 and 15 mg groups, respectively.
    - The most common reasons for discontinuation were GI AEs.
- The side effects of tirzepatide treatment can be managed by following the guidance in the SmPC and monitored via routine pharmacovigilance.

The safety and tolerability of tirzepatide in people with obesity was evaluated as an endpoint in SURMOUNT-1 and SURMOUNT-2.The safety and tolerability of tirzepatide was also investigated in two other trials (SURMOUNT-3; SURMOUNT-4) among people with obesity that will be published in October 2023 (Section B.2.2). The remaining five studies in the SURMOUNT trial program will seek to further characterise the safety profile of tirzepatide in people with obesity, although the date that these studies will be published is currently unclear (Section B.2.11).

The safety and tolerability of tirzepatide has also been investigated extensively in people with T2DM across 19 Phase 1, Phase 2, and Phase 3 clinical studies as part of the SURPASS clinical trial program. Over the course of these investigations, the safety profile of tirzepatide has been well-characterised and robust management strategies have been developed and refined for AEs.

In the current submission, safety evaluations are only presented from the SURMOUNT-1, since SURMOUNT-1 represents the most relevant clinical data for this appraisal. However, for transparency, both the integrated safety analysis for SURMOUNT-1/SURMOUNT-2[122] and the CSR for SURMOUNT-2[91] are provided alongside this submission.

In the following sections, AEs and other safety evaluations from SURMOUNT-1 are reported by the treatment group to which participants were randomly assigned. It should be noted that since the dose escalation was performed up to 20 weeks, the actual dose of tirzepatide that the participant was receiving at the time of an AE or other safety outcome may have been lower than the final assigned dose by treatment group. In SURMOUNT-1, all safety analyses were conducted on the safety analysis set (Section B.2.4.3).

B.2.10.1 Summary of adverse events

A summary of adverse events that occurred during SURMOUNT-1 is provided in Appendix F. Overall, the treatment with tirzepatide was well tolerated, and no unexpected safety findings were identified. A similar proportion of participants in the tirzepatide and placebo treatment arms reported TEAEs (78.9% to 81.8% of participants in the tirzepatide groups, as compared to 72.0% of participants in the placebo group).[3]

B.2.10.2 Treatment emergent adverse events

TEAEs that occurred in ≥5% of participants

Table 53 summarizes the TEAEs by decreasing frequency, focusing on those TEAEs that occurred in ≥5% of participants in any treatment group. The majority of the TEAEs (7 out of the 13) were GI in nature and were more common in the tirzepatide groups compared with the placebo group. The most common of these GI TEAEs were nausea, diarrhoea, and constipation. COVID-19 was the third most common TEAE overall (after nausea and diarrhoea), was the most common non-GI TEAE, and was reported in a similar percentage of participants across all 4 treatment groups. TEAEs by system organ class and maximum severity, serious adverse events and details regarding deaths that occurred during the study are presented in Appendix F.

Table 53. Summary of treatment-emergent adverse events occurring in ≥5% of participants in the safety analysis set

Preferred Term	n (%)				Pairwise p-values*		
	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	TZP 5 mg vs. Placebo	TZP 10 mg vs. Placebo	TZP 15 mg vs. Placebo
Nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)	<0.001	<0.001	<0.001
Diarrhoea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)	<0.001	<0.001	<0.001
COVID-19	90 (14.0)	94 (14.9)	98 (15.4)	82 (13.0)	0.690	0.479	0.624
Constipation	37 (5.8)	106 (16.8)	109 (17.1)	74 (11.7)	<0.001	<0.001	<0.001
Dyspepsia	27 (4.2)	56 (8.9)	62 (9.7)	71 (11.3)	<0.001	<0.001	<0.001
Vomiting	11 (1.7)	52 (8.3)	68 (10.7)	77 (12.2)	<0.001	<0.001	<0.001
Decreased appetite	21 (3.3)	59 (9.4)	73 (11.5)	54 (8.6)	<0.001	<0.001	<0.001
Headache	42 (6.5)	41 (6.5)	43 (6.8)	41 (6.5)	>0.999	0.911	>0.999
Abdominal pain	21 (3.3)	31 (4.9)	34 (5.3)	31 (4.9)	0.157	0.074	0.157
Alopecia	6 (0.9)	32 (5.1)	31 (4.9)	36 (5.7)	<0.001	<0.001	<0.001
Dizziness	15 (2.3)	26 (4.1)	35 (5.5)	26 (4.1)	0.081	0.004	0.081
Eructation	4 (0.6)	24 (3.8)	33 (5.2)	35 (5.6)	<0.001	<0.001	<0.001
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)	<0.001	<0.001	<0.001

Abbreviations: N: number of subjects in the analysis population; n: number of subjects with events meeting specified criteria; TZP: tirzepatide.
Footnotes: * p-value for pairwise treatment comparisons were computed using Fisher's Exact test.
Source: Jastreboff (2022);[3] SURMOUNT-1 CSR.[100]

B.2.10.3 Adverse events leading to permanent discontinuation from study treatment

A total of 137 (5.4%) participants permanently discontinued from study drug due to an AE or death (Appendix F), including 21 (3.3%) participants in the placebo group and 30 (4.8%), 46 (7.2%), and 40 (6.3%) participants in the tirzepatide 5, 10 and 15 mg groups, respectively. AEs in the gastrointestinal disorders system organ class (SOC) were the most common AEs that led to

study drug discontinuation. Compared with the placebo group, more participants in the tirzepatide groups discontinued study drug due to AEs in the gastrointestinal disorders SOC.

B.2.10.4 Adverse events of special interest (AESI)

Based on therapeutic experience with other incretin therapies, a number of safety focus areas were of special interest during the safety analyses, including gastrointestinal adverse events, hepatobiliary disorders and exocrine pancreas safety. As detailed in the SURMOUNT-1 CSR provided alongside this submission, no new safety signals were identified in participants treated with tirzepatide with respect to the safety topics of interest.[100] Given gastrointestinal disorders represent the most frequently reported TEAEs, a summary is provided below.

Gastrointestinal disorders

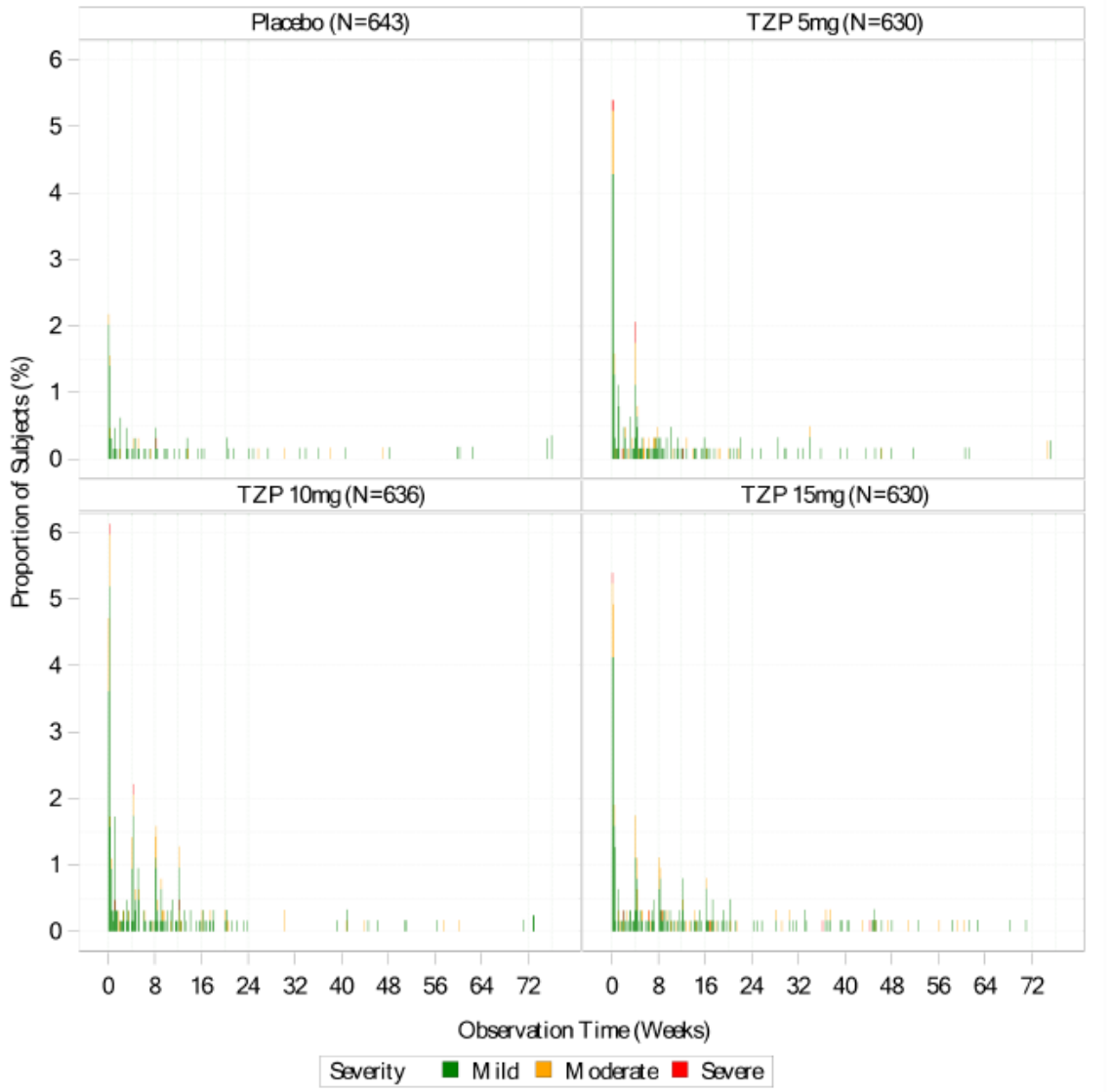
In SURMOUNT-1, GI TEAEs were identified using Medical Dictionary for Regulatory Activities preferred terms (MedDRA PTs) of the Gastrointestinal disorders SOC. Overall, GI disorders were more frequently reported for tirzepatide-treated participants compared with placebo-treated participants (Table 54). Most GI TEAEs were transient, mild to moderate in severity, and occurred primarily during the dose-escalation period, as shown in Figure 42.

Table 54. Summary of GI TEAEs occurring in ≥2% of participants in any treatment group in the safety analysis set

Event category or term	n (%)			
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Participants with ≥1 TEAE in the GI disorders SOC	195 (30.3)	350 (55.6)	387 (60.8)	373 (59.2)
Nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)
Diarrhoea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)
Constipation	37 (5.8)	106 (16.8)	109 (17.1)	74 (11.7)
Dyspepsia	27 (4.2)	56 (8.9)	62 (9.7)	71 (11.3)
Vomiting	11 (1.7)	52 (8.3)	68 (10.7)	77 (12.2)
Abdominal pain	21 (3.3)	31 (4.9)	34 (5.3)	31 (4.9)
Gastroesophageal reflux disease	14 (2.2)	27 (4.3)	25 (3.9)	31 (4.9)
Eructation	4 (0.6)	24 (3.8)	33 (5.2)	35 (5.6)
Flatulence	13 (2.0)	21 (3.3)	19 (3.0)	25 (4.0)
Abdominal distension	11 (1.7)	22 (3.5)	19 (3.0)	23 (3.7)
Abdominal pain upper	10 (1.6)	17 (2.7)	25 (3.9)	23 (3.7)
Abdominal discomfort	7 (1.1)	13 (2.1)	10 (1.6)	21 (3.3)

Abbreviations: GI: gastrointestinal; mITT: modified intent-to-treat; N: number of participants who were randomly assigned and received at least 1 dose of study drug; n: number of participants in the specified category; TEAE: treatment-emergent adverse event; TZP: tirzepatide.
Source: SURMOUNT-1 CSR.[100]

Figure 42. Incidence of nausea/vomiting/diarrhoea in the safety analysis set



Abbreviations: N: number of subjects in specified treatment group; TZP: tirzepatide.
Footnotes: Proportions are based on number of subjects at risk.
Source: **Source:** SURMOUNT-1 CSR.[100]

B.2.11 Ongoing studies

Additional data of interest for the efficacy and safety of tirzepatide to treat people with obesity are summarised in Table 55.

Table 55. Summary of ongoing studies for tirzepatide.

Study	Study design and status (ongoing/complete)	Status
SURMOUNT-CN	Phase 3, randomised, double-blind, multicentre, placebo-controlled trial of once-weekly tirzepatide in 210 Chinese participants without diabetes who have obesity (BMI ≥28 kg/m^2) or are overweight (BMI ≥24 kg/m^2) with weight-related comorbidities	Completed, not yet published; patient population not generalisable to this appraisal (Chinese study)
SURMOUNT-J	Phase 3, randomised, double-blind, multicentre, placebo-controlled trial of once-weekly tirzepatide in 261 Japanese participants without diabetes with BMI ≥27 kg/m² and <35 kg/m² with at least two weight-related comorbidities or ≥35 kg/m² with at least one weight-related comorbidity	Completed, not yet published; patient population not generalisable to this appraisal (Japanese study)
SURMOUNT-OSA	Phase 3, randomised, double-blind, placebo-controlled trial in 469 participants without diabetes with obesity, who have OSA and obesity both those who are unwilling or unable to use Positive Airway Pressure (PAP) therapy and those who are and plan to stay on PAP therapy. The purpose of this study is to investigate the effect of tirzepatide on the treatment of OSA in people with obesity	Ongoing, estimated completion date March 2024
SURMOUNT-5	Phase 3, randomised, controlled, multicentre trial of one-weekly tirzepatide versus semaglutide 2.4 mg in 700 participants without diabetes who have obesity (BMI ≥30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with weight-related comorbidities	Ongoing, expected completion date March 2025
SURMOUNT-MMO	Phase 3, randomised, double-blind, placebo-controlled trial in 15,000 adults of at least 40 years of age without diabetes who have BMI ≥27 kg/m² and either established CVD, peripheral arterial disease or specified CV risk factors. The purpose of the study is to investigate the effect of tirzepatide on the reduction of morbidity and mortality	Ongoing, estimated completion date October 2027

Abbreviations: BMI: body mass index; OSA: obstructive sleep apnoea; PAP: positive airway pressure; T2DM: type 2 diabetes mellitus.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principle findings from the clinical evidence base

The SURMOUNT-1 trial has demonstrated that treatment with once-weekly tirzepatide at doses of 5, 10 and 15 mg results in statistically significant and clinically meaningful reductions in body weight for people with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity at 72 weeks. Compared to placebo, tirzepatide 5, 10 and 15 mg each achieved superiority for both mean percent change in body weight reduction and percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks in the EAS. Tirzepatide 10 and 15 mg also achieved superiority compared with placebo for the percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks.

Additionally, this substantial weight reduction with tirzepatide was accompanied by greater improvements in all measured cardiovascular and metabolic risk factors; compared with placebo, tirzepatide-treated participants achieved significant mean reductions in waist circumference, which is an important indicator of central adiposity. Lipid parameters, which are another indicator of weight-related health, also demonstrated improvement from baseline to Week 72 in participants treated with tirzepatide.

The results of the post-hoc subgroup analyses in people with a BMI of ≥30 kg/m^2 and at least one weight-related comorbidity were consistent with those of the EAS. Considering the clear unmet need among people with a BMI ≥30kg/m^2 and at least one weight-related comorbidity, these results indicate that tirzepatide may serve as an important tool in the medical management of obesity, offering a substantial degree of weight reduction compared with findings reported in other Phase 3 clinical trials investigating other anti-obesity medications. Results of the subgroup analyses in people with a BMI of ≥35 kg/m^2, BMI ≥30 kg/m2 (both irrespective of comorbidities) and a BMI ≥35 kg/m^2 with prediabetes and high CV risk were also consistent with those of the EAS, which similarly indicate that tirzepatide may represent an important tool in the management of obesity compared to diet and exercise alone in these subpopulations.

Importantly, the clinical benefit observed in the SURMOUNT-1 trial was not achieved at the detriment of participant wellbeing. Greater improvements in the SF-36v2 acute form Physical Functioning domain from baseline to 72 Weeks relative to placebo were observed in SURMOUNT-1, demonstrating that treatment with tirzepatide also results in an improvement in HRQoL relative to placebo. Regarding the safety profile of tirzepatide, the most frequently reported TEAEs in SURMOUNT-1 among tirzepatide-treated participants were gastrointestinal, but were most mild-to-moderate, occurring primarily in the dose-escalation period; this is in line with the well-established safety profile of other incretin therapies for the treatment of obesity.[3] The safety profile of tirzepatide was also consistent with previous findings from the SURPASS clinical trials in people with T2DM.[3] As such, the safety profile of tirzepatide will be familiar to the healthcare community and can be managed by following the guidance in the SmPC and monitored via routine pharmacovigilance.

In the absence of head-to-head evidence, an NMA was conducted to assess the relative efficacy of tirzepatide versus semaglutide and liraglutide in the populations considered in the economic analysis (Section B.2.9). The relative efficacy of tirzepatide versus semaglutide and liraglutide was also assessed in the whole trial population. Overall, the NMA provides robust results on the comparative safety of tirzepatide 5 mg, 10 mg and 15 mg versus relevant comparators within

patients with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity, and should be considered generalisable to the use of tirzepatide as a more efficacious option than the current standard of care for obesity management for these patients.

B.2.12.2 Strengths and limitations of the clinical evidence base

The global, Phase 3 SURMOUNT-1 trial was designed and adequately powered to demonstrate that tirzepatide provides a superior reduction in body weight from baseline relative to placebo among people with BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with at least one weight-related comorbidity. As a randomised, double-blind, placebo-controlled trial, SURMOUNT-1 provides good quality and robust evidence for the efficacy and safety of tirzepatide as a treatment for people with obesity. Moreover, the endpoints investigated are clinically relevant and of importance to the population of relevance for this appraisal. Finally, the 72-week duration of the trial allowed time for participants to achieve substantial weight loss, with a planned two-year extension for participants with prediabetes expected to provide further information on the maximum and long-term weight-lowering effect of tirzepatide in this population. It should be noted that recently available top-line results from SURMOUNT-4 (Appendix M) indicate that weight loss had not yet reached a plateau at Week 72.

Limitations of the SURMOUNT-1 trial include the absence of any trial sites in the UK or Europe. However, given the global nature of the trial, the large sample size and high completion rate, the results still remain generalisable to UK clinical practice. In addition, the consistently significant results observed across the population suggest that this limitation is unlikely to be important point within this evaluation. It should also be noted that data are not available beyond 72 weeks, meaning there is some uncertainty around the long-term clinical risks or benefits of tirzepatide and the impact of the significant weight loss on clinical outcomes.

Strengths of the NMA include that the NMA was conducted based on a robust SLR identifying RCTs assessing the efficacy and safety of tirzepatide or key comparators, meaning that evidence informing the analysis was systematically identified. As all included studies were randomised trials, within-trial bias was reduced, and randomisation is expected to be preserved in the analysis. In addition, a systematic feasibility assessment was conducted to ensure that studies informing the NMA were comparable in terms of study design, patient populations and the reported outcomes. Robust NMA analyses were then conducted, with methodology used in line with key methodological guidance documents (in particular, NICE DSU TSDs 2, 3 and 4).[114-116]

Limitations of the NMA include restrictions within the SLR on which the NMA was based. For example, the NMA was restricted to publications written in English and did not cover documentation from HTA bodies. In addition, a small, but robust, evidence base of only six studies was used to inform the NMA. As a result, the networks of studies formed for each outcome included only between one to three studies reporting for each comparator of interest, and not all outcomes were reported by each comparator of interest, so not all studies could be included in each analysis network, particularly for subgroup analyses.

B.2.12.3 Overall conclusion

The clinical effectiveness evidence presented above demonstrates that tirzepatide addresses the clear unmet need for people with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity, offering a substantial and sustained weight reduction, alongside a well-established and tolerable safety profile, and will represent a step-change for chronic weight management in this population.

B.3 Cost effectiveness

Rationale for model

- An SLR was performed to search for previously published health economic evaluations. None of the identified analyses addressed the decision problem relevant to this submission. Therefore, a *de novo* model was developed.
- An individual patient simulation (IPS) was deemed the most appropriate model structure given it allows patient history to be tracked, facilitates modelling of events with long-term implications as well as treatment discontinuation and the effect of bariatric surgery. The model was developed in Microsoft Excel.

Methodology

- The patient population considered in the model base case is patients with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity:
  - Baseline characteristics were derived from patients in SURMOUNT-1 with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity where these data were available, and from the average cohort baseline values reported in the risk equations where additional baseline characteristics were required.
- Treatment efficacy was captured via surrogate endpoints and are based on the NMA. These outcomes were employed in risk equations which informed the incidence of complications and comorbidities in the model.
- In the base case analysis, tirzepatide 5, 10 and 15 mg (each adjunct to diet and exercise) were compared to semaglutide as an adjunct to diet and exercise, and diet and exercise alone.
- Subgroup populations considered in the model include patients with BMI ≥35 kg/m^2 non-diabetic hyperglycaemia and high risk for CVD (aligning with the recommended population for liraglutide 3.0 mg), patients with a BMI ≥35 kg/m^2 (irrespective of comorbidities) and patients with a BMI ≥30 kg/m^2 (irrespective of comorbidities):
  - In the subgroup analysis that included patients with BMI ≥35 kg/m^2,prediabetes and high risk for CVD, tirzepatide 5, 10 and 15 mg (each adjunct to diet and exercise) were compared to liraglutide and semaglutide, each as an adjunct to diet and exercise, and diet and exercise alone.
  - In the subgroups that included patients with a BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2, tirzepatide 5, 10 and 15 mg (each as an adjunct to diet and exercise) were compared to diet and exercise alone.
- Based on the literature and clinical input, the comorbidities considered relevant for inclusion in the model were T2DM, MI, angina, stroke, OSA, knee osteoarthritis and NAFLD.
- Cost categories included in the model include acquisition costs, administration costs, background resource use, comorbidity resource use and clinical event costs. Costs were sourced from appropriate UK databases, consistent with the NICE reference case.[123]
- A lifetime time horizon was adopted to reflect the chronic nature of obesity, as well as the chronic and progressive nature of many of its comorbidities, in line with the NICE reference case.

Results

- The base-case results show that all three doses of tirzepatide are cost-effective versus each of semaglutide and diet and exercise in the target population of people with a BMI of ≥30 mg/kg^2 and at least 1 weight-related comorbidity.
  - The probabilistic base case ICERs versus diet and exercise were £11,684/QALY for tirzepatide 5 mg, £11,813/QALY for tirzepatide 10 mg and £13,203/QALY for tirzepatide 15 mg.
  - It should be noted that the ICERs for the comparisons to semaglutide are anticipated to be artificially high due to the assumption that the price of semaglutide does not vary between the disclosed price of the initial titration doses

(0.25 mg, 0.5 mg, 1 mg) and the higher titration dose (1.7 mg) and maintenance dose (2.4 mg), where the price was redacted in TA875 and remains undisclosed at the time of this submission. Nonetheless, even assuming semaglutide prices do not vary across doses, the probabilistic base case ICERs versus semaglutide 2.4 mg were £14,841/QALY for tirzepatide 5 mg, £15,183/QALY for tirzepatide 10 mg and £16,293/QALY for tirzepatide 15 mg.
    - The multi-way CEACs unambiguously show that each dose of tirzepatide versus semaglutide 2.4 mg and diet and exercise is the most cost-effective option at a willingness-to-pay threshold of £20,000/QALY.
- The deterministic scenario results reveal that the most influential model drivers relate to assumptions regarding the HbA1c values of simulated patients for normoglycaemia and prediabetes, which each affect the future risk of the development of diabetes; given the significant efficacy on glycaemia seen in the SURMOUNT trial, the model base case assumptions on HbA1c taken from TA875 are likely to underestimate the beneficial effect of tirzepatide on these parameters.
- Scenario analyses found the model results to be robust to the tested assumptions, literature sources, and inputs, with only a single scenario, of a risk equation that with very limited sensitivity to weight loss, falling above the £20,000/QALY willingness-to-pay threshold.
- Subgroup results in other populations revealed that:
    - Tirzepatide was highly cost-effective in the TA664 population, where liraglutide 3.0 mg is available in addition to semaglutide 2.4 mg.
    - The ICER, versus diet and exercise, in people with a BMI of ≥35 mg/kg^2, both those with and without comorbidities, was very similar to the base case target population.
    - ICERs, versus diet and exercise, in the population including all obese trial participants, and in the whole trial populations, were above the base case ICER but remained below the £20,000/QALY willingness-to-pay threshold.

Conclusions

- In summary, tirzepatide, adjunct to diet and exercise, offers the greatest weight loss yet seen in Phase 3 trials for any licensed pharmacological therapy and has been shown to be a cost-effective use of NHS resources, with the economic model predicting lower incidences of many modelled comorbidities and increased quality and length of life as a result.
- The availability of tirzepatide offers the NHS a paradigm shift from weight management being offered only in capacity-constrained SWMS to being achievable in any setting.

B.3.1 *Published cost-effectiveness studies*

An SLR was performed between October 2022 (database searches) and December 2022 (conference and HTA agency searches) to identify existing cost-effectiveness analyses in obesity. Systematic searches for cost-effectiveness analyses, relevant risk equations, studies describing health-state utility values and costs and healthcare resource use were carried out simultaneously as a combined search to identify all relevant studies on adult patients with obesity, as detailed in Appendix G.

In total, 1,867 records were retrieved for the economic evaluations SLR from searches of MEDLINE, Embase, the NHS Economic Evaluation Database and the International Health Technology Assessment database. Of these, 135 were duplicates and were subsequently removed, resulting in 1,732 novel records. Following title/abstract screening, 70 publications were identified for full-text review, from which 11 articles were identified for inclusion. Supplementary congress, HTA and bibliography searches identified 16 additional articles, resulting in a total of 27 economic evaluations that were included as part of the economic

evaluations SLR. These 27 economic evaluations comprised 16 economic evaluations and 11 studies reporting only on risk equations.

Of the 16 economic evaluations identified, the majority evaluated the cost-effectiveness of orlistat (six studies), while the remaining studies evaluated the cost-effectiveness of liraglutide (five studies) and semaglutide (five studies). Models were primarily Markov models (thirteen studies), while the remaining evaluated utilised individual patient simulation (IPS) models (three studies).

From the 16 economic evaluations identified, focus was given to cost-effectiveness evaluations published in the last decade that reported results from the NHS England perspective; these two analyses are summarised in Table 56. Both analyses utilised a Markov model, although it should be noted that the evaluation of semaglutide [TA875] was adapted from the model used for the previous NICE appraisal for liraglutide [TA664].[1, 2]

Table 56: Previous relevant cost-effectiveness analyses

Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
TA664 (Liraglutide)[1]					
2020	**Study and model type:** Cost-utility, Markov **Rationale for study/model type:** State-transition models have been previously used in obesity modelling. Additionally, state-transition models are widely used in modelling of diabetes and cardiovascular disease, which is appropriate given the nature of the condition characterised by recurrent risks **Health states:** Prediabetes, normal glucose tolerance, type 2 diabetes, sleep apnoea, knee replacements, bariatric surgery, post-acute coronary syndrome (MI, angina, or stroke) or death. Hypertension and dyslipidaemia were modelled as comorbidities **Intervention(s) and comparator(s):** Liraglutide 3.0 mg in combination with diet and exercise (liraglutide treatment was daily and lasted for 2 years or stopped after the first cycle if no response; diet and exercise continued for the duration of the model) vs diet and exercise (for the duration of the model). Diet and exercise consisted of: dietary and physical activity counselling (either group or individual sessions); hypocaloric diet (e.g. reduce calorie intake by 500 calories per day); increased physical activity **Time horizon:** 40 years **Cycle length:** 3 months for the first year, annual cycles thereafter **Discount rate for costs/benefits and rationale:** 0.035; 0.035; NR **Cost year and currency:** 2018; GBP **Sensitivity analyses:** Deterministic analysis; Probabilistic analysis; Scenario analysis	Adult patients with: BMI ≥35 kg/m^2; prediabetes, defined as a HbA1c level of 42–47 mmol/mol (6.0–6.4%) or a fasting plasma glucose level of 5.5–6.9 mmol/L; and high risk of cardiovascular disease, defined as either of the following: (A) total cholesterol >5mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women	Liraglutide: 15.336 (18.584 LYs) Diet and exercise: 15.216 (18.496 LYs) Incremental: 0.12 (0.088 LYs)	Liraglutide: £20,988 Diet and exercise: £19,419 Incremental: £1,568	£13,059/QALY

TA875 (Semaglutide)[2]					
2023	**Study and model type**: Cost-utility, Markov **Rationale for study/model type**: Adapted from the model used for the previous NICE appraisal for liraglutide 3.0 mg for managing overweight and obesity (TA664) and is consistent with other models that have been used for obesity and diabetes modelling **Health states:** Normal glucose tolerance, prediabetes, T2DM, temporary prediabetes reversal, post ACS, T2DM and post ACS, post stroke, T2DM and post stroke, post ACS and post stroke, T2DM, post stroke and post ACS, death. Patients could also have a knee replacement, bariatric surgery or obstructive sleep apnoea in any of the health states **Intervention(s) and comparator(s):** Semaglutide 2.4 mg in combination with diet and exercise (semaglutide treatment was once weekly SC injections and lasted for 2 years or stopped after 28 weeks if no response; diet and exercise continued for the duration of the model) vs diet and exercise (for the duration of the model) **Time horizon:** 40 years **Cycle length:** 3 months for the first year, annual cycles thereafter **Discount rate for costs/benefits and rationale:** 0.035; 0.035; in line with NICE guidelines **Cost year and currency:** 2020/21; NR **Sensitivity analyses:** Deterministic analysis; Probabilistic analysis; Scenario analysis	Adult patients with BMI ≥30 kg/m^2 and with one or more obesity related comorbidities	Semaglutide: 15.361 (17.957 LYs) Diet and exercise: 15.269 (17.924 LYs) Incremental: 0.092 (0.034 LYs)	Semaglutide: NR Diet and exercise: NR Incremental: NR	£14,827/QALY
		Adult patients with BMI ≥35 kg/m^2, prediabetes and high risk for CVD	Semaglutide: 14.444 (17.349 LYs) Liraglutide: 14.401 (17.331 LYs) Incremental: 0.043 (0.018 LYs)	Semaglutide: NR Liraglutide: NR Incremental: NR	Semaglutide dominant

Abbreviations: ACS: acute coronary syndrome; BMI: body mass index; CVD: cardiovascular disease; HbA1c: glycated haemoglobin;; ICER: incremental cost-effectiveness ratio; LY: life year; MI: myocardial infarction; NICE: National Institute for Health and Care Excellence; NR: not reported; QALY: quality-adjusted life year; SBP: systolic blood pressure; SC; subcutaneous; T2DM, type 2 diabetes mellitus.

B.3.2 *Economic analysis*

Neither of the cost-effectiveness analyses listed in Table 56 addressed the decision problem relevant to this submission given that neither analyses include tirzepatide as an intervention (or comparator); therefore, a *de novo* model was developed. The *de novo* cost-effectiveness model supporting this appraisal is an individual patient simulation (IPS) that was designed to quantify the long-term health economic impact of tirzepatide adjunct to diet and exercise compared with the relevant comparators for the treatment of obesity in NHS England clinical practice. The key comparators considered in the base case are semaglutide adjunct with diet and exercise, and diet and exercise alone, while liraglutide as an adjunct to diet and exercise is considered only in the population for whom it is recommended by NICE is TA664 (Section B.3.2.3.2).[1] Although the model type deviates from TA875 and TA664 (both of which were cohort Markov models), it should be noted that the model inputs and assumptions employed are largely aligned with the Committee decisions in these previous TAs.[1, 2] The rationale for choosing an IPS over a cohort Markov structure is discussed further in Section B.3.2.2. Aligned with previous TAs, the model employs risk equations for extrapolation and captures the benefit of weight loss on the progression of key weight-related comorbidities. In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) and included direct medical costs only.[123]

Table 57 provides an overview of the key features of the economic model supporting this appraisal, with further details relating to the patient population considered in the model, the model structure, and the included interventions and comparators is provided in Section B.3.2.1, B.3.2.2 and B.3.2.3, respectively.

Table 57: Key features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	**TA664 (Liraglutide)[1]**	**TA875 (Semaglutide)[2]**	**Chosen values**	**Justification**
Model type	Cohort Markov	Cohort Markov	IPS	An IPS was deemed to be the more suitable approach as it allows tracking of individual patients' history over time. This is of particular relevance to cost-effectiveness analysis in obesity, because there are several clinical events that have long-term effects on patients and implications for the probability of future events. Further justification is provided in Section B.3.2.2
Time horizon	40 years	40 years	Lifetime	A lifetime horizon in the base case was adopted to reflect the chronic nature of obesity, as well as the chronic and progressive nature of many of its comorbidities. Prior NICE appraisals had used a 40-year horizon, but this choice was criticised by NICE as it was felt that the full costs and benefits of treatment had not been captured.[1, 2]
Weight gain after treatment discontinuation	Assumed that the treatment benefit of liraglutide for all surrogate endpoints was lost over 3-years and assumed all physiological parameters (BMI, SBP, total and HDL cholesterol) returned to natural progression in diet and exercise	Assumed that the treatment benefit of semaglutide was lost for all surrogate endpoints over 3-years and assumed all physiological parameters (BMI, SBP, total and HDL cholesterol) returned to value of natural progression in diet and exercise	Assumed that the treatment benefit of tirzepatide (and pharmacological comparators) was lost for all surrogate endpoints over 3-years and assumed all physiological parameters (BMI, SBP, total and HDL cholesterol) returned to value of natural progression in diet and exercise	Since there is also no long-term data demonstrating the change in the tirzepatide treatment effect following treatment discontinuation, the use of a 3-year time period over which the treatment advantage of tirzepatide returns to the value of natural progression in diet and exercise is also included in the model base case. The application of a constant rate of loss of 33.33% per year over 3 years following treatment cessation is in line with Ara *et al.* 2012 and the previous appraisals in this indication.[124]

Surrogate outcomes	Risk equations are used to estimate the incidence of clinical events based on short term surrogate outcomes	Risk equations are used to estimate the incidence of clinical events based on short term surrogate outcomes	Risk equations are used to estimate the incidence of clinical events based on short term surrogate outcomes	The use of risk equations is required to capture the long-term benefits of weight loss on the progression of key weight-related comorbidities. The risk equations employed in the model are mostly aligned with previous TAs, as outlined in Section B.3.3.5.
Mortality	General population mortality, adjusted for with/without T2DM. RRs were applied for post-ACS and post-stroke. Acute death probabilities were applied for bariatric surgery, MI, angina, stroke and knee replacement	General population mortality adjusted by excluding mortality of obesity related comorbidities, with a BMI-specific HR applied	General population mortality adjusted by excluding mortality of obesity related comorbidities, with a BMI-specific HR applied	Mortality was broadly aligned with TA875. Further explanation of mortality in the model is provided in Section B.3.3.4
Source of utilities	Utility and disutility values were derived from Søltoft *et al.* 2009, with some disutilities sourced from Sullivan *et al.* 2011	Utility and disutility values were derived from Søltoft *et al.* 2009, with some disutilities sourced from Sullivan *et al.* 2011	Utility values were determined by sex, age and BMI as well as long-term and short-term disutilities for clinical events and AEs and were primarily derived from Søltoft *et al.* 2009.[125] Some disutilities were sourced from Sullivan *et al.* 2011 and a one-off disutility for bariatric surgery was sourced from Campbell *et al.* 2010 as per Kim *et al.* 2022.[126, 127] Disutilities for GI events were sourced from Matza *et al.* 2007, in line with the source used for severe GI events for the NICE appraisal of tirzepatide in T2DM	The utility values were broadly aligned with TA875 and TA664.[1, 2] Further justification of utility values is available in Section B.3.4.5
Measure of health effects	QALYs	QALYs	QALYs	The measure of health effects was aligned with both TA875 and TA664

Source of costs	Drug acquisition costs were based on EMA-approved prescribing information as given by the relevant SmPC	Drug acquisition costs were based on EMA-approved prescribing information as given by the relevant SmPC	Drug acquisition costs were based on MHRA-approved prescribing information as given by the relevant SmPC and unit costs per pack were derived from publicly available databases (e.g. BNF/eMIT)	Sources of costs were broadly in line with those used in both TA875 and TA664

Abbreviations: AE: adverse events; BNF: British National Formulary; BMI: body mass index; EMA: European Medicines Agency; QALY: quality-adjusted life years; HDL: high-density lipoprotein; HR: hazard ratio; IPS: individual patient simulation; MHRA: Medicines and Healthcare products Regulatory Agency; SBP: systolic blood pressure; SmPC: summary of product characteristics; TA: technology appraisal; T2DM: type 2 diabetes mellitus.
Source: TA875[2], TA664 [1].

B.3.2.1 Patient population

The population considered within the base case is **patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity**.

Patient characteristics for the base case population are summarised in Table 58, alongside the equivalent data for the whole trial population. These patient characteristics inform the various risk equations, time horizon of the model and the general population utility values. Where possible, the characteristics of the patient cohort needed for the risk equations were derived from the relevant subgroup population from SURMOUNT-1, as reported by Jastreboff *et al.* 2022[3] or the SURMOUNT-1 CSR. However, certain baseline characteristics were not available in these resources for specific subgroups, so separate analyses were used from SURMOUNT-1. In addition, there are a number of other patient characteristics that were required (not reported in SURMOUNT-1), based on the risk equations (further information in Section B.3.3.5). These remaining patient characteristics were derived from the average cohort baseline values reported in the risk equations, in line with the approach from TA875 and TA664; these characteristics and their sources are summarised in Appendix N.[1, 2]

In order to generate patient characteristics for individual patients simulated in the cohort, parameter values are sampled with the appropriate corresponding distributions, aligned with the mean (and standard deviation [SD], if appropriate) of the distributions observed in the relevant population from SURMOUNT-1; the relevant statistics are given for the base case population and the whole trial population in Table 58 below. The model incorporates explicit correlations between patient characteristics, such as the fact that only males can experience erectile dysfunction.

Table 58: Relevant baseline patient characteristics used in the model for the target population and the whole trial population

Parameter	BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity mean (SD)	Whole trial population mean (SD)	Source
Age (years)	47.40 (12.00)	44.90 (12.50)	**Subgroup:** Lilly data on file 2023 **Whole trial population:** Jastreboff *et al.* 2022[3]
Sex (% female)	66.2% (-)	67.5% (-)	
Weight (kg)*	107.05 (22.47)	104.80 (22.12)	
Height (m)	1.66 (0.10)	1.66 (0.09)	
BMI (kg/m^2)	38.75 (6.81)	38.00 (6.81)	
SBP (mmHg)	124.75 (12.75)	123.30 (12.70)	
Total cholesterol (mg/dL)†	194.02 (39.58)	187.90 (38.14)	
HDL (mg/dL)†	48.71 (12.87)	47.30 (12.44)	
% of Patients with Hypertension	43.52% (-)	32.26% (-)	
eGFR (ml/min/1.73 m^2)	95.44 (17.99)	98.10 (19.62)	
Triglycerides (mg/dL)†	133.86 (67.12)	128.40 (25.68)	
% of Female Patients with PCOS	2.04% (-)	2.28% (-)	

% of Patients with T1DM	0.00% (-)	0.00% (-)	
FPG (mmol/L)	5.41 (0.56)	5.41 (0.57)	
% of Patients with Treated Hypertension	40.00% (-)	29.81% (-)	**Subgroup:** Lilly data on file 2023 **Whole trial population:** SURMOUNT-1 CSR[100]
% of Patients with COPD	1.17% (-)	10.52% (-)	
% of Patients with Hypothyroidism	12.49% (-)	10.87% (-)	
% of Patients with Gestational Diabetes	1.15% (-)	0.93% (-)	
% of Patients with Systemic Lupus Erythematosus	0.18% (-)	0.12% (-)	
% of Patients with Acromegaly	0.00% (-)	0.04% (-)	
% of Male Patients with Erectile Dysfunction	6.08% (-)	4.61% (-)	
% of Patients using Corticosteroids	1.88% (-)	1.58% (-)	Lilly data on file 2023
% of Patients using Statins	17.83% (-)	13.43% (-)	
% of Patients with Prediabetes	57.54% (-)	40.65% (-)	

Footnotes: *Calculated from BMI and height †These SDs are calculated from the coefficient of variation.
Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CSR: clinical study report; DBP: diastolic blood pressure; eGFR; estimated glomerular rate, FPG: fasting plasma glucose; HDL: high-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation.

B.3.2.1.1 *Subgroup populations*

Several subgroups are also considered within the model, the inputs and results for which are summarised in the following section, including:

- BMI ≥35 kg/m^2, prediabetes and high risk for CVD, aligning with the recommended target population for liraglutide 3.0 mg which was recommended by NICE in TA664[1]
- BMI ≥35 kg/m^2 (irrespective of any weight-related comorbidities)
- BMI ≥30 kg/m^2 (irrespective of any weight-related comorbidities)

The baseline characteristics for these subgroups are shown in Table 59. Aligned with the approach taken for the base case analyses, any patient characteristics that were required for the model that were not reported in SURMOUNT-1 were derived from the average cohort baseline values reported in the risk equations, as summarised in Appendix N.

It should be noted that treatment randomisation in SURMOUNT-1 was stratified by country, sex, and the presence or absence of prediabetes, randomisation was not stratified by the subgroup population factors.[3] Therefore, there is a risk that patient characteristics may be unbalanced between arms for the subpopulations; however, this is not expected to have a major impact on results as the patient characteristics are broadly similar within each arm for all subgroups.

Table 59: Relevant baseline patient characteristics for the subgroup populations and the whole trial population

Parameter	BMI ≥30 kg/m^2 mean (SD)	BMI ≥35 kg/m^2 mean (SD)	BMI ≥35 kg/m^2, prediabetes and high CVD risk mean (SD)	Whole trial population mean (SD)	Source
Age (years)	44.50 (12.52)	43.70 (12.30)	46.60 (11.80)	44.90 (12.50)	**Subgroup:** Lilly data on file 2023 **Whole trial population:** Jastreboff *et al.* 2022[3]
Sex (% female)	68.5% (-)	69.2% (-)	66.4% (-)	67.5% (-)	
Weight (kg)*	106.18 (21.85)	115.68 (20.96)	117.68 (21.64)	104.80 (22.12)	
Height (m)	1.66 (0.09)	1.66 (0.10)	1.66 (0.10)	1.66 (0.09)	
BMI (kg/m^2)	38.53 (6.81)	41.92 (6.02)	42.56 (6.29)	38.00 (6.81)	
SBP (mmHg)	123.30 (12.70)	124.14 (12.77)	126.46 (13.38)	123.30 (12.70)	
Total cholesterol (mg/dL)†	187.90 (105.22)	188.31 (37.34)	158.77 (79.18)	187.90 (38.14)	
HDL (mg/dL)†	48.69 (12.92)	47.87 (12.45)	45.34 (11.38)	47.30 (12.44)	
% of Patients with Hypertension	30.93% (-)	32.96% (-)	40.73% (-)	32.26% (-)	
eGFR (ml/min/1.73 m2)	98.42 (18.06)	99.90 (18.18)	96.51 (18.56)	98.10 (19.62)	
Triglycerides (mg/dL)†	128.15 (63.91)	126.27 (60.00)	144.08 (64.82)	128.40 (25.68)	
% of Female Patients with PCOS	2.37% (-)	2.94% (-)	1.10% (-)	2.28% (-)	
% of Patients with T1DM	0.00% (-)	0.00% (-)	0.00% (-)	0.00% (-)	
FPG (mmol/L)	5.30 (0.57)	5.35 (0.58)	5.69 (0.56)	5.41 (0.57)	
% of Patients with Treated Hypertension	28.80% (-)	30.73% (-)	37.80% (-)	29.81% (-)	**Subgroup:** Lilly data on file 2023 **Whole trial population:**
% of Patients with COPD	0.83% (-)	0.66% (-)	1.47% (-)	10.52% (-)	
% of Patients with Hypothyroidism	10.92% (-)	11.29% (-)	11.74% (-)	10.87% (-)	

% of Patients with Gestational Diabetes	0.97% (-)	1.14% (-)	1.93% (-)	0.93% (-)	SURMOUNT-1 CSR[100]
% of Patients with Systemic Lupus Erythematosus	0.13% (-)	0.07% (-)	0.12% (-)	0.12% (-)	
% of Patients with Acromegaly	0.00% (-)	0.00% (-)	0.00% (-)	0.04% (-)	
% of Male Patients with Erectile Dysfunction	4.77% (-)	4.26% (-)	4.37% (-)	4.61% (-)	
% of Patients using Corticosteroids	1.46% (-)	1.18% (-)	1.83%(-)	1.58% (-)	Lilly data on file 2023
% of Patients using Statins	12.67% (-)	11.23% (-)	12.66% (-)	13.43% (-)	
% of Patients with Prediabetes	40.89% (-)	44.25% (-)	100.00% (-)	40.65% (-)	

Footnotes: *Calculated from BMI and height †These SDs are calculated from the coefficient of variation.
Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CSR: clinical study report; DBP: diastolic blood pressure; eGFR; estimated glomerular rate, FPG: fasting plasma glucose; HDL: high-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation.

B.3.2.2 Model structure

B.3.2.2.1 *Justification of model structure*

The model supporting this appraisal is an IPS developed in Microsoft Excel with visual basic for application (VBA). In an IPS model, a cohort of individual patients are simulated with patient characteristics sampled from distributions of baseline characteristics for the target population. For each patient in the cohort, their own surrogate endpoints are tracked and clinical events are simulated to occur at discrete time points ('cycles') throughout the time horizon of the model. This is repeated for all patients in the cohort, and the outcomes for the full cohort are obtained by averaging across the outcomes for each simulated patient.

An IPS modelling approach was deemed most appropriate for the current appraisal as this model type is associated with several key advantages over a cohort Markov model type, which has been used in previous technology appraisals in obesity [TA875; TA664].[1, 2] The primary advantage of an IPS, relative to a Markov cohort model, is that it is possible to track individual patients' history over time. This is of particular relevance to this indication, because there are several clinical events that have long-term effects on patients and implications for the probability of future events. Two key examples are treatment discontinuation and bariatric surgery; both of these events may occur to some patients (but not all) at any time, and both have ongoing implications on expected drivers of the model results after their occurrence (e.g., weight, which would have ongoing effects for the occurrence of clinical events and development of comorbidities, and hence costs/utilities), which are dependent on the time since the event occurred. Clinical events (such as cardiovascular events) similarly impact the risk of future events.[128, 129] Since patient outcomes in a given cycle may be affected by events which occurred more than one cycle ago, it is advantageous to include a mechanism to track patient history in the model. Therefore, the ability to individually model a patient is important to more accurately simulate the disease area. In contrast to an IPS, tracking patient history is not possible in a cohort Markov model due to the 'memoryless' property of Markov structures. This constraint could only be overcome with the introduction of additional health states and tunnel states (for example, duplicating health states to reflect pre- and post-treatment discontinuation patient groups), which would make the model unwieldy, or using simplifying assumptions which would introduce uncertainty and bias. Moreover, due to the increasingly complex assumptions required to accommodate a Markovian model structure, it was expected that a Markov cohort model could ultimately be less transparent than an IPS which relied on fewer assumptions.

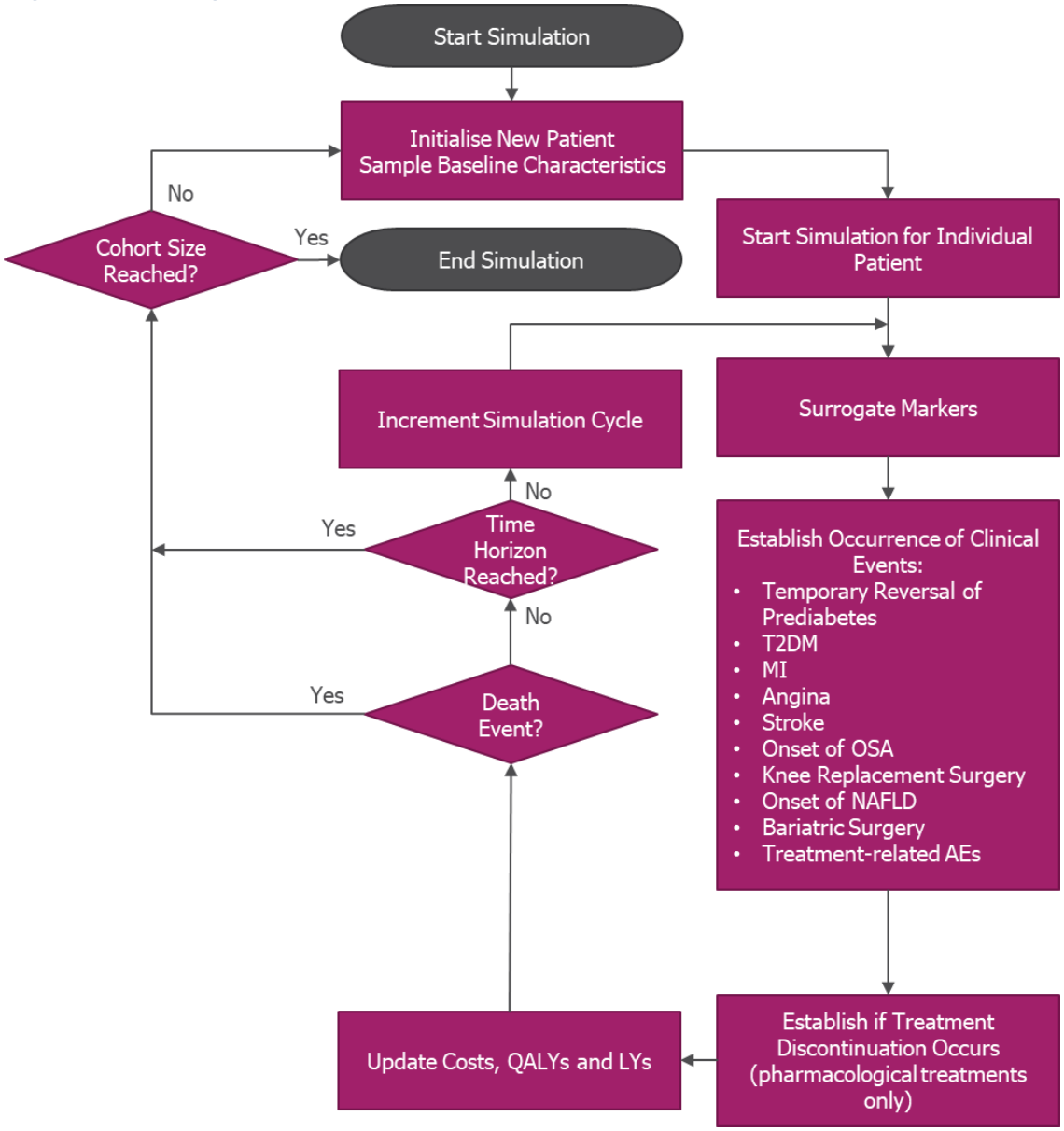
B.3.2.2.2 *Implementation of model structure*

Before entering the model, simulated 'patients' are generated by sampling baseline characteristics from distributions aligned with the population of interest. Simulated patients have a number of characteristics which inform their risk of experiencing onset of comorbidities or other clinical events (including AEs, treatment discontinuation and bariatric surgery). Key surrogate endpoints (patient weight, SBP, HDL, and total cholesterol) are tracked dynamically for each patient over time; the change in each endpoint is informed by efficacy data from the relevant NMA results (Section B.3.3.1.1). Other patient characteristics are assumed to remain constant over time.

Patient characteristics are used as inputs for risk equations, which determine the per-cycle risk of experiencing clinical events, including cardiovascular events, onset of comorbidities, bariatric surgery, and death (further details are given in B.3.2.1 and Section B.3.2.2.3). Some events are

also determined by other factors, such as treatment discontinuation, which occurs due to the SWMS limit that caps the maximum treatment duration for a given treatment, primary treatment failure or discontinuation due to AEs (Section B.3.3.3). The algorithm used to implement the methodology described above is summarised in Figure 43 below. The same set of simulated patients is used in each treatment arm, to ensure results are directly comparable; however, due to the differing efficacy of patients between treatment arms, the same patient will have different trajectories through the model for each treatment arm.

Figure 43: IPS algorithm



Abbreviations: AE: adverse event; IPS: individual patient simulation; LY: life year; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; QALY: quality-adjusted life year; T2DM: type 2 diabetes mellitus.

Initiation of simulation

At initiation of simulation, baseline characteristics from the simulated cohort are randomly sampled from the distributions of the relevant patient populations (as reported in Table 58 and Table 59); random sampling in the model is generated based on a fixed seed to allow repeatable deterministic results. The same generated patient cohort is used for each treatment arm in the model to ensure that results are directly comparable. However, it should be noted that in the probabilistic sensitivity analysis (PSA), parameter variation is not seeded (although the cohort generated remains seeded; cohort characteristics are not further varied in the PSA). The sensitivity of the model to seeding is explored in Section B.3.11.4.

All patients, when the simulation is initiated, are assumed to be on treatment, and to have no comorbidities that are explicitly modelled later as the outcome of the risk equations (T2DM, angina, stroke, MI, OSA, NAFLD, knee replacement, bariatric surgery). The rationale for this assumption was:

- With respect to T2DM, some risk equations required time since onset of diabetes as an input, and furthermore this was an exclusion criterion in SURMOUNT-1.[3]
- With respect to prior CV events (angina, stroke, MI), some risk equations required the time elapsed since their last CV events for use in the CVD risk equations.
- With respect to bariatric surgery, implementation of this in the model applies an efficacy value to weight, which would have been illogical at baseline.
- With respect to OSA, NAFLD and knee replacement, there was no inherent barrier to inclusion at baseline but this general approach is aligned with other obesity models reviewed and in particular the approach taken by TA875 and TA664 which both assumed patients entered their Markov cohort models with no existing comorbidities that are later captured in the time horizon.[1, 2]

Moreover, based on Table S1 in Jastreboff *et al.* 2021,[3] only a small proportion of patients are likely to have had a prior CV event (or other explicitly modelled comorbidity), as reflected in the number of patients with the comorbidity atherosclerotic cardiovascular disease (ASCVD) (n=78/2,539 [3.1%]). Importantly, while patients were assumed to have no prior explicitly modelled comorbidities at baseline, patients were assumed to have a range of other comorbidities at baseline, since these were required parameters for the risk equations used. These comorbidities are outlined in Table 58, Table 59 and Appendix N and include, but are not limited to, PCOS, hypertension, COPD, hypothyroidism, schizophrenia and systemic lupus erythematosus.

B.3.2.2.3 *Occurrence of clinical events*

As discussed in Section B.1.3.2, there are numerous comorbidities that patients with obesity can develop, including T2DM, CVD, OSA, among others. Comorbidities were considered for inclusion in the model if:

- There is strong evidence of an association with obesity
- There are sufficient data to support the inclusion of the comorbidity in the model to avoid too many assumptions needing to be made

- It is expected or clinically plausible that tirzepatide or another modelled treatment affects the risk of developing or maintaining the condition
- The condition results in a clinically significant cost and/or impact on patient quality of life, or affects the risk of other outcomes in a clinically significant manner (e.g. mortality)

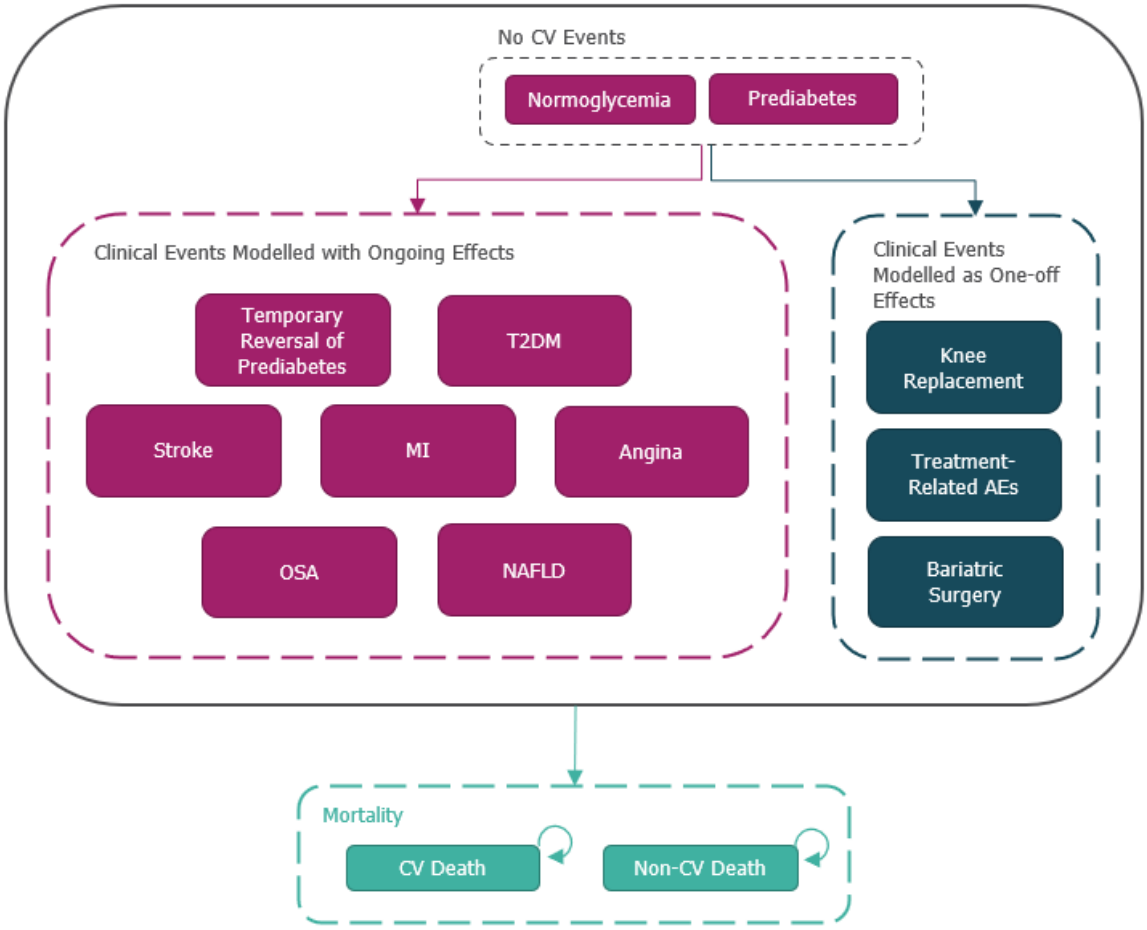
Furthermore, input from a clinical expert was sought in order to determine which comorbidities were relevant. Finally, comorbidities that had been included in other existing economic models were considered, including those in the model supporting TA875 and TA664.[1, 2]

The comorbidities ultimately included in the model were T2DM, stroke, MI, angina, NAFLD, OSA, prediabetes and knee osteoarthritis (Figure 44). This is similar to the approach taken in TA875 and TA664, although the CEMs presented in these appraisals consider MI and angina jointly as acute coronary syndrome (ACS), and do not include NAFLD (the omission of modelled benefit on liver disease was noted by the Committee in TA875, paragraph 3.21).[1, 2] Additionally, bariatric surgery is included in the model as a clinical event.

Due to a lack of data, and to ensure that the computational complexity was kept to a minimum whilst still ensuring that the most clinically and economically relevant comorbidities were selected, not all comorbidities that met the criteria outlined above were included (e.g. hip osteoarthritis). A complete justification for the inclusion and exclusion of these comorbidities is provided in Appendix N.

At each model cycle, patients are at risk of experiencing clinical events, which are associated with costs, disutilities, and changes in risk of future events (including death). For some events (knee replacement, treatment-related AEs, bariatric surgery) patients incur a one-off cost and disutility, whereas others (OSA, NAFLD, T2DM) incur an ongoing cost and disutility. Some events (stroke, MI, angina) incur both a one-off and ongoing cost and disutility. A summary of the clinical events included in the model is given in Figure 44, with further explanation of the inclusion of prediabetes, reversal of prediabetes and bariatric surgery provided ion Section B.3.3.2.

Figure 44: IPS model structure



Footnote: Pink boxes correspond to the major comorbidities (stroke, MI, angina, OSA, NAFLD, T2DM) which are expected to affect patients' costs, utility and mortality risk. Blue boxes represent clinical events or comorbidities (knee replacement, treatment related AEs, bariatric surgery) that can occur to patients at any time with a specified probability which may be dependent on existing comorbidities or surrogate endpoints. Green boxes represent death states (CD death or non-CD death); patients can die at any time. Arrows indicate permitted events in the model.
Abbreviations: AE: adverse events; CV: cardiovascular; IPS: individual patient simulation; MI; myocardial infarction; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus.

B.3.2.2.4 *Cycle length*

A dual-cycle length approach was employed for this model, with half-cycle correction where appropriate (Table 60). The shorter initial 4-week cycles allow for the incorporation of treatment discontinuation that may occur shortly after initiating treatment as well as for more accurate tracking of dose titration and surrogate endpoints over the period that trial data of treatments are available. The subsequent 1-year cycle is considered suitable to capture the likely frequency of complications and to avoid a model that is excessively computationally intense.

The 1-year cycle length commences after two years, rather than one year used in TA664 and TA875,[1, 2] based on the longer follow-up of the SURMOUNT-1 trial (72 weeks). In order to ensure that trial data (and therefore tirzepatide efficacy) is captured as accurately as possible, 4-week cycles were adopted as close as possible to two years after treatment initiation to allow patients to discontinue treatment at two years, in line with the NICE-recommended maximum duration for SWMS in which semaglutide and liraglutide must be provided.[1, 2]

Table 60. Implementation of half-cycle correction in the model

Model calculation	Half-cycle correction	Rationale
All calculations during the 4-week cycle period	No	To minimise complexities associated with half-cycle correcting across the period of transitioning between two different cycle lengths (4 weeks and 1 year), no half-cycle correction is applied during the 4-week cycle period. Given the short duration of the cycle length, this is expected to have a minimal impact on results.
Ongoing comorbidities (i.e. number of patients alive with maintained comorbidities) including associated costs/disutilities	Yes - in Trace	Half-cycle correction is applied as the total costs and disutilities incur depend on when in each cycle the comorbidity is developed or resolved (generally because a patient dies). To avoid introducing bias of assuming comorbidities are always developed/resolved at the start or end of a cycle, it is assumed that it occurs at the mid-point of each cycle.
Treatment status (i.e. number of patients on/off treatment)	Yes - in Trace	Similarly to the costs associated with ongoing comorbidities, treatment costs and disutilities due to AEs should be half-cycle corrected (i.e. patients are assumed to accrue costs/AE-associated disutilities for half a cycle of treatment in the cycle in which they discontinue treatment). This is accomplished by applying the full treatment cost/disutility per cycle to the half-cycle corrected number of patients on treatment.
Occurrence of one-off events	No	The occurrence of one-off events is used only to calculate the costs/disutilities associated with one-off events, which do not require half-cycle correction; further explanation is given below.
Costs/disutilities associated with one-off events	No	Costs and disutilities associated with one-off events do not require half-cycle correction, since all patients experiencing an event with a one-off cost/disutility accrue the full cost/disutility for that event, regardless of what point in the cycle the event occurred.
Number of CV/non-CV deaths	No	Number of CV/non-CV deaths are not used to calculate any costs or outcomes and therefore do not require half-cycle correction.
Cumulative number of deaths	Yes - in Trace	The cumulative number of deaths is used to calculate the total LYs; similarly to the costs/disutilities for ongoing comorbidities and treatment, a patient should accrue half a LY in the cycle in which they die. This can be accomplished by using the half-cycle corrected cumulative number of deaths to calculate the half-cycle corrected number of patients alive in each cycle, and summing these to calculate the total LYs.
BMI-based utilities and HCRU costs	Yes - in VBA	Since the BMI changes over the course of the cycle, the costs and utilities accrued in one cycle are assumed to be the average of the costs/utilities that would be accrued for the BMI at the start of the cycle, and the costs/utilities accrued for the BMI at the end of the cycle. Please note that a 'weighting' is applied for the first long cycle (to account for the fact that the previous and current cycles are different lengths, but should contribute equally to the average cost/utility over the cycle)

Abbreviations: AE: adverse event; BMI: body mass index; CV: cardiovascular; HCRU: healthcare resource use; LY: life year; VBA: visual basic for application.

B.3.2.2.5 *Time horizon and discounting*

A lifetime horizon is used in the base case to reflect the chronic nature of obesity as well as the chronic and progressive nature of many of its comorbidities, and is also aligned with NICE reference case.[7] TA875 and TA664 both used a 40-year time horizon, but this choice was criticised by the Committee as it was considered that the full costs and benefits of treatment had not been captured.[1, 2] Both costs and effects were discounted at 3.5% per annum in accordance with the NICE reference case.[123] Discounting is implemented in the model from the first cycle and is used in the treatment traces to calculate the total costs and QALYs seen in the primary results. At each cycle in the traces, the discount factor is calculated using the following formula:

$$Discount\ applied\ in\ Year\ n\ = \frac{1}{(1+discount\ rate)^n}.$$

These values are then used as a multiplicative factor to relevant cost and benefit outcomes.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 *Intervention*

The intervention of interest is tirzepatide 5 mg, 10 mg or 15 mg, each as an adjunct to diet and exercise, which is administered via injection every week (QW), using a SC pre-filled pen device. Tirzepatide is initiated at 2.5 mg QW. After 4 weeks, the dose is increased to 5 mg QW. If needed, the dose can be increased in 2.5 mg increments every 4 weeks up to 15 mg (Section B.2.3.1.1). The recommended maintenance doses are 5 mg, 10 mg and 15 mg.

In the base case, it is assumed that tirzepatide would be administered indefinitely, unless patients discontinue treatment due to adverse events. This reflects the expected use of tirzepatide in clinical practice (Section B.1.3.5), given that tirzepatide is not anticipated to be isolated to use in SWMS and is instead anticipated to be used both in primary and secondary care. It is therefore not anticipated that use of tirzepatide would be limited to a particular timeframe.

B.3.2.3.2 *Comparators*

The following comparators are included in the model, since these interventions represent the current treatment options for patients with obesity in England and Wales (Section B.1.1):

- A reduced calorie diet and increased exercise alone, which constitutes standard management in obesity[7] (referred to as diet and exercise)
- Semaglutide (2.4 mg) as an adjunct to a reduced calorie diet and increased exercise (referred to as semaglutide)
- Liraglutide (3.0 mg) as an adjunct to a reduced calorie diet and increased exercise (referred to as liraglutide)

Importantly, the modelled comparator/s are dependent on the population considered (detailed in Table 61) given that the populations for whom these treatments are recommended by NICE are not directly comparable (Table 62).

In the base case analysis, tirzepatide 5 mg, 10 mg or 15 mg (each as an adjunct to diet and exercise) are compared to diet and exercise and semaglutide.

For both semaglutide and liraglutide (in the populations for whom these treatments are relevant comparators), it is assumed that treatment would be administered for a maximum duration of 2 years, aligned with the maximum treatment duration for SWMS in which use of these treatments is recommended by NICE (Section B.3.3.3.3). For diet and exercise, it is assumed that this comparator would be provided indefinitely, aligning with the assumption in TA875 (Section B.3.3.3).[2]

Table 61. Relevant comparator/s considered in the cost-effectiveness analyses in the base case and subpopulations considered

Population	Comparator/s	Explanation
BMI ≥30 kg/m^2 with at least one weight-related comorbidity (base case)	• Diet and exercise • Semaglutide	For the population with BMI ≥30 kg/m^2 with at least one weight-related comorbidity, the relevant comparator is diet and exercise, since this represents a broader population than the NICE recommendations for semaglutide and liraglutide (Table 62). However, no efficacy data were available for the population for whom treatment with semaglutide is recommended by NICE specifically (data were only available from the TA875 Committee papers which only include data for patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity and patients with BMI ≥35 kg/m^2, prediabetes and high risk for CVD). As such, it was not possible to compare tirzepatide to semaglutide in the population for whom semaglutide is recommended by NICE. Therefore, the base case analysis also includes semaglutide as a comparator, with the caveat that semaglutide is not currently recommended by NICE for patients with a BMI ≤35 kg/m^2 outside of SWMS.
BMI ≥35 kg/m^2, prediabetes and high risk for CVD (subpopulation)	• Diet and exercise • Semaglutide • Liraglutide	Liraglutide 3.0 mg is recommended by NICE for BMI ≥35 kg/m^2, prediabetes and high risk for CVD, as in TA664. Therefore, this treatment is a relevant comparator to tirzepatide only in this specific subpopulation.
BMI ≥35 kg/m^2 (subpopulation)	• Diet and exercise	For these subgroups, the relevant comparator is diet and exercise since NICE do not recommend pharmacotherapy with semaglutide and liraglutide in these populations.
BMI ≥30 kg/m^2 (subpopulation)		

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; NICE: national institute for health and care excellence; SWMS: specialist weight management service; TA: technology appraisal.

Table 62: Population and dosing recommendations for semaglutide and liraglutide

Drug	Reimbursement population	Dose schedule	Source
Semaglutide (2.4 mg)	Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if: • It is used for a maximum of 2 years, and within a SWMS providing multidisciplinary management of overweight or obesity (including but not limited to Tiers 3 and 4), and • They have at least 1 weight-related comorbidity and: ○ A BMI of at least 35.0 kg/m2, or ○ A BMI of 30.0 kg/m2 to 34.9 kg/m2 and meet the criteria for referral to specialist weight management services in NICE's guideline on obesity: identification, assessment and management. Lower BMI thresholds (usually reduced by 2.5 kg/m^2) are used for people from south Asian, Chinese, and Black African or Caribbean family backgrounds	• Titration doses administered QW SC over a 16-week period: ○ Week 1–4: 0.25 mg, ○ Week 5–8: 0.5 mg, ○ Week 9–12: 1.0 mg, ○ Week 13–16: 1.7 mg • Maintenance dose: 2.4 mg QW SC, up to 2 years	**Population:** NICE TA875[2] **Dose schedule:** Wegovy SmPC; in line with NICE TA875[104]
Liraglutide (3.0 mg)	Liraglutide is indicated in secondary care by a specialist multidisciplinary Tier 3 weight management service. Liraglutide is recommended as an option for managing patients with obesity, alongside a reduced-calorie diet and increased physical activity in adults fulfilling all the following criteria: • BMI ≥35.0 kg/m^2 or at least 32.5 kg/m^2 for members of ethnic minority groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population, • Prediabetes • A high risk of CVD based on risk factors such as hypertension and dyslipidaemia	• Titration dose over a 4-week period: dose initiation of 0.6 mg QD, increased by 0.6 mg QW up to 2.4 mg QD SC • Maintenance dose: 3.0mg QD SC, up to 2 years • Treatment should be stopped if patients have not lost at least 5% of their initial body weight after 12 weeks of treatment with 3 mg per day	**Population:** NICE TA664[1, 2] **Dose schedule:** Saxenda SmPC; in line with NICE TA664[105]

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; NICE: national institute for health and care excellence; QD: once daily; QW: once weekly; SmPC: summary of product characteristics; SC: subcutaneously; TA: technology appraisal; TID: three times daily.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Treatment efficacy

Treatment efficacy was captured via the following surrogate endpoints: CfB weight (%), CfB SBP, CfB HDL and CfB total cholesterol. These surrogate endpoints are employed in risk equations (Section B.3.3.5), which determine the incidence of clinical events and comorbidities.

B.3.3.1.1 *Effect on surrogate outcomes*

Change in weight (%) is the main driver of clinical effectiveness. Changes in weight influence the risk of all obesity complications in the model (except the incidence of secondary cardiovascular events). Changes in SBP, HDL and total cholesterol influence the risk of developing T2DM, CVD in those with no prior history of CVD, and CVD in those with a prior history of CVD. Table 63 describes how the effect on surrogate outcomes, measured through changes in physiological parameters, is quantified in the model. Figures showing the projected changes in these surrogate endpoints over the time horizon of the model is provided in Section B.3.10.

Table 63. Definition of treatment effects on physiological parameters included in the model

Physiological parameter	Treatment effect included in the model
Change in weight (%)	Percentage change in weight versus baseline; this ultimately feeds into the calculation of BMI, assuming constant height over the modelled time frame
Change in SBP	Absolute change in SBP versus baseline
Change in HDL (%)	Percentage change in HDL cholesterol versus baseline
Change in total cholesterol (%)	Percentage change in total cholesterol versus baseline

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; SBP, systolic blood pressure.

Treatment effects for tirzepatide 5, 10 and 15 mg and its comparators were derived from the NMA for the subgroups for whom indirect treatment comparisons were required (i.e. in the base case analysis, treatment effects were derived from NMA analysis which considered the population with BMI ≥30 kg/m^2 with at least one weight-related comorbidity). As discussed in Section B.2.9, the NMA consolidated all available efficacy data for liraglutide and semaglutide to provide a comprehensive estimate of the efficacy for these treatments, relative to tirzepatide. In the NMA, efficacy data were derived from the following studies:

- O'Neil *et al.* 2018
- SCALE Obesity and Prediabetes
- STEP 1
- STEP 5
- STEP 8
- SURMOUNT-1

The specific surrogate endpoint data informing the base case are presented in Table 64 to

Table 67. As discussed in Section B.2.9.4.1, the NMA results informing the model base case are FE results from the efficacy estimand NMA analyses for the BMI ≥30 kg/m^2 with one weight-related comorbidity subgroup. The efficacy estimand NMA results, which estimate the treatment effect of tirzepatide versus its comparators for all randomised patients assuming they remained on their randomised treatment (as discussed in more detail in B.2.4.1.1) were considered most appropriate for the base case because in the CEM patients who discontinue treatment are explicitly modelled to lose the benefit of treatment efficacy and no longer incur drug acquisition costs. In contrast, use of the treatment regimen estimand in the CEM would have resulted in the effect of treatment discontinuation on population-level efficacy being applied to all patients remaining on treatment in the CEM in addition to the loss of efficacy from treatment discontinuation being separately modelled for each simulated patient in the CEM. This rationale and choice of estimand is aligned with that taken and accepted in TA875.[2]

The equivalent NMA results for the whole trial population are presented in Section B.2.9.5.2 and for the BMI ≥35 kg/m^2, prediabetes and a high risk of CVD subpopulation in the model in Appendix D. As noted previously, efficacy data for the BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2 subgroups (both irrespective of comorbidities) were derived directly from the SURMOUNT-1 post-hoc analyses, and are therefore presented in Section B.2.7.3.

Table 64: Change from baseline in weight for each treatment arm in base case population

Treatment	Time point (weeks)	Weight (%)	Source
Tirzepatide (5.0 mg)	72	[redacted]	NMA [Section B.2.9.5]
Tirzepatide (10.0 mg)	72	[redacted]	
Tirzepatide (15.0 mg)	72	[redacted]	
Semaglutide (2.4 mg)	68	[redacted]	
Diet and exercise	68	[redacted]	

Abbreviations: NMA: network meta-analysis.

Table 65: Change from baseline SBP for each treatment arm in base case population

Treatment	Time point (weeks)	SBP (mmHg)	Source
Tirzepatide (5.0 mg)	72	[redacted]	NMA [Section B.2.9.5]
Tirzepatide (10.0 mg)	72	[redacted]	
Tirzepatide (15.0 mg)	72	[redacted]	
Semaglutide (2.4 mg)	68	[redacted]	
Diet and exercise	68	[redacted]	

Abbreviations: NMA: network meta-analysis; SBP: systolic blood pressure.

Table 66: Change from baseline in HDL for each treatment arm in base case population

Treatment	Time point (weeks)	HDL (%)	Source
Tirzepatide (5.0 mg)	72	[redacted]	NMA [Section B.2.9.5]
Tirzepatide (10.0 mg)	72	[redacted]	
Tirzepatide (15.0 mg)	72	[redacted]	
Semaglutide (2.4 mg)	68	[redacted]	
Diet and exercise	68	[redacted]	

Abbreviations: HDL: high-density lipoprotein; NMA: network meta-analysis.

Table 67: Change from baseline in total cholesterol for each treatment arm in base case population

Treatment	Time point (weeks)	Total cholesterol (%)	Source
Tirzepatide (5.0 mg)	72	[redacted]	NMA [Section B.2.9.5]
Tirzepatide (10.0 mg)	72	[redacted]	
Tirzepatide (15.0 mg)	72	[redacted]	
Semaglutide (2.4 mg)	68	[redacted]	
Diet and exercise	68	[redacted]	

Abbreviations: NMA: network meta-analysis.

An additional surrogate endpoint that is relevant for T2DM is HbA1c. In the model, it is assumed that once patients develop T2DM, their HbA1c remains constant at 7.5%, in line with TA875 and TA664.[1, 2] This is a simplifying assumption since HbA1c would be expected to increase over time as beta-cell function deteriorates, but be maintained (at a minimum) due to patients receiving medication for T2DM. This is considered to be a reasonable simplification, because this model focuses on the progression of obesity, not T2DM. Furthermore, testing the model demonstrated that altering the fixed HbA1c value in patients with T2DM had minimal impact on the results. It can be inferred that this is due to the same assumption being consistently applied to all treatment interventions.

B.3.3.1.2 *Post-trial follow-up*

The SURMOUNT-1 trial follow up for the whole trial population is 72 weeks; beyond this time point, no trial data were available at the time of submission to inform changes in the surrogate endpoints of interest. It is assumed therefore that the surrogate endpoints for tirzepatide and diet and exercise will remain constant from Week 72 until treatment discontinuation, in line with similar assumptions made in TA664 and TA875.[1, 2] With regards to semaglutide, data were not available beyond Week 68, so the same assumption was applied to this treatment arm beyond week 68 in the model until treatment discontinuation.

B.3.3.2 Clinical events

B.3.3.2.1 *Prediabetes*

Aligning with the approach taken in TA875 and TA664, prediabetes is included as an event in the model.[1, 2] This is implemented through assuming that a proportion of patients entering the model have prediabetes at baseline. These proportions are based on data from SURMOUNT-1 for tirzepatide and diet and exercise, and on the STEP-1 and SCALE trials for semaglutide and liraglutide, respectively, as detailed in Table 68.

Normoglycaemia, prediabetes and T2DM are considered as mutually-exclusive states in the model; once patients develop T2DM, they lose their normoglycaemia/prediabetes status. In line with TA875 and TA664, it is assumed that patients' HbA1c is determined by their glycaemic status (i.e. T2DM, prediabetes or normoglycaemia).[1, 2] In the absence of available data for this population, it is assumed that patients' HbA1c aligns with the higher threshold for each glycaemic status category – patients with normoglycaemia are assumed to have an HbA1c of 5.7%, patients with prediabetes have an HbA1c of 6.4%, and patients with T2DM have an HbA1c of 7.5%, as noted above. Since HbA1c is a covariate in the risk equations for T2DM estimates (with

a higher HbA1c resulting in a higher risk of developing T2DM), patients with prediabetes have a higher risk of developing T2DM than patients with normoglycaemia.

It should be noted that the HbA1c thresholds implemented in the model for each glycaemic status represent conservative assumptions for patients receiving tirzepatide; data from the SURPASS clinical trial program in patients with T2DM demonstrated that people receiving tirzepatide achieve significant reductions in their HbA1c frequently well below the levels assumed in both the prediabetes and diabetes states in the model.[89, 94-97, 130] These results have also been seen in the SURMOUNT-2 trial in patients with obesity and T2DM (Appendices M). In this respect, the treatment benefit of tirzepatide in terms of reducing the incidence of T2DM is likely to be underestimated.

Table 68. Starting prediabetes distributions for populations considered in the economic model

Population	Proportion in normal glucose tolerance (%)	Proportion with prediabetes (%)	Source
ITT	59.35%	40.65%	SURMOUNT-1 CSR
BMI ≥30 kg/m^2	[redacted]	[redacted]	Lilly data on file
BMI ≥35 kg/m^2	[redacted]	[redacted]	Lilly data on file
BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity (base case)	[redacted]	[redacted]	Lilly data on file
BMI ≥35 kg/m^2, prediabetes and a high risk for CVD	0%	100%	Lilly data on file

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; ITT: intention-to-treat.

B.3.3.2.2 *Reversal of prediabetes*

Aligning with the approach taken in TA875 and TA664, an immediate effect of treatment on prediabetes is captured in the model, such that patients in the simulated cohort may temporarily transition to normoglycaemia following intervention, referred to as prediabetes reversal.[1, 2] To capture this effect in the model, a proportion of the simulated patient cohort with prediabetes (Section B.3.2.2) experiences temporary reversal and transitions to normal glucose levels after the first model cycle. Following treatment discontinuation, reversal is interrupted and patients return to prediabetes.

Aligning with the approach in TA875, prediabetes reversal is applied at the end of the first cycle. However, it should be noted that the cycle length applied in the current model is shorter (4 weeks; Section B.3.2.2.4) as compared to the TA875 model (3 months). The proportion of patients in the simulated cohort experiencing prediabetes reversal is informed by the Week 72 data from SURMOUNT-1 for tirzepatide and diet and exercise. Equivalent data for semaglutide is sourced from Week 52 data from the STEP-1 trial, while data for liraglutide that is applied in the subgroup analyses of patients with BMI ≥35 with prediabetes and high risk for CVD is derived from the SCALE trial.

Longer-term data on glycaemic status from the tirzepatide/semaglutide/liraglutide clinical trials was applied in the first cycle (Week 4) because it is expected based on the known efficacy profile of GLP-1 RAs that reversal would occur shortly after pharmacological treatment.

While it was considered appropriate to apply prediabetes reversal in the first cycle for pharmacological treatments, the same assumption may not be appropriate in the diet and exercise arm since no GLP-1 RA efficacy is being received. Therefore, the application of longer-term data in the first cycle may significantly underestimate the treatment benefit of pharmacological treatments in terms of reducing the incidence of T2DM compared to diet and exercise. Despite this, the Company were unable to locate any relevant data regarding the dynamics of prediabetes reversal for patients receiving diet and exercise alone. Several scenarios were therefore explored to investigate the effect of varying the time at which prediabetes reversal occurs in the diet and exercise arm (12 weeks, 24 weeks). For the base case, it was conservatively assumed that prediabetes reversal would occur in the first cycle for diet and exercise, aligned with the approach taken in TA875 in terms of application at first cycle but differing in time due to the shorter cycles in the present model (4 weeks vs 3 months).[2]

The percentage of patients with prediabetes experiencing glycaemic status reversal for each subpopulation considered in the model is provided below in Table 69.

Return to prediabetes

In the pharmacological treatment arms, it is assumed after treatment discontinuation that prediabetes reversal is interrupted, and patients return to prediabetes in the cycle following the end of the treatment waning period (3 years in the base case; Section B.3.3.3). For patients receiving semaglutide and liraglutide, the maximum duration before returning to prediabetes in the base case is 5 years after starting treatment, reflecting the maximum 2-year treatment duration (due to the SWMS limit) and the subsequent 3-year treatment waning period until a patient returns to prediabetes. For tirzepatide, no discontinuation due to the SWMS limit is modelled, so patients return to prediabetes gradually over time as they discontinue due to primary treatment failure or AEs and experience the waning period. This assumption is largely aligned with TA875, in which patients receiving semaglutide and liraglutide were assumed to return to prediabetes over a 3-year period (reflecting the 3-year waning period post-discontinuation for weight loss). However, a notable difference in this case is that rather than assuming that patients return to prediabetes gradually at a rate of 33.33% per year over a 3-year period as per TA875, the IPS assumes that all patients return to prediabetes in the cycle following the end of the treatment waning period (3 years in the base case; Section B.3.3.3). This difference stems from the fact that prediabetes is implemented as a categorical variable in the IPS model and therefore cannot be gradually waned in the current IPS in an analogous way to the cohort Markov model structure i.e. the IPS either models that a patient does or does not have prediabetes, whereas in a cohort model a proportion of patients can revert to prediabetes in a given time frame, allowing a ‘gradual’ transition over three years.

For the diet and exercise arm, no discontinuation is modelled as no data were identified to inform the efficacy of diet and exercise post-discontinuation (Section B.3.3.3.1). However, as a result of this assumption, patients receiving diet and exercise would be modelled to have greater benefits in terms of T2DM prevention compared to those receiving pharmacological treatment, which was considered to lack face validity. Therefore, to adjust for the lack of discontinuation modelled in the diet and exercise arm and counteract this bias, an arbitrary time point is included in the model at which patients receiving diet and exercise are assumed to return to prediabetes. In the base case, it is assumed this re-reversal in the diet and exercise arm occurs at 2 years to reflect the SWMS limit that applies to semaglutide, but alternative time points (3 years, 5 years) are explored as scenario analyses.

Table 69. Percentage of patients with prediabetes at baseline experiencing glycaemic status reversal

Treatment	Whole trial population	BMI ≥30 kg/m^2	BMI ≥35 kg/m^2	BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity (base case)	BMI ≥35 kg/m^2 with prediabetes and high CVD risk	Source
Diet & Exercise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Lilly data on file
Tirzepatide (5.0 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Lilly data on file
Tirzepatide (10.0 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Lilly data on file
Tirzepatide (15.0 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Lilly data on file
Liraglutide (3.0 mg)	83.60%	83.60%	83.60%	83.60%	83.60%	TA875[2]
Semaglutide (2.4 mg)	90.40%	90.40%	90.40%	90.40%	90.40%	TA875[2]

Abbreviations: BMI: body mass index; CVD: cardiovascular disease.

B.3.3.2.3 *Bariatric surgery*

In TA875, bariatric surgery was excluded as a parameter and treated as a one-off event. As highlighted in Section B.1.1, bariatric surgery is not considered a relevant comparator for tirzepatide; however, it was considered as a clinical event that a proportion of patients might receive in clinical practice. In the model, patients undergoing bariatric surgery incur a one-off cost associated with the procedure, as well as a one-off disutility associated with surgery. There is also an additional probability of experiencing a complication as a result of surgery. The model incorporates a number of different bariatric surgeries, apportioned based on their relative frequency, to inform the assigned cost for the procedure. An additional mortality risk from undergoing bariatric surgery was not included in the model because the identified risk was not considered significant (for example, the case fatality rate for bariatric surgery used in TA875 was 0.0007).[2] This methodology for including bariatric surgery aligns with TA875 and TA664, with the exception of the mortality risk.[1, 2]

In addition to the costs and disutility associated with the event, patients also experience weight reduction following surgery, with the extent of weight reduction varying based on the specific type of surgery received. On the basis of clinician input, it was assumed that a patient's BMI initially reduces after bariatric surgery and is constant thereafter.[131] This assumption may overestimate the long-term effect of bariatric surgery as it was noted by the patient expert in TA875 that even after bariatric surgery, maintaining weight loss is challenging.

Benefits for bariatric surgery (reduction in body weight and resolution of comorbidities) were informed by recent data from the National Bariatric Surgery Registry (NBSR).[132] Treatment efficacy inputs were taken as weighted averages across the different types of bariatric surgery offered by the NHS: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, gastric band and one-anastomosis gastric bypass (OAGB)/mini gastric bypass (MGB); the frequency of the different types of procedure are given in Table 70. Details of the input values for efficacy parameters for each type of procedure are given in Table 71, which include changes in comorbidities post-surgery (OSA and T2DM remission) as well as weight loss; again, these efficacy inputs were assumed to vary based on the type of surgery received.

In TA664 and TA875, change in SBP, total cholesterol, HDL and HbA1c at 1 year following bariatric surgery were included based on mean change from baseline reported in Demssie *et al.* 2012.[133] However, the same approach was not taken for the current model in order to simplify the model and to avoid additional assumptions that would have affected only a small number of patients (given the low incidence of bariatric surgery), and therefore would have a limited impact on results. For instance, to avoid assumptions required to derive relevant costs and disutilities, complication data for some of the bariatric surgeries were excluded even though they were reported by NBSR. Nevertheless, the mean weight loss after 1 year (%) by surgery is fairly aligned with the data used in TA875 based on Sjöström *et al.* 2004 (GB-type procedures: 32%, gastric band: 20% and sleeve gastrectomy: 25%) and TA664 based on Miras *et al.* 2018 (28.27% for all procedures), but represents more recent data.[134, 135] Finally, hypertension is not explicitly modelled (i.e. the model does not track hypertension as a binary category), but it is indirectly captured by patients' SBP, as individuals are defined as having hypertension if their SBP level is greater than 140 mmHg.

Table 70: Proportional frequency of types of bariatric surgery procedure

Parameter	Value	Source
RYGB	48.9%	NBSR Third Registry Report 2020 (NHS-funded primary bariatric surgery procedures, 2013—2018)[132]
Sleeve gastrectomy	35.4%	
Gastric band	11.5%	
OAGB/MGB	3.9%	
Other*	0.3%	

Footnotes: *The overall proportions of the four main types of procedure (RYGB, sleeve gastrectomy, gastric band and OAGB/MGB) was reweighed to account for the 0.3% of procedures which did not fall into these categories.
Abbreviations: MGB: mini gastric bypass; NBSR: National Bariatric Surgery Registry; NHS: National Health Service; OAGB: one-anastomosis gastric bypass; RYGB: Roux-en-Y gastric bypass.

Table 71: Efficacy parameters for bariatric surgery

Parameter	RYGB	Sleeve gastrectomy	Gastric band	OAGB/MGB	Source
Surrogate endpoints					NBSR Third Registry Report 2020 (NHS-funded primary bariatric surgery procedures, 2013–2018)[132]
Mean weight loss after 1 year (95% CI)	32.9% (32.7%–33.2%)	29.2% (28.9%–29.5%)	16.3% (15.8%–16.8%)	33.7% (32.7%–34.7%)	
Complications post-surgery					
% of patients with T2DM pre-surgery achieving remission post-surgery	60.4%	55.3%	30.3%	50.0%	
% of patients with OSA pre-surgery achieving remission post-surgery	57.7%	53.6%	31.8%	58.2%	

Abbreviations: CI: confidence interval; mgB: mini gastric bypass; NBSR: National Bariatric Surgery Registry; NHS: National Health Service; OAGB: one-anastomosis gastric bypass; OSA: obstructive sleep apnoea; RYGB: Roux-en-Y gastric bypass; T2DM: type 2 diabetes mellitus.

B.3.3.3 Treatment discontinuation

Patients may discontinue treatment for different reasons, including primary treatment failure, AEs, or due to the SWMS limit defining how long patients can continuously receive treatment (2 years). The impact of treatment discontinuation on each patient's surrogate endpoints (i.e. treatment efficacy) is dependent on the reason for discontinuation, as described in the following sections.

It should be noted that no discontinuation was modelled for patients in the diet and exercise arm, aligning with TA875.[2] While evidence suggests that a proportion of patients may struggle to adhere to dietary and exercise intervention in the long term and therefore may discontinue diet and exercise intervention over time,[136-138] no evidence was identified to inform modelling of the efficacy of diet and exercise post discontinuation. Given this lack of data, it was therefore

assumed that diet and exercise support would be provided indefinitely, which reflects the fact that diet and exercise is an integral part of lifelong obesity management, and represents a conservative assumption that was considered more appropriate than making multiple additional assumptions with regards to diet and exercise efficacy post-discontinuation.

B.3.3.3.1 *Discontinuation due to AEs*

The probability of discontinuing due to AEs for each treatment arm (as well as each subgroup and dosing regimen for tirzepatide) was informed by the corresponding clinical trial, as shown in Table 72. AE-related discontinuation is modelled on a per-cycle basis; a per-cycle probability is derived by dividing the total number of discontinuation events by the duration of the trial (person-years). While in TA875, the probability of discontinuation per cycle was taken from a Kaplan–Meier curve of time to discontinuation, this alternative approach was not taken for tirzepatide given that only data for overall AE discontinuation over the entire follow-up duration were available for all comparators. Gastrointestinal AEs were the most common AE leading to study drug discontinuation.

For each simulated patient in an active treatment arm, the per-cycle probability was used to determine if treatment was discontinued at each cycle.

Table 72: AE-related discontinuation

Treatment	Discontinuation	Follow-up period	Source
Tirzepatide 5 mg	27/630 (4.3%)	72 weeks	Jastreboff *et al.* 2022 (SURMOUNT-1)[3]
Tirzepatide 10 mg	45/636 (7.1%)	72 weeks	
Tirzepatide 15 mg	39/630 (6.2%)	72 weeks	
Semaglutide 2.4 mg	92/1306 (7.0%)	68 weeks	Wilding *et al.* 2021 (STEP 1 trial)[12]
Liraglutide 3.0 mg	246/2487 (9.9%)	56 weeks	Pi-Sunyer *et al.* 2015 (SCALE Obesity and Prediabetes)[80]

Abbreviations: AE: adverse event.

Efficacy post AE discontinuation

Efficacy post-discontinuation was modelled applying the same approach for patients discontinuing treatment due to AEs and after discontinuation due to the SWMS limit (Section B.3.3.3.3).

Given the lack of efficacy data following discontinuation of tirzepatide, the treatment effect of tirzepatide was assumed to return to the value of natural progression in diet and exercise over the course of 3 years after discontinuation, aligning with the approach taken in TA875 and TA664 for semaglutide and liraglutide, respectively.[1, 2] However, the Company acknowledges that there is some uncertainty both in the extent to which the treatment benefit of tirzepatide is lost and also in the time-period over which the treatment benefit is lost compared to diet and exercise and notes that further relevant data will become available after the submission date, in October 2023 when the SURMOUNT 4 trial reports (the initial top-line data from SURMOUNT 4 reported shortly before submission are provided in Appendix M). As such, scenario analyses have been provided in which the time period over which the benefit of treatment is lost is explored (1 year and 2 years, as opposed to 3 years in the model base case). As discussed in Section B.3.3.3, it was assumed for diet and exercise that no discontinuation would occur (AE discontinuation or

otherwise), therefore, the efficacy of diet and exercise was assumed to remain constant over the time horizon of the model.

Following the period in which the benefit of treatment is lost, all surrogate endpoints (with the exception of BMI) were assumed to remain constant. It is understood that some natural variation is expected over a patient's lifetime, however for simplicity in the model – as indeed patients may receive standard blood pressure and lipid lowering medication – the levels of these parameters are not modelled to change over time. This is aligned with the approach taken in TA875.[2]

In the base case, patients' BMI is assumed to increase by an annual absolute value depending on their sex, in line with TA875 (Table 73).[2] After the age of 68 years a patient's BMI was assumed to remain constant, in line with TA875.[2] A scenario analysis was then conducted to test an alternative literature source for natural weight gain following treatment discontinuation that was explored by the EAG in TA875 (Iyen *et al*. 2021[139]). However, it should be noted that Iyen *at al.* does not provide a breakdown by sex; therefore, based on this source, an annual BMI increase of 0.1060 kg/m^2 per year is modelled for both men and women. This is lower per year compared to the base case source, which means that in this scenario patients modelled to discontinue pharmacological therapies to experience a slower increase in BMI compared to the model base case.

Table 73: Expected annual increase in BMI following waning period

Treatment	Change in BMI (kg/m^2)	Source
Male	0.1447	Ara *et al.* 2012[124]
Female	0.1747	

Abbreviations: BMI: body mass index.

B.3.3.3.2 *Discontinuation due to primary treatment failure*

The cost-effectiveness model includes discontinuation due to primary treatment failure, in order to align with anticipated clinical practice. In TA875 for semaglutide in obesity it states: "*Consider stopping semaglutide if less than 5% of the initial weight has been lost after 6 months of treatment*".[2] A similar statement is included in the licences for liraglutide in obesity, which stipulates discontinuation after 12 weeks of maintenance treatment if patients have not recorded a weight reduction of at least 5%, exclusive of the titration periods (4-weeks titration for liraglutide).[140] For tirzepatide, primary treatment failure was also modelled as the anticipated marketing authorisation wording [redacted] No discontinuation was modelled for diet and exercise, in line with the approach taken in TA875.[2]

The proportion of patients discontinuing treatment due to primary treatment failure is detailed in Table 74. As discontinuation due to primary treatment failure was not a design feature of the SURMOUNT-1 trial, the proportion of patients achieving <5% body weight reduction at 72 weeks in the SURMOUNT-1 trial efficacy estimand analysis was applied at an earlier time point aligned with 6-months post reaching maintenance dose, as per the SmPC,[16] as a proxy for discontinuation due to primary treatment failure.

Table 74: Discontinuation due to primary treatment failure

Treatment	Primary treatment failure	Discontinuation time point (Weeks)	Source
Tirzepatide (5.0 mg)	9.65%	30.00	SURMOUNT-1 CSR[100]
Tirzepatide (10.0 mg)	3.77%	38.00	
Tirzepatide (15.0 mg)	3.74%	46.00	
Liraglutide (3.0 mg)	17.00%	16.00	TA875, Table 50[2]
Semaglutide (2.4 mg)	10.00%	26.00	Clinical opinion[131]

Abbreviations: CSR: clinical study report.

Efficacy following primary treatment failure

Patients who discontinued pharmacological treatment due to primary treatment failure were assumed to return to baseline levels at the point of discontinuation given the short duration for which they received treatment, and the lack of response experienced by patients. Once returned to baseline, as per discontinuation due to AEs or due to the SWMS limit, all surrogate endpoints remained constant throughout the time horizon except for BMI, which increased at a natural history of BMI progression.

B.3.3.3.3 *Discontinuation due to SWMS limit*

Finally, a 2-year maximum treatment duration is included in the model for semaglutide and liraglutide. This was included to reflect NICE recommendations which stipulate these treatments can only be provided in SWMS, which are provided for a maximum 2-year duration.[1, 2] However, based on initial top-line results from SURMOUNT-4 (Appendix M), discontinuation from tirzepatide would be expected to result in weight regain for many patients,[141] potentially limiting the long-term benefits of tirzepatide in reducing the impact of weight-related comorbidities and complications vs diet and exercise alone. Furthermore, as discussed in Section B.1.3.5, it is anticipated that tirzepatide will not be limited to SWMS to ensure access for more patients who would benefit from this treatment. As such, no stopping rule is included in the base case analysis for tirzepatide.

Efficacy post discontinuation due to the SWMS limit

The efficacy applied to patients after discontinuation of treatment due to the SWMS limit is as described for patients who discontinue due to adverse events (see Section B.3.3.3.1).

B.3.3.4 Mortality

Patient death was recorded as either a CV or non-CV death, dependent on whether the death is directly attributable to a modelled CVD event (stroke, MI or angina) or not. This allows death specifically caused by CV events (a potential downstream complication of obesity) to be compared between treatment arms. CV mortality occurs for a proportion of CV events, so is separate to general population mortality. Non-CV death is then calculated by considering general population mortality with CV death removed. A summary of the classification and calculation of mortality in the model is provided in Table 75, with further justification provided in the following sections.

Table 75: Summary of mortality

Comorbidity/event	Classification	Calculation of mortality
No CV events without T2DM	Non-CV	GPM excluding deaths related to CVD events, with a BMI-specific HR applied
Post-MI/angina	Non-CV	RR applied to baseline mortality (see above) to capture any additional mortality specific to patients who have experienced this complication
Post-stroke	Non-CV	
T2DM	Non-CV	HR applied to the patient's baseline mortality (see above) to capture any additional mortality specific to T2DM
NAFLD	Non-CV	HR applied to the patient's baseline mortality to capture any additional mortality specific to NAFLD
Stroke/MI	CV	A proportion of all events are modelled as 'fatal', based on the corresponding risk equations
OSA/knee osteoarthritis	N/A	No additional mortality is assumed to be associated with OSA and knee osteoarthritis,

Abbreviations: BMI: body mass index; CV: cardiovascular; GPM: general population mortality; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus.

B.3.3.4.1 *Non-CV death*

General mortality

General population mortality, defined as age and sex-specific all-cause mortality, was informed based on UK lifetables.[142] To avoid double-counting, general population mortality was adjusted by excluding the mortality of obesity-related comorbidities accounted elsewhere in the model (e.g. fatal CV events and T2DM); the number of these deaths was informed using UK life tables by mortality cause of death, using ICD-10 codes.[143] The general population mortality obtained with the approach described above was then applied to patients with no prior CV events and without T2DM.

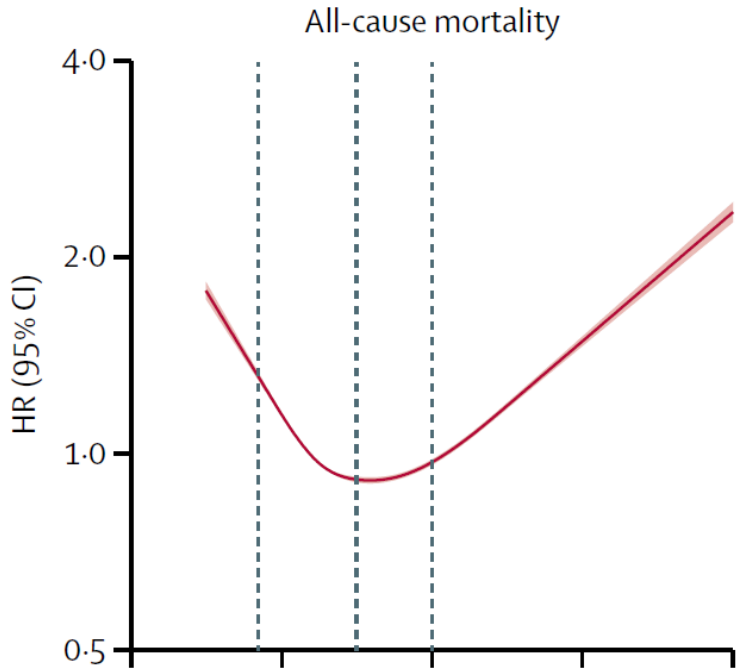
This implicitly assumes that the mortality of patients with obesity are equal to the general population, withstanding any additional impact of CVD and T2DM which is expected to underestimate true mortality, (i.e. disease-specific mortality), as clinical opinion suggests BMI has a direct impact on mortality, independent of these modelled comorbidities.[131]

In an attempt to address this, the cohort Markov model presented in TA875 adjusted baseline mortality rates for each health state by the patients' BMI to determine the disease specific mortality rate.[2] The associated all-cause mortality and BMI were obtained from Bhaskaran *et al.* 2018.[144] This was a refinement to the approach taken in TA664, which estimated a mortality lower than the validation data.[1] Therefore, to align with TA875 and to ensure the independent association of BMI on mortality is captured in the model, BMI-specific HRs were included in the base case. To ensure the mortality results were aligned with clinical expectation, the model mortality results (with and without this BMI-adjustment) were then discussed with an external expert clinician to ascertain whether general disease-mortality was being inappropriately estimated, and were deemed appropriate by the clinician consulted.[131]

Bhaskaran *et al.* 2018 is a population-based cohort study using UK Clinical Practice Research Datalink (CPRD) data with a sample of 1,969,648 people and 188,057 deaths, and a median follow-up of 11.6 years.[144] All-cause mortality, adjusted for age at BMI record, deprivation, calendar year, diabetes, alcohol status and smoking, were estimated and a Cox-regression

model was used to estimate the impact of BMI on all-cause mortality. This is shown in Figure 45 which was digitised to inform the model inputs.

Figure 45: Relationship between BMI and all-cause mortality[144]



Footnotes X-axis labels not shown however represent 5 10-unit increments of BMI starting at 10 kg/m^2 (at Y-axis intercept) up to 50 kg/m^2. Dashed lines represent BMI categories of less than 18.5 kg/m^2, 25 kg/m^2 and 30 kg/m^2.
Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio.

Patients with T2DM

Patients who developed T2DM have a HR for T2DM-related mortality applied to their baseline population mortality. A study by Mulnier *et al.* 2006 (also referenced in TA875) used the General Practice Research Database (GPRD) to identify a cohort of 44,230 patients aged 35–89 years of patients with T2DM; the cohort was followed from January 1992 until October 1999 and compared with a group of 219,797 people, matched by year of birth and sex with no record of diabetes at any time and without diabetes: the study found higher mortality in individuals with diabetes, and the HR for all-cause mortality in T2DM compared with no diabetes was 1.93.[145]

Patients with a history of CVD

Patients with a history of CVD (i.e. those who have previously experienced stroke and/or MI and/or angina) were subject to a higher mortality than those with no prior history of CVD events, with the application of a relative risk (RR) to baseline mortality (age- and sex-adjusted).

A RR=1.30 was applied for patients who experience prior MI or angina based on an SLR by Johansson *et al.* 2017 that reported on the mortality and morbidity of patients who have experienced an MI.[128]

In most instances, the inputs were aligned with TA875 and TA664.[1, 2] The exception for this is the increased mortality associated with patients who have had a stroke; prior TAs assumed this would be equal to patients who have experienced a stroke and ACS, however clinical opinion has indicated this would not be appropriate and patients who have experienced both events

would have a higher risk of mortality than patients who have had a stroke only.[131] This is also supported by the literature.[146 147]

The RR for patients who experience a stroke is therefore based on a Danish registry study of 4,162 patients who had had a stroke and were followed up for at least 5.5 years with the trial running from 1982 to 1991.[129] Although this source is outdated and a more recent input source would be desirable, none were identified. However, this input was found to have minimal impact on the incremental cost-effectiveness ratio (ICER) and so the source was deemed acceptable. Nevertheless, the Company has also provided a scenario in which the RRs for patients who experience a stroke are aligned with TA875 and TA664. Standardised mortality ratios (observed to expected number of deaths) used in the base case are reported based on patient age, sex and years since stroke, as summarised in Table 76.

Table 76: RR for patients with a stroke

Age group	Years after stroke	RR		Source
		Male	Female	
25–69 years	0–1	4.64 (3.71–5.72)	9.27 (6.94–12.1)	Brønnum-Hansen *et al.* (2001)[129]
	1–5	3.01 (2.63–3.43)	3.52 (2.80–4.35)	
	5–10	2.75 (2.39–3.15)	3.32 (2.66–4.09)	
	10–15	2.50 (1.94–3.18)	2.45 (1.60–3.59)	
≥70 years	0–1	3.70 (3.15–4.32)	5.18 (4.54–5.87)	
	1–5	1.92 (1.68–2.18)	2.05 (1.81–2.30)	
	5–10	1.89 (1.56–2.27)	1.99 (1.67–2.36)	
	10–15	2.49 (1.48–3.93)	1.67 (1.08–2.47)	

Abbreviations: RR: relative risk.

NAFLD

The Committee in TA875 noted that the long-term benefits of weight loss on reduced risk of liver disease had not been captured in the model.[2] Patients with NAFLD are at an increased risk of mortality relative to patients without. A nationwide, matched cohort study conducted amongst 10,568 biopsy-confirmed NAFLD patients in Sweden (from 1996 to 2017), with a median follow-up of 14.2 years found an increased risk of mortality relative to a population matched on age, sex, calendar year and county.[148] A mortality HR=1.93 (95% CI 1.86–2.00) was applied, based on Cox-regression analysis adjusting for baseline age, sex, country, calendar year, education level, CVD and metabolic syndrome (a composite categorical variable given for the presence/absence of diabetes, obesity, hypertension and/or dyslipidaemia).

Other events

It was conservatively assumed that other complications included in the model (bariatric surgery, OSA and knee osteoarthritis) are not associated with any additional impact on mortality. This is in contrast to the method taken in TA875 and TA664 which stipulated that 0.3% of all knee replacements were fatal and patients who received bariatric surgery were at an additional 0.07% risk of mortality (a value that is expected to be even smaller based on the NBSR).[1, 2, 132] Given the small proportion of events expected to be fatal, coupled with the number of assumptions required to derive this input and possibility of double-counting, this was excluded from the model.

B.3.3.4.2 *CV death*

In addition to a longer-term increased risk of mortality (i.e. the subsequent elevated risk of mortality among patients who have had a prior CVD event), CVD events are also associated with an 'acute' impact on mortality (i.e. fatal CVD events). It is assumed that only MI and stroke, but not angina, can be fatal. Fatal events incurred the corresponding cost and disutility (time-adjusted, as required) of that event, and were recorded as a 'CV-death' in the model.

The number of CVD-related deaths per cycle was directly calculated from the corresponding CVD risk equation, multiplied by the proportion of CVD events considered to be fatal. This was estimated based on case fatality rates observed for stroke and MI in the UK, stratified by age, in a retrospective study of hospitalisation data in England (Table 77 and Table 78).

It should be noted that TA875 and TA664 informed case fatality rates using statistics reported by the British Heart Foundation (BHF) in 2012;[149] the case fatality statistics reported in Table 77 and Table 78 are preferred since they include stratification by age. Furthermore, the case fatality for stroke events reported in Table 78 applies to all patients experiencing stroke events, rather than only patients hospitalised for stroke, as in the BHF dataset. However, the BHF-reported case fatality rates are provided in a scenario analysis. Notably, the sources for the case fatalities related to MI and stroke events are outdated and more recent input sources would be desirable, however these were not identified. Further, the inputs do not affect the model results and so the dates were deemed acceptable.

Table 77: Case fatality for MI events

Age (years)	Probability of fatality (male)	Probability of fatality (female)	Source
30–54	13.8%	13.3%	30-day case fatalities for MI in England in 2010, Smolina *et al.* (2012)[150]
55–64	14.2%	17.4%	
65–74	19.5%	25.3%	
75–84	28.0%	35.8%	
≥85	37.9%	45.7%	

Abbreviations: MI: myocardial infarction.

Table 78: Case fatality for stroke events

Age (years)	Probability of fatality (male)	Probability of fatality (female)	Source
20–34	11.2%	9.3%	30-day case fatalities for stroke in England in 2010, Seminog *et al.* 2019[151]
35–54	11.5%	11.4%	
55–64	12.5%	15.0%	
65–74	17.1%	18.0%	
75–84	23.4%	25.9%	
≥85	34.3%	38.3%	

B.3.3.5 Risk equations

As outlined previously, risk equations were used to estimate the incidence of clinical events and complications of obesity. Relevant risk equations were identified through the economic SLR (Appendix G), and review of risk equations used in TA664 and TA875.[1, 2] A summary of the risk equations used in the model is provided in Table 79 and Table 80, including a justification for the

risk equations used in the base case analysis. Further justification for and an explanation of the implementation of risk equations is then provided in the following sections for OSA, knee osteoarthritis and NAFLD and in Appendix N for all other events/complications. As detailed in Table 79, the majority of sources of risk equations used in the base case analysis were aligned with those used in TA664 and TA875.[1, 2]

Each risk equation estimates the risk of the event occurrence over a specific time frame; often aligned with that in the source publication. This is converted to align with the cycle length in the base case using the following formula:

$$Risk\ per\ cycle = 1 - (1 - Probability_{t_0})^{t_1/t_0}$$

Where: t_0 = reported time frame (e.g. 10 years) and t_1 = time frame of the model cycle length (e.g. 1 year)

Inputs for the risk equations depend on patient comorbidities/clinical events and surrogate endpoints for which values were tracked for the patient cohort over time (e.g. BMI, SBP). For variables which were not tracked over time, either for variables which were not expected to change over time (e.g. sex, smoking status), or for which time-varying data were not available (e.g. treatment for hypertension), the input value was held constant over the full time horizon of the model.

Table 79: Summary of sources for risk equations

Population	Event/complication	Source	Base case source in previous TAs	Justification for base case selection
Patients without T2DM	Development of T2DM	**Base case:** Hippisley-Cox *et al.* 2017a (QDiabetes)[152] **Scenario:** Wilson *et al.* 2007 (Framingham Offspring Study)	**TA875 and TA664:** Hippisley-Cox *et al.* 2017a (QDiabetes)[152] (aligned)	In addition to being aligned with both TA875 and TA664, this source was considered more suitable for use in the base case as it has been externally validated, had a larger patient cohort than the Framingham Offspring Study and has been widely used in the UK, given this study was conducted in England (whereas the Framingham Heart Study was based in the US).
	CVD (stroke, MI and angina): Initial	**Base case:** Hippisley-Cox *et al.* 2017b (QRisk3)[153] **Scenario:** D'Agostino *et al.* 2008 (Framingham Heart Study)[154]	**TA875 and TA664:** Hippisley-Cox *et al.* 2017b (QRisk3)[153] (aligned)	Similarly to the QDiabetes risk equations for T2DM, the use of the QRISK3 risk equation in the base case is aligned with both TA875 and TA664 and this source has been externally validated, had a larger patient cohort than the Framingham Heart Study and has been widely used in the UK since this study was conducted in England (whereas the Framingham Heart Study was based in the US).
	CVD (stroke, MI and angina): Recurrent	**Base case:** D'Agostino *et al.* 2000 (Framingham Heart Study)[155] **Scenario:** Cui *et al.* 2009 (LIPID Study)	**TA875 and TA664:** D'Agostino *et al.* 2000 (Framingham Heart Study)[155] (aligned)	This risk equation was chosen for the base case as it is considered robust and is widely used. This risk equation also explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It also included a larger patient cohort compared with the LIPID study, and has previously been used and accepted in prior TAs for obesity. Although it was developed specifically in a US context, no suitable alternative in a UK context were identified.
Patients with T2DM	CVD (stroke, MI and angina): Initial	Hayes *et al.* 2013 (UKPDS82)[156]	**TA875 and TA664:** Hayes *et al.* 2013 (UKPDS82)[156] (aligned)	This risk equation was chosen for the base case since it explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It has also been externally validated, is widely used in the UK and is aligned with both TA875 and TA664.
	CVD (stroke, MI and angina): Recurrent			
All patients	Knee replacement	Wendelboe *et al.* 2003[157]	**TA875 and TA664:** Wendelboe *et al.* 2003[157] (aligned)	This study was chosen as no appropriate alternative risk equations were identified. It was also used in the base case of the models presented in TA664 and TA875, and

				was deemed appropriate by the Committee in these appraisals.
	OSA	Erridge *et al.* 2021[158]	**TA875 and TA664:** Young *et al.* 2002 (Sleep Heart Study)[159] (not aligned)	Erridge et al, 2021 is a UK study which included 276,600 patients with obesity (BMI ≥30 kg/m^2) identified during a data extraction of the CPRD in 2017, with median follow-up of 147.0 months.[158] This source was preferred compared to the study used in TA664 and TA875 (Young *et al.* 2002) due to its larger sample size, UK population, recency, and the granularity of the BMI covariate, in particular between 30 and 40 BMI kg/m^2 where the majority of the patient population is expected to be upon entering the model.[1, 2, 159]
	NAFLD	Loomis *et al.* 2016[160]	N/A – not included in previous appraisals (and noted by the Committee in TA875 as an omission of benefit)[2]	The incidence rate for patients in the model developing NAFLD are based on a study by Loomis *et al.* 2016, a retrospective population-based longitudinal cohort study conducted using The Health Improvement Network (THIN) database in the UK.[160] Loomis *et al.* fitted Cox proportional hazard models to a cohort of 1,133,525 patients (followed up for a median of 4.96 years) to derive hazard ratios (HRs) based on BMI category, sex and diabetes status. The patient data used were collected between 2007 and 2013. Although no internal or external validation was conducted to assess the discrimination or calibration of the models, no suitable alternative sources were identified.

Abbreviations: CVD: cardiovascular disease; CPRD: Clinical Practice Research Datalink; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus; UKPDS: United Kingdom prospective diabetes study.

Table 80. Summary of risk equation characteristics

Risk Equation	Year of study	Time of data collection	Size of patient cohort	Study location	Source of data
QDiabetes[152] (Development of T2DM)	2017	2005–2016	8,186,705 (derivation), 2,629,940 (validation)	England	QRearch data from 1,457 general practices
Framingham Offspring Study[161] (Development of T2DM)	2007	1991–2001	3,140	US	Patients attending fifth clinic examination of the Framingham Offspring Study without existing T2DM
QRISK3[153] (Initial CVD in people without T2DM)	2017	1998–2015	7,889,803 (derivation), 2,671,298 (validation)	England	QRESEARCH data from 1,309 general practices
Framingham Heart Study[154] (Initial CVD in people without T2DM)	2008	1968–1987	8,491	US	Framingham Study participants without existing CVD
Framingham Heart Study [155] (recurrent CVD in people without T2DM)	2000	1968–1979	10,156	US	Patients from the Framingham Heart Study and Framingham Offspring Study with at least one prior CHD event or stroke
LIPID Study[162] (recurrent CVD in people without T2DM)	2009	1990–1997	5,654 (derivation), 2,903 (validation)	Australia (derivation), New Zealand (validation)	Patients recruited to the LIPID RCT for pravastatin
UKPDS82[156] (Initial and recurrent CVD in people with T2DM)	2013	1977–1997	5,102	UK	Patients enrolled in the UKPDS Study
Wendelboe *et al.*[157] (Knee replacement)	2003	1992–2000	1,764	US	
Erridge *et al.*[158] (OSA)	2021	Data extracted 2017; time frame of data collection not reported	276,600	UK	CPRD database
Loomis *et al.*[160] (NAFLD)	2016	2007–2013	1,133,525	UK	THIN database

Footnotes: Emboldening indicates the risk equations used in the base case analysis.

Abbreviations: CVD: cardiovascular disease; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus; UKPDS: United Kingdom prospective diabetes study.

B.3.3.5.1 *OSA*

The probability of developing OSA is based on a study by Erridge *et al.* 2021, which used logistic regression model to calculate odds ratios for developing OSA according to other patient characteristics. The UK study included 276,600 patients with obesity (BMI ≥30 kg/m^2) identified during a data extraction of the CPRD in 2017, with median follow-up of 147.0 months (the time period over which data were collected is not reported).[158] This source was preferred compared to the study used in TA664 and TA875 (Young *et al.* 2002) due to its larger sample size, UK population, recency, and the granularity of the BMI covariate, in particular between 30 and 40 BMI kg/m^2 where the majority of the patient population is expected to be upon entering the model.[1, 2, 159]

The multivariate logistic regression included 14 risk factors that were significantly and independently associated with the development of OSA. The odds ratios from the multivariate analysis derived in the study are shown in Table 81. These ORs are applied to the baseline incidence of OSA, which is assumed to have a 5-year incidence of 7.5% based on Tishler *et al.* 2003.[163]

Table 81: OSA risk factors by Erridge *et al.* 2021[158]

Variable	Type	Range/Categories	OR (95% CI)
Age	Categorical	<60 ≥60	Reference 0.932 (0.896–0.969)
Sex	Categorical	Female Male	Reference 3.273 (3.154–3.396)
T2DM	Categorical	Absent Present	Reference 1.343 (1.292–1.395)
BMI	Categorical	30–35 BMI kg/m^2 35–40 BMI kg/m^2 >40 BMI kg/m^2	Reference 1.640 (1.556–1.739) 3.768 (3.539–3.955)
Hypertension	Categorical	Absent Present	Reference 1.174 (1.130–1.220)
Hyperlipidaemia*	Categorical	Absent Present	Reference 1.157 (1.099–1.219)
Smoking status*	Categorical	Non-smoker Smoker	Reference 1.179 (1.138–1.223)
COPD	Categorical	No diagnosis Positive diagnosis	Reference 1.722 (1.622–1.828)
GERD*	Categorical	No diagnosis Positive diagnosis	Reference 1.557 (1.493–1.625)
Chronic renal disease*	Categorical	No diagnosis Positive diagnosis	Reference 1.088 (0.972–1.217)
Hypothyroidism*	Categorical	No diagnosis Positive diagnosis	Reference 1.311 (1.239–1.387)
Acromegaly	Categorical	No diagnosis Positive diagnosis	Reference 3.543 (2.108–5.956)

Benzodiazepines*	Categorical	Not prescribed Prescribed	Reference 1.492 (1.439–1.548)
Bariatric surgery†	Categorical	No surgery Surgery	Reference 0.260 (0.199–0.340)

Footnote: *Variable not reported in SURMOUNT-1 and is assumed equal to the average cohort baseline value from the suggested source given in Appendix N.1 † Variable tracked over modelled time horizon.
Abbreviations: BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; OR: odds ratio; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus.

B.3.3.5.2 *Knee replacement*

The risk equation for estimating the incidence of knee replacements (e.g. as a result of osteoarthritis) was derived from Wendelboe *et al.* 2003, a US case-control study which investigated the relationship between BMI and surgical replacements of knee and hip joints by fitting a logistic regression model to observed data; it included 1,764 knee procedures (based on ICD-9 codes 81.45–55) between 1992 and 2000, and provided OR estimates by 5-unit BMI categories up to 40kg/m^2.[157] It should be noted that no internal or external validation was conducted to assess the discrimination or calibration of the model.

This study was chosen as no appropriate alternative risk equations were identified. It was also used in the base case of the models presented in TA664 and TA875, and was deemed appropriate by the Committee members of these appraisals.[1, 2] However, in order to generate ORs with a finer precision based on BMI, a regression analysis was reported in TA875 and TA664, to convert BMI from a categorical to a continuous covariate in the logistic regression model.[1, 2] Since details of this analysis were not available, a similar analysis was independently re-run. Linear models including linear and quadratic terms for BMI, as well as adjustment for sex, were fitted to the ORs reported by Wendelboe *et al.* A weighted analysis was conducted as weights could be derived from reported sample sizes and 95% CIs. The quadratic model for BMI without adjustment for sex was found to provide the best fit for the data based on the Akaike information criterion (AIC); the resulting model is as follows:

$$OR = 2.9174 + 0.5004(BMI - 28.12) + 0.0311((BMI - 28.12)^2)$$

The baseline risk of having a knee replacement is derived from the population-based incidence reported in the publication (Table 82). For each patient, the annual probability of requiring a knee replacement is calculated by applying the ORs obtained from the regression analysis described above to the baseline risk in the relevant age category.

Table 82: Population-based incidence of knee replacements

Age Category	Incidence Rate/100,000 Person Years	Source
<65 Years	53.52	Wendelboe *et al.* 2003[157]
≥65 Years	120.22	

B.3.3.5.3 *NAFLD*

The incidence rate for patients in the model developing NAFLD are based on a study by Loomis *et al.* 2016, a retrospective population-based longitudinal cohort study conducted using The Health Improvement Network (THIN) database in the UK.[160] Loomis *et al.* fitted Cox proportional hazard models to a cohort of 1,133,525 patients (followed up for a median of 4.96 years) to

derive hazard ratios (HRs) based on BMI category, sex and diabetes status. The patient data used were collected between 2007 and 2013.

Diabetes status is included as a covariate in this risk equation, and was considered to be inclusive of Type 1 and Type 2; however, Loomis *et al.* estimated that ~90% of cases are Type 2. It should be noted that no internal or external validation was conducted to assess the discrimination or calibration of the models.

The HRs for BMI reported in Loomis *et al.* 2016 are only reported in 2.5-unit increments; given that BMI is a major driver of the cost-effectiveness model, a regression analysis was conducted on the reported HRs to convert BMI from a categorical to a continuous variable in the Cox proportional hazard model.[164] Linear regression models with linear and quadratic terms for BMI, as well as interactions with sex and T2DM status, were fitted to the HRs reported in Loomis *et al.* 2016. The quadratic model adjusted for T2DM was found to have a strong predictability for resultant HRs. The resultant HRs are summarised in Table 83.

These are applied to a baseline incidence of the reference group's incidence rate of NAFLD, assumed to be 0.12 per 1,000 person-years, sourced from Vusirikala *et al.* 2020.[165] Vusirikala *et al.* 2020 is a THIN data base study that reports on the relation between BMI status and the incidence of NAFLD. Loomis *et al.* 2016 was used instead of Vusirikala *et al.* 2020 due to the wider range of BMI values supported (15–60 versus 18.5–30), more granular BMI categories (2.5-unit increments versus 5 unit increments) and direct reporting of HRs based on the presence or absence of diabetes, opposed to metabolic health status (a composite variable of diabetes, dyslipidaemia and hypertension).[160] However, Vusirikala *et al.* 2020 is a more recent and larger (4,121,049 patients) study, which reports baseline incidence rates and is therefore used in conjunction with the results from Loomis *et al.* 2016 to inform the resultant incidence rate of NAFLD.[160, 165]

Table 83: Incidence of onset of NAFLD

T2DM Category	HR Regression Equation	Source
With T2DM	$12.8599 + 0.9783(BMI - 26.81) - 0.0213((BMI - 26.81)^2)$	Original HRs sourced from Loomis *et al.* 2016
Without T2DM	$5.7689 + 0.9783(BMI - 26.81) - 0.0213((BMI - 26.81)^2)$	

Abbreviations: BMI: body mass index; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; T2DM: type 2 diabetes mellitus.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

SURMOUNT-1 assessed HRQoL via two distinct measures: Short Form Survey-36 Version 2 (SF-36v2) and the Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT), at baseline and again at Week 72.[3] However, given the misalignment with the NICE reference case to derive utility values, data from the literature were used instead, as detailed in Section B.3.4.3.

B.3.4.2 Mapping

No mapping techniques were employed as part of the present analyses.

B.3.4.3 Health-related quality-of-life studies

As described in Section B.3.1, an SLR was conducted to identify cost-effectiveness evidence associated with tirzepatide and relevant comparators for people with obesity or overweight.

A total of 1,867 records were retrieved, of which 135 were duplicates, resulting in 1,732 novel records that were screened at the title/abstract review stage. Subsequently, 70 publications were screened against the cost-effectiveness eligibility criteria (Table 4) at full-text review. Following this, 59 publications were excluded. This resulted in 11 articles included from the electronic database searches. Utility values used in the model are described in Section B.3.4.5.

B.3.4.4 Adverse reactions

Data from SURMOUNT-1 indicated there is no single serious adverse event (SAE) of Grade 3 or 4 which would meet common inclusion criteria (e.g. ≥2 or 5% in any treatment arm). As such, gastrointestinal (GI) events are grouped together, as these are the most relevant for inclusion. The GI AEs included are detailed in Table 84 for each treatment in the base case, where annual probabilities have been calculated based on length of follow-up (as reported in Section B.3.3.1).

Table 84: Severe or serious GIs* for inclusion in the economic model

Treatment	Annual probability	Source
Tirzepatide (5.0 mg)	1.23%	SURMOUNT-1 CSR[100]
Tirzepatide (10.0 mg)	2.26%	
Tirzepatide (15.0 mg)	2.40%	
Diet & Exercise	0.80%	Jastreboff *et al.* 2022[3]
Semaglutide (2.4 mg)	4.90%	TA875 (Table 24 Company Submission; STEP 1 trial)[2]
Liraglutide (3.0 mg)	7.10%	TA875 (Table 24 Company submission; SCALE trial)[2]

Footnote: *GI disorders included are source dependent however include nausea, diarrhoea and constipation as the most common. † Values refer to annual probabilities.
Abbreviations: GI: gastrointestinal; TA: technology appraisal.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The model incorporates utility values determined by sex, age and BMI as well as long-term and short-term disutilities for clinical events and AEs. The model does not additionally incorporate any treatment-specific differentiation of HRQoL; however, this was implicitly captured by the incidence of events, changes in BMI and AEs.

B.3.4.5.1 *Baseline utilities*

The baseline utility values for patients are aligned with TA875 and TA664.[1, 2] For patients with BMI ≤35 kg/m^2, sex-, age- and BMI-dependent utility values were sourced from Søltoft *et al.* 2009, a study which analysed EuroQol-5 Dimension (EQ-5D) responses of 14,416 adults from the Health Survey for England.[1, 2, 125] Utility values by sex were fitted to polynomial models with age and BMI as covariates.

The coefficients for deriving EQ-5D utilities by BMI and age for patients with a BMI ≤35kg/m^2 are as reported in TA664. It was noted in TA664 that the reporting of the coefficients to four decimal places by Søltoft *et al.* 2009 lacks sufficient precision to generate plausible utility values; therefore, the coefficients were re-derived to a higher precision based on digitised values from a figure in the original publication (Figure 46).[1, 125]

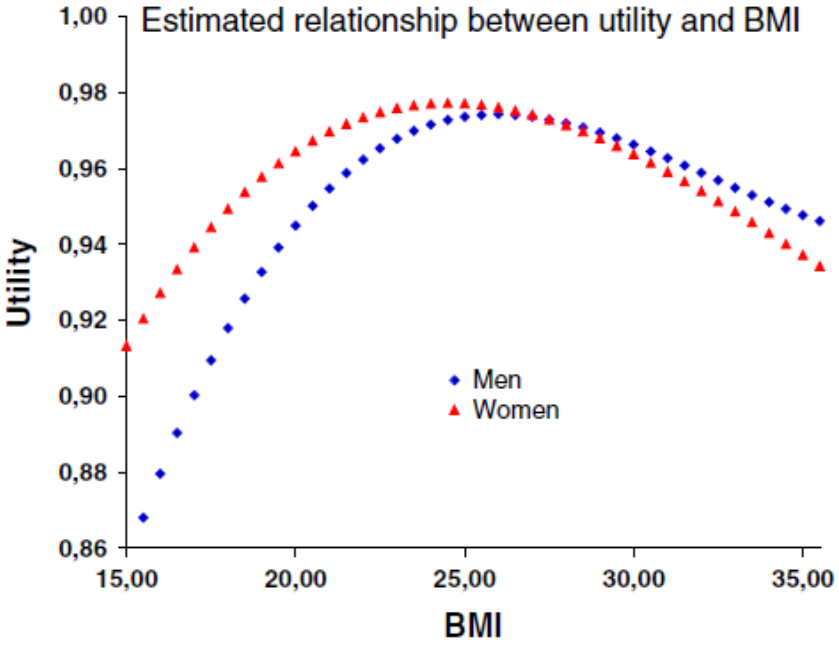
In line with TA664 and TA875, a logarithmic function was used to derive utility values for patients with a BMI >35kg/m^2, as Søltoft *et al.* 2009 only reported the function up to a BMI of 35kg/m^2, and HRQoL appeared to be linearly declining from a BMI of ~25kg/m^2 (Figure 46).

Table 85: Function for deriving EQ-5D by BMI

Parameter	BMI 15–35kg/m^2 Mean (SE)		BMI >35kg/m^2 Mean (SE)		Source
	Male	Female	Male	Female	
Age 25–35	Reference	Reference	As per the coefficients reported for patients with a BMI 15–35kg/m^2, assuming the relationship between age and EQ-5D does not differ between these groups of patients		Søltoft *et al.* 2009 with additional precision for BMI from TA664 (Table 35 CS)[1, 125]
Age 35–44	−0.0028 (0.0064)	−0.0213 (0.0059)			
Age 45–54	−0.0081 (0.0071)	−0.0336 (0.0068)			
Age 55–64	−0.0430 (0.0077)	−0.0425 (0.0072)			
Age 65–74	−0.0223 (0.0089)	−0.0619 (0.0092)			
Age 75–100	−0.0565 (0.0121)	−0.0754 (0.0014)			
BMI^3	0.000033 (0.000)	0.00017 (0.0000)	-	-	
BMI^2	−0.0032 (0.0009)	−0.0018 (0.0006)	-	-	
BMI	0.0990 (0.0265)	0.0572 (0.0183)	−0.105431 (NR)	−0.147297 (NR)	
Intercept	−0.0228 (0.2575)	0.4010 (0.1786)	1.323834 (NR)	1.462846 (NR)	

Abbreviations: BMI: body mass index; EQ-5D: EuroQol-5 Dimension; NR: not reported; SE: standard error.

Figure 46: Relationship between EQ-5D and BMI, as reported in Søltoft et al. 2009[125]



Abbreviations: BMI: body mass index; EQ-5D: EuroQol-5 Dimension.

B.3.4.5.2 *Clinical comorbidity and event disutilities*

Disutilities were applied to the baseline utility values for long-term and acute obesity-related complications. Where possible, disutilities were derived from the same regression analysis described above (Søltoft *et al.* 2009); where this was not possible, disutilities were sourced from Sullivan *et al.* 2011, a UK-based catalogue of EQ-5D index scores covering a range of health conditions based on UK preferences, derived from a sample of 79,522 individuals.[166] Sullivan *et al.* 2011 calculates the condition-specific utility decrement for each event, using regression methods to control for covariates; conditions were defined using International Classification of Diseases (ICD)-9 and complex chronic conditions (CCC) codes. Sullivan *et al.* 2011 was also utilised in TA664 and TA875.[1, 2]

Both long-term and event disutilities were implemented using an additive approach, whereby the HRQoL decrement associated with each single comorbidity or event was summed together and the total is then subtracted from the baseline utility. This approach is aligned with that critiqued and accepted in TA875 and TA664.[1, 2] In TA875 Southampton Health Technology Assessments Centre (SHTAC), acting as evidence review group (ERG), noted "*that Gough et al. concluded that HRQoL decrements associated with T2D and obesity showed no significant interaction and thus could be assumed to be additive*."[2, 67] Further, SHTAC concluded that, despite NICE TSD12 suggesting that a multiplicative approach to combining multiple comorbidities is generally preferred (which statement is now included in the NICE Evaluations Manual January 2022), "*from studies that have reported multiple co-morbidities for diabetes, we agree with the company and consider it is reasonable to treat co-morbidities as independent and add utility decrements*".[123, 166, 167] Nevertheless, a multiplicative approach is explored in scenario analyses in the model.

Long-term disutilities

Patients who developed diabetes, experienced a stroke or had an MI had an ongoing disutility applied to their baseline utility value, after the complication had developed (diabetes or angina)

or occurred (stroke/MI). The decrements applied every cycle after a patient had experienced a relevant event are summarised in Table 86. The T2DM disutility was applied to all patients who have experienced onset of T2DM; in the event that a patient has experienced multiple prior events with associated long-term disutilities (e.g. both onset of T2DM and prior CVD event), disutilities were applied in an additive manner to the baseline utility value.

Table 86: Disutilities applied for comorbidities

Health State	Mean (SE)	Source	Justification
T2DM	Male: −0.0528 (0.0145) Female: −0.0325 (0.0183)	Søltoft *et al.* 2009; weighted average of male and females to be applied based on modelled population[125]	Aligned with TA875 and TA664 since no alternative appropriate sources were identified.[1, 2]
Post MI/with angina	−0.037 (0.026)	Sullivan *et al.* 2011[166]	Aligned with the source used in TA875 and TA664 and is widely used and validated as a source for UK-specific utility values.
Post stroke	−0.035 (0.021)		

Abbreviations: AE: adverse event; SE: standard error; T2DM: type 2 diabetes mellitus.

Event disutilities

Patients who experienced acute events, such as a stroke, incurred a one-off utility decrement applied in the same cycle as the event incidence. The following should be noted:

- The disutility for OSA and NAFLD, which are not acute events, were applied to patients affected by OSA and NAFLD in any cycle on a per cycle basis (in line with TA664 and TA875)[1, 2]
- The disutility associated with a knee replacement was derived from severe musculoskeletal disorders, and recommended to be multiplied by a factor of three to reflect three years of living with a debilitating condition before receiving surgery. This is in line with TA664 and TA875, and was supported by clinical opinion as an appropriate time frame between development of condition and receiving surgery (and hence living with the impairment).[1, 2, 131]
- As no granular data on disutilities related to particular types of bariatric procedures were identified, a single one-off disutility was applied, in line with TA664 and TA875[1, 2]

It should be noted that the disutility for stroke is derived from Sullivan *et al.* 2011 as per TA664 and TA875, however the specified value differs; its value is based on the ICD-9 codes for acute cerebrovascular disease which is used by the author of the paper to reflect stroke. The stroke disutility from prior TAs (-0.1171) was based on ICD-9 436, which is acute, but ill-defined, cerebrovascular disease which explicitly excludes stroke. The disutility for NAFLD is derived from Sullivan *et al.* 2011 based on the ICD-9 code for other disorders of the liver; this was chosen as the most reasonable proxy for NAFLD as no other clinical events related to the liver were available.

Table 87: Disutilities applied to events

Event	Type of Disutility	Mean (SE)	Source
Knee replacement	One-off	Male: −0.1721 (0.0078)	

		Female: −0.2014 (0.0074)	Søltoft *et al.* 2009; Musculoskeletal problems assumed reflective of knee replacement[125]
OSA	Annual	Male: −0.0242 (0.0084) Female: −0.0430 (0.0097)	
MI/angina	One-off	−0.06257 (0.01317)	Sullivan *et al.* 2011[166] – ICD-9 Code 410 (acute MI), 433 (acute cerebrovascular disease)* and 573 (other disorders of the liver)†
Stroke	One-off	−0.0349 (0.02126)	
NAFLD	Annual	−0.09558 (0.03123)	
Bariatric surgery	One-off	−0.22 (−)	Campbell *et al.* 2010 as per Kim *et al.* 2022[126, 127]

Footnote: * Please note the disutility for stroke is derived from Sullivan *et al.* 2011 as per TA664 and TA875, however the specified value differs; its value is based on the ICD-9 codes for acute cerebrovascular disease which is used by the author of the paper to reflect stroke. The stroke disutility from prior TAs (-0.1171) was based on ICD-9 436, which is acute, but ill-defined, cerebrovascular disease which explicitly excludes stroke. † The disutility for NAFLD is derived from Sullivan *et al.* 2011 based on the ICD-9 code for other disorders of the liver; this was chosen as the most reasonable proxy for NAFLD as no other clinical events related to the liver were available.
Abbreviations: MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; SE: standard error; TA: technology appraisal.

B.3.4.5.3 *AE disutilities*

Disutilities associated with the experience of severe GI events were based on the decrement for nausea and vomiting from Matza *et al.* 2007.[168] This is aligned with the source used for severe GI events for the NICE appraisal for tirzepatide in T2DM. Matza *et al.* 2007 aimed to elicit utility values (based on health state descriptions) of diabetes medication-related attributes that may influence patient preference, including GI side effects. The isolated incidence of experiencing nausea and vomiting is estimated at −0.04802 and was applied per incidence of AE. Aligned with the approach for clinical comorbidity and event disutilities, AE disutilities were applied additively in the base case; this same approach was also taken for TA875 and TA664.[1, 2]

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

The model includes the following costs:

- Treatment acquisition and administration costs
- Monitoring and resource use costs
- Clinical event costs
- AE management costs

Costs were sourced from the 2020/21 National Schedule of Reference costs, 2021 Personal Social Services and Research Unit (PSSRU) unit costs, British National Formulary (BNF) and the 2022 electronic market information tool (eMIT) in England. If applicable, costs were inflated to the latest cost year using the NHS cost inflation index (NHSCII).

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 *Acquisition costs*

Drug acquisition costs were based on the recommended dosing of drugs from the MHRA-approved prescribing information (e.g. fixed-dose, based on mean patient-weight, or based on average body surface area) as given by the relevant SmPC. The total treatment cost per cycle is calculated by multiplying the cost per mg by the dose in mg required in a given cycle. The dosing regimen for tirzepatide was based on the anticipated licensing for this indication, as per the SURMOUNT-1 trial.[3] The dosing regimens for tirzepatide and the comparators are provided in Table 88.

Unit cost per pack were derived from publicly available databases (e.g. BNF/eMIT). If more than one treatment formulation with similar strength was available, the conservative assumption of selecting the lowest priced treatment was used to provide cost. Drug wastage was considered in the model. The drug pack acquisition costs are displayed in Table 89.

Table 88: Dosing regimens for relevant treatments

Drug	Titration dose	Maintenance dose	Source
Tirzepatide (5.0 mg)	4-week period; dose initiation at 2.5 mg QW	5 mg QW SC	SURMOUNT-1[3]
Tirzepatide (10.0 mg)	12-week period; dose initiation at 2.5 mg QW, increased by 2.5 mg Q4W	10 mg QW SC	
Tirzepatide (15.0 mg)	20-week period; dose initiation of 2.5 mg QW, increased by 2.5 mg Q4W	15 mg QW SC	
Semaglutide (2.4 mg)	16-week period; QW SC Week 1–4: 0.25 mg Week 5–8: 0.5 mg Week 9–12: 1.0 mg Week 13–16: 1.7 mg	2.4 mg QW SC	Wegovy SmPC; stopping in line with NICE TA875[2, 104]
Liraglutide (3.0 mg)	4-week period; dose initiation of 0.6 mg QD, increased by 0.6 mg QW up to 2.4 mg QD SC	3.0 mg QD SC	Saxenda SmPC; stopping in line with NICE TA664[1, 105]
Diet and exercise	N/A	N/A	N/A

Abbreviations: CG: clinical guideline; N/A: not applicable; NICE: National Institute of Health and Care Excellence; QD: once daily; QW: once weekly; SmPC: summary of product characteristics; SoC: standard of care; SC: subcutaneously; TA: technology appraisal.

Table 89: Drug pack acquisition costs

Drug (Dose)	Regimen	Pack cost	Doses per pack	Cost per week	Source
Tirzepatide (2.5 mg)	Weekly, SC	[redacted]	4	[redacted]	Eli Lilly Data on File
Tirzepatide (5.0 mg)	Weekly, SC	[redacted]	4	[redacted]	
Tirzepatide (7.5 mg)	Weekly, SC	[redacted]	4	[redacted]	
Tirzepatide (10.0 mg)	Weekly, SC	[redacted]	4	[redacted]	
Tirzepatide (12.5 mg)	Weekly, SC	[redacted]	4	[redacted]	
Tirzepatide (15.0 mg)	Weekly, SC	[redacted]	4	[redacted]	
Semaglutide (0.25 mg)	Weekly, SC	£73.25	4	£18.31	TA875,[2] combined with an assumption: Semaglutide 1.7 mg and 2.4 mg have not been launched and therefore no price is available on the BNF. Note that TA875 discloses prices for 0.25 mg, 0.5 mg and 1.0 mg doses, however, the cost of the 1.7 mg and 2.4 mg doses were redacted in TA875, and therefore the disclosed cost for the lower doses was used
Semaglutide (0.5 mg)	Weekly, SC	£73.25	4	£18.31	
Semaglutide (1.0 mg)	Weekly, SC	£73.25	4	£18.31	
Semaglutide (1.7 mg)	Weekly, SC	£73.25	4	£18.31	
Semaglutide (2.4 mg)	Weekly, SC	£73.25	4	£18.31	
Liraglutide (0.6 mg)	Daily, SC	£196.20	150	£9.16	BNF 2023[169] NB: dose-adjustable pen contains 18 mg liraglutide, capable of administering a variable number of doses, dependent on the dose level chosen; price for a pack of 5 x 18 mg pens During the titration phase 42mg of liraglutide is used to titrate to 3.0mg daily over a 4 week period costing £91.56
Liraglutide (1.2 mg)	Daily, SC		75	£18.31	
Liraglutide (1.8 mg)	Daily, SC		50	£27.47	
Liraglutide (2.4 mg)	Daily, SC		37.5	£36.62	
Liraglutide (3.0 mg)	Daily, SC		30	£45.78	
Orlistat (120 mg)	Daily, oral	£22.65		£5.66	eMIT 2022[170]

Abbreviations: BNF: British national formulary; eMIT: electronic market information tool; SC: subcutaneously.

B.3.5.1.2 *Administration costs*

The unit costs of administration are shown below in Table 90. Semaglutide and liraglutide are self-administered subcutaneously; both treatments are supplied as pre-filled disposable injection pens and therefore it can be assumed there is no additive cost of the SC injection itself.[46] Tirzepatide is self-administered subcutaneously through a pre-filled disposable injection pen.

SC injections were assumed to be self-administered and therefore incur no costs (in line with TA875 and TA664), beside two initial training sessions (20 minutes each), which were assumed to be administered by a nurse, aligned with the approach taken for the NICE submission for tirzepatide in T2DM.[1, 2]

Table 90: Treatment administration unit costs

Administration method	Unit cost	Source
First SC injection	£24.00*	Hospital based nurse, Band 4. PSSRU 2021; 2 x 20 minute trainings[171]
Subsequent SC injection pen (self-administration)	£0.00	Assumption

Footnote: *This is based on the cost of a nurse being £32/hour and two 20-minute appointments in line with the approach taken for the NICE appraisal for tirzepatide in T2DM (ID3938).
Abbreviations: PSSRU: personal social services research unit; SC: subcutaneous.

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 *Background resource use*

Background disease-related resource use in the model encompasses general practitioner (GP) visits, nurse visits and blood tests. The input values for the frequency of resource use in each category are based on Ara *et al.* 2012, a National Institute for Health and Care Research (NIHR) technology assessment of use of drugs for treating patients with obesity in primary care.[124] Resource use is applied irrespective of treatment and for the full time horizon of the model. This approach is consistent with the approach used in TA875 and TA664.[1, 2] The incidence of resource use for each category is summarised in Table 91.

It should be noted that clinician expert opinion highlighted that the reported resource use in Ara *et al.* 2012 was lower than expected and that resource use would vary by BMI independently of comorbidities. Targeted searches were therefore conducted to identify an alternative source based on BMI. The only appropriate alternative source identified was Le Roux *et al.* 2021, a retrospective, observational database study in the UK was considered, including 1,600,709 patients, considering the effect of obesity (by BMI category) and cardiovascular risk status on healthcare resource use.[172] However, the number of GP contacts reported by Le Roux *et al.* was considered to lack face validity and was difficult to quantify from a cost perspective. This was because patients were found to have at least 30 GP contacts per year, and 'contact' was a broader definition which included physical, phone/email and administrative contact. Therefore, the resource use estimates from Ara *et al.* 2012 were retained for the model base case, in line with TA875.[2]

The costs for each resource use are also summarised in Table 91. GP and nurse visits are assumed to last for 10 minutes, with a pro-rata hourly cost derived from the PSSRU. Blood test costs are derived from the NHS reference costs.

Table 91: Annual HCRU for obesity

Category	Quantity per year	Unit cost	Annual cost	Source
GP visits*	4	£232/hour	£154.67	Quantity per year: Ara *et al.* 2012 Cost of GP visit: GP - Unit costs (including direct care). PSSRU 2022[171] Cost of nurse visit: Band 6 Nurse. PSSRU 2022[171] Cost of blood tests : DAPS05, NHS Reference Costs 2021/2022[173]
Nurse visits*	8	£57/hour	£76.00	
Blood tests	1	£2.96	£2.96	

Footnote: *Assumed 10-minute duration.
Abbreviations: BMI: body mass index; GP: general practitioner; HCRU: healthcare resource utilisation; PCA: prescription cost analysis; PSSRU: personal social services research unit.

B.3.5.2.2 *Comorbidity resource use*

Table 92 presents the annual costs associated with the estimated healthcare resource use depending on ongoing comorbidities including T2DM and CVD; these were applied to the relevant health state on a per-cycle basis. All cost sources are consistent with those used in TA875 (which were updated from TA664 to more recent sources following a targeted literature review [TLR]), excluding the cost of T2DM.[1, 2] In TA875, annual resource use costs for T2DM included the costs for T2DM treatment and macrovascular complications, which were both sourced from Capehorn *et al.* 2021.[174] This cost source was updated to more recent cost data, though it should be noted that the resulting costs are broadly aligned with those used in TA875.

The costs associated with clinical events (such as MI and stroke) were accrued upon event occurrence (see Section B.3.5.2.3). Following the CV event, patients accrue additional healthcare resource use costs associated with the previous CV event.

Table 92: Annual ongoing resource use costs (excluding event costs)

Comorbidity	Cost	Source
T2DM annual resource use costs (excluding event costs)		
T2DM	£1,770.52	Weighted average cost for number of activity and national average unit costs from Total HRGs tab for Diabetes with Hypoglycaemic Disorders (NHS direct costs): KB01C, KB01D, KB01E, KB01F, KB02G, KB02H, KB02J, KB02K. NHS Reference Costs 2021[175]
Post-MI/angina annual resource use costs (excluding event costs)		
MI, first year	£1,121.30	Alva *et al.* 2015[176]*

MI, subsequent years	£781.30	
Angina, first year	£1,006.02	Alva *et al.* 2015[176]*
Angina, subsequent years*	£761.50	
Post-stroke annual resource use costs (excluding event costs)		
First year	£1,270.34	Alva *et al.* 2015[176]
Subsequent years	£880.27	

Footnotes: *Costs inflated to 2020/21 costs using NHSCII.
Abbreviations: HRG: healthcare resource group; MI: myocardial infarction; NHS: national health service; NHSCII: national health service cost inflation index; T2DM: type 2 diabetes mellitus.

B.3.5.2.3 *Clinical event costs*

The per patient costs associated with managing each event are shown in Table 93 (acute clinical events),

Table 94 (non-acute clinical events) and Table 95 (bariatric surgery). Costs for acute clinical events and bariatric surgery were applied as a one off upon the event occurring, whereas costs of non-acute clinical events (i.e. OSA and NAFLD), were applied on an annual basis. Reference costs were based on what is expected to be clinically appropriate and aligned with TA875 and TA664.

OSA costs were also included in TA875; initially a cost of £1,018.19 was used, based on the NHS reference costs, although the ERG believed this estimate was too high, and preferred an annual cost of £274 based on the annual costs for a continuous positive airway pressure (CPAP) machine. The cost used in the model has therefore been aligned with ERG preferences in TA875,[2] although the cost has been inflated from 2014/15 (price year used in the source) to 2021/2022 costs using a combination index of NHSCII and pay and price index. With regards to the ongoing cost for NAFLD, the same approach used for OSA in TA664 and TA875 has been implemented, although NAFLD is not included as a potential complication in these appraisals.[1, 2]

Table 93: Cost of acute clinical events (one-off)

Clinical event	Cost	Source
MI (fatal or non-fatal)	£3,120.22	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: EB10A, EB10B, EB10C, EB10D, EB10E. NHS Reference Costs 2021[175]
Stroke (fatal or non-fatal)	£6,089.36	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: AA35A, AA35B, AA35C, AA35D, AA35E, AA35F. NHS Reference Costs 2021[175]
Knee osteoarthritis	£8,186.07	Weighted average cost for number of FCE's and national average unit costs from Elective Inpatient for codes: HN22A, HN22B, HN22C, HN22D, HN22E. NHS Reference Costs 2021[175]
Angina	£2,172.93	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: EB13A, EB13B, EB13C, EB13D. NHS Reference Costs 2021[175]

Abbreviations: FCE: finished consultant episode; MI: myocardial infarction; NHS: national health service; TIA: transient ischemic attack.

Table 94: Cost of non-acute clinical events (annual)

Clinical event	Cost	Source
OSA*	£287.61	Sharples *et al.* 2014. Cost inflated from 2014/15 (price year used in the source) to 2021/2022 costs using a combination index of NHSCII and pay and price index
NAFLD†	£3,108.37	Weighted average cost for number of activity and national average unit costs from Total HRGs tab for liver failure disorder codes (NHS direct costs): GC01C, GC01D, GC01E, GC01F. NHS Reference Costs 2021[175]

Footnotes: *OSA costs were also included in TA875; initially a cost of £1,018.19 was used, based on the NHS reference costs, although the EG believed this estimate was too high, and preferred an annual cost of £274 based on the annual costs for a continuous positive airway pressure (CPAP) machine. Ultimately, clinical experts suggested that the £1,0819 cost was more appropriate.[2] † The approach used to calculate an ongoing cost for NAFLD is the same as the approach used for OSA in TA664 and TA875 (NAFLD is not included as a potential complication in these appraisals).[1, 2]
Abbreviations: HRG: healthcare resource group; NAFLD: non-alcoholic fatty liver disease; NHS: national health service; OSA: obstructive sleep apnoea; SE: standard error.

Table 95: Cost of bariatric surgery (one-off)

Category	Cost	Source
RYGB procedure	£8,334.84	Weighted average cost for number of activity and national average unit costs for complex surgical procedures for obesity (FF10Z) and major surgical procedures for obesity (FF11Z). NHS Reference Costs 2021[175]
Sleeve gastrectomy procedure	£6,779.00	National average unit cost for sleeve gastrectomy for obesity (FF12Z). NHS Reference Costs 2021[175]
Gastric band procedure	£4,031.00	National average unit cost for gastric band procedures for obesity (FF13Z). NHS Reference Costs 2021[175]
OAGB/MGB procedure	£8,334.84	Weighted average cost for number of activity and national average unit costs for complex surgical procedures for obesity (FF10Z) and major surgical procedures for obesity (FF11Z). NHS Reference Costs 2021[175]

Abbreviations: mgB: mini gastric bypass; NHS: National Health Service; OAGB: one-anastomosis gastric bypass; RYGB: Roux-en-Y gastric bypass.

B.3.5.3 Adverse reaction unit costs and resource use

Costs for the management and treatment of severe GI events were based on the cost of total outpatient attendances for gastroenterology as reported in the NHS Reference Costs.[175] This amounts to an average cost of £165.04, which was applied per incidence of AE.

B.3.6 *Severity*

No severity weights were used in the evaluation of quality-adjusted life expectancy.

B.3.7 *Uncertainty*

Given the chronic nature of obesity and the long-term health impacts associated with the disease, it was not possible to directly measure the incidence of obesity comorbidities and complications during the SURMOUNT-1 trial. This necessitated the use of surrogate endpoints to capture the treatment benefits, meaning that any cost-effectiveness estimates are associated with some level of inherent uncertainty due to the nature of the disease area; this uncertainty was

also present in the previous NICE technology appraisals TA664 and TA875 where it did not preclude a positive recommendation.[1, 2]

B.3.8 *Managed access proposal*

No managed access proposal is included as part of this submission, as it is anticipated that routine commissioning can be achieved through this appraisal, as in the previous NICE technology appraisals TA664 and TA875.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

The model inputs used in the base case are summarised in Table 96 to Table 101. A default margin of error of 20% was assumed where standard errors of the mean were not available/not reported, with the exception of HbA1c for each category, which was varied at 10% in the DSA to preserve logical ordering of the normoglycaemia, prediabetes and T2DM categories, and which was not varied in the PSA (discussed further in Sections B.3.11.1 and B.3.11.2).

Table 96: Summary of base case analysis inputs (model settings)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Discount rate, %	3.5%	N/A	Section 0
Time horizon	Lifetime		Section 0
Perspective	NHS/PSS		Section B.3.2
Cycle length	Dual-cycle length with a half-cycle correction (4-week cycles for two years, followed by 1-year cycle length until end of model)		Section B.3.2.2.4

Abbreviations: CI: confidence interval; NHS: National Health Service; PSS: Personal Social Services.

Table 97: Summary of base case analysis inputs (baseline characteristics)*

Variable	Value	Measurement of uncertainty and distribution: SD (distribution for cohort sampling)	Reference to section in submission
Age (years)	47.40	12.00 (Normal)	Section B.3.2.1
Sex (% female)	66.22%	-	
Height (m)	1.66	0.10 (Normal)	
BMI (kg/m^2)	38.75	6.81 (Normal)	
SBP (mmHg)	124.75	12.75 (Normal)	
Total cholesterol (mg/dL)	194.02	39.58 (Normal)	
HDL (mg/dL)	48.71	12.87 (Normal)	

% of Patients who are White	82.30%	-	Appendix N
% of Patients who are Indian	3.17%	-	
% of Patients who are Pakistani	1.71%	-	
% of Patients who are Bangladeshi	1.38%	-	
% of Patients who are Other Asian	2.07%	-	
% of Patients who are Caribbean	1.36%	-	
% of Patients who are Black African	3.02%	-	
% of Patients who are Chinese	1.11%	-	
% of Patients who are Other	3.88%	-	
% of Patients with Hypertension	43.52%	-	Section B.3.2.1
eGFR (ml/min/1.73 m^2)	95.44	17.99 (Normal)	
Triglycerides (mg/dL)	133.86	67.12 (Normal)	
% of Female Patients with PCOS	2.04%	-	
% of Patients with T1DM	0.00%	-	
FPG (mmol/L)	5.41	0.56 (Normal)	
% of Patients with Treated Hypertension	40.00%	-	
% of Patients with COPD	1.17%	-	
% of Patients with Hypothyroidism	12.49%	-	
% of Patients with Gestational Diabetes	1.15%	-	
% of Patients with Systemic Lupus Erythematosus	0.18%	-	
% of Patients with Acromegaly	0.00%	-	
% of Male Patients with Erectile Dysfunction	6.08%	-	
Townsend Score	0.50	3.30 (Normal)	Appendix N
% of Patients who are Smokers	22.89%	-	
% of Patients with Family History of Diabetes	14.89%	-	
% of Patients with Schizophrenia or BPD	0.76%	-	
% of Patients with a Learning Disability	0.69%	-	
% of Patients Using Atypical Antipsychotics	0.72%	-	
% of Patients with CKD (Stage 3, 4 or 5)	0.40%	-	
% of Patients with Family History of CHD	10.64%	-	
% of Patients with Rheumatoid Arthritis	0.85%	-	
% of Patients with Atrial Fibrillation	0.45%	-	
% of Patients with Migraine	4.59%	-	
% of Patients with Severe Mental Illness	5.59%	-	

SBP SD (mmHg)	9.60	6.50 (Normal)	
% of Patients with Macroalbuminuria	1.90%	-	
% of Patients with Peripheral Vascular Disease	0.00%	-	
% of Patients with Amputation	0.00%	-	
% of Patients without Vascularisation	54.88%	-	
% of Patients with Vascularisation before ACS	13.60%	-	
% of Patients with Hyperlipidaemia	24.20%	-	
% of Patients with GERD	38.26%	-	
% of Patients using Benzodiazepines	71.01%	-	
WBC (10^6/ml)	6.80	1.36 (Normal)	
% of Patients using Corticosteroids	1.88%	-	Section B.3.2.1
% of Patients using Statins	17.83%	-	
% of Patients with Prediabetes	[redacted]	-	
Expected HbA1c for Patients with Prediabetes (%)	6.40%	5.76%, 7.04% (Normal)	Section B.3.3.2.1
Expected HbA1c for Patients with Normoglycaemia (%)	5.70%	5.13%, 6.27% (Normal)	
Expected HbA1c for Patients with T2DM (%)	7.50%	6.75%, 8.25% (Normal)	

Footnotes: * Baseline characteristics were not varied in the DSA or PSA as they are already varied when sampling patients for the modelled cohort. Expected HbA1c was varied in the DSA but not PSA.
Abbreviations: ACS: acute coronary syndrome; BMI: body mass index; BPD: borderline personality disorder; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CSR: clinical study report; DBP: diastolic blood pressure; eGFR; estimated glomerular rate, FPG: fasting plasma glucose; HDL: high-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation; WBC: white blood cell count.

Table 98: Summary of base case analysis inputs (efficacy) applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: DSA bounds (PSA distribution)	Reference to section in submission
Change from Baseline, Weight (%), Diet and Exercise	[redacted]	[redacted]	Section B.3.3.1
Change from Baseline, Weight (%), Tirzepatide (5.0 mg)	[redacted]	[redacted]	
Change from Baseline, Weight (%), Tirzepatide (10.0 mg)	[redacted]	[redacted]	
Change from Baseline, Weight (%), Tirzepatide (15.0 mg)	[redacted]	[redacted]	
Change from Baseline, Weight (%), Liraglutide (3.0 mg)	[redacted]	[redacted]	
Change from Baseline, Weight (%), Semaglutide (2.4 mg)	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Diet and Exercise	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Tirzepatide (5.0 mg)	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Tirzepatide (10.0 mg)	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Tirzepatide (15.0 mg)	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Liraglutide (3.0 mg)	[redacted]	[redacted]	
Change from Baseline, SBP (mmHg), Semaglutide (2.4 mg)	[redacted]	[redacted]	
Change from Baseline, HDL (%), Diet and Exercise	[redacted]	[redacted]	
Change from Baseline, HDL (%), Tirzepatide (5.0 mg)	[redacted]	[redacted]	
Change from Baseline, HDL (%), Tirzepatide (10.0 mg)	[redacted]	[redacted]	
Change from Baseline, HDL (%), Tirzepatide (15.0 mg)	[redacted]	[redacted]	
Change from Baseline, HDL (%), Liraglutide (3.0 mg)	[redacted]	[redacted]	
Change from Baseline, HDL (%), Semaglutide (2.4 mg)	[redacted]	[redacted]	
Change from Baseline, Total Cholesterol (%), Diet and Exercise	[redacted]	[redacted]	
Change from Baseline, Total Cholesterol (%), Tirzepatide (5.0 mg)	[redacted]	[redacted]	
Change from Baseline, Total Cholesterol (%), Tirzepatide (10.0 mg)	[redacted]	[redacted]	
Change from Baseline, Total Cholesterol (%), Tirzepatide (15.0 mg)	[redacted]	[redacted]	

Change from Baseline, Total Cholesterol (%), Liraglutide (3.0 mg)	[redacted]	[redacted]	
Change from Baseline, Total Cholesterol (%), Semaglutide (2.4 mg)	[redacted]	[redacted]	
Reversal of Prediabetes, Diet & Exercise	[redacted]	[redacted]	Section B.3.3.2.2
Reversal of Prediabetes, Tirzepatide (5.0 mg)	[redacted]	[redacted]	
Reversal of Prediabetes, Tirzepatide (10.0 mg)	[redacted]	[redacted]	
Reversal of Prediabetes, Tirzepatide (15.0 mg)	[redacted]	[redacted]	
Reversal of Prediabetes, Liraglutide (3.0 mg)	[redacted]	[redacted]	
Reversal of Prediabetes, Semaglutide (2.4 mg)	[redacted]	[redacted]	
Annual Incidence of Bariatric Surgery	0.20%	0.20%, 0.21% (Normal)	Section B.3.3.2.3
Change in Weight (%), Average	29.70%	23.76%, 35.64% (Normal)	
Post −Surgery Remission for T2DM, Average	54.69%	43.75%, 65.63% (Normal)	
Post −Surgery Remission for OSA, Average	53.29%	42.63%, 63.95% (Normal)	
Primary Treatment Failure, Time Adjusted % Discontinuation, Tirzepatide (5.0 mg)	9.65%	7.34%, 11.96% (Normal)	Section B.3.3.3.2
Primary Treatment Failure, Time Adjusted % Discontinuation, Tirzepatide (10.0 mg)	3.77%	2.29%, 5.25% (Normal)	
Primary Treatment Failure, Time Adjusted % Discontinuation, Tirzepatide (15.0 mg)	3.74%	2.26%, 5.22% (Normal)	
Primary Treatment Failure, Time Adjusted % Discontinuation, Liraglutide (3.0 mg)	17.00%	15.52%, 18.48% (Normal)	
Primary Treatment Failure, Time Adjusted % Discontinuation, Semaglutide (2.4 mg)	10.00%	8.00%, 12.00% (Normal)	
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (5.0 mg)	4.29%	2.70%, 5.87% (Normal)	Section B.3.3.3.1
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (10.0 mg)	7.08%	5.08%, 9.07% (Normal)	
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (15.0 mg)	6.19%	4.31%, 8.07% (Normal)	
Ongoing Discontinuation due to AE, % Discontinuation, Liraglutide (3.0 mg)	9.89%	8.72%, 11.06% (Normal)	
Ongoing Discontinuation due to AE, % Discontinuation, Semaglutide (2.4 mg)	7.04%	5.66%, 8.43% (Normal)	
Expected Annual Change in BMI Up To 68 Years, Male	0.14	0.12, 0.17 (Gamma)	Section B.3.3.3.1

Expected Annual Change in BMI Up To 68 Years, Female	0.17	0.14, 0.21 (Gamma)	

Table 99: Summary of base case analysis inputs (adverse events) applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: DSA bounds (PSA distribution)	Reference to section in submission
Severe or serious GI events (%), Tirzepatide (5.0 mg)	1.23%	0.99%, 1.48% (Beta)	Section B.3.4.4
Severe or serious GI events (%), Tirzepatide (10.0 mg),	2.26%	1.81%, 2.71% (Beta)	
Severe or serious GI events (%), Tirzepatide (15.0 mg),	2.40%	1.92%, 2.88% (Beta)	
Severe or serious GI events (%), Liraglutide (3.0 mg)	7.10%	5.68%, 8.52% (Beta)	
Severe or serious GI events (%), Semaglutide (2.4 mg)	4.90%	3.92%, 5.88% (Beta)	
Severe or serious GI events (%), Diet and Exercise	0.80%	0.64%, 0.96% (Beta)	
Unit Cost, Severe or Serious GIs	£148.93	119.15, 178.72 (Gamma)	
AE Disutility, Severe or Serious GIs	-0.04	-0.03, -0.05 (Beta)	

Abbreviations: CI: confidence interval; GI: gastrointestinal.

Table 100: Summary of base case analysis inputs (utilities and costs) applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: DSA bounds (PSA distribution)	Reference to section in submission
Utility inputs			
Clinical Event Disutilities, T2DM, Male	−0.05	−0.08, −0.03 (Beta)	Section B.3.4.5.2
Clinical Event Disutilities, T2DM, Female	−0.03	−0.07, −0.01 (Beta)	
Clinical Event Disutilities, Post −ACS	−0.04	−0.1, −0.01 (Beta)	
Clinical Event Disutilities, Post −Stroke	−0.04	−0.08, −0.01 (Beta)	
Clinical Event Disutilities, Knee Replacement, Male	−0.17	−0.19, −0.16 (Beta)	
Clinical Event Disutilities, Knee Replacement, Female	−0.20	−0.21, −0.19 (Beta)	
Clinical Event Disutilities, OSA, Male	−0.02	−0.04, −0.01 (Beta)	
Clinical Event Disutilities, OSA, Female	−0.04	−0.06, −0.03 (Beta)	
Clinical Event Disutilities, ACS	−0.06	−0.09, −0.04 (Beta)	
Clinical Event Disutilities, Stroke	−0.03	−0.08, −0.01 (Beta)	

Clinical Event Disutilities, NAFLD	−0.10	−0.16, −0.05 (Beta)	
Clinical Event Disutilities, Bariatric Surgery	−0.22	−0.18, −0.26 (Beta)	
Resource use			
Annual Health Care Resource Costs, BMI: ≥18.5 to 40+	£233.63	£186.90, £280.35 (Gamma)	Section B.3.5.2.1
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,770.52	£1416.41, £2124.62 (Gamma)	Section B.3.5.2.2
Annual Comorbidity Resource Use (Excluding Event Costs), Post −MI, First Year	£1,121.30	£897.04, £1345.56 (Gamma)	
Annual Comorbidity Resource Use (Excluding Event Costs), Post −MI, Subsequent Years	£781.30	£625.04, £937.56 (Gamma)	
Annual Comorbidity Resource Use (Excluding Event Costs), Angina, First Year	£1,006.02	£804.82, £1207.23 (Gamma)	
Annual Comorbidity Resource Use (Excluding Event Costs), Angina, Subsequent Years	£761.50	£609.20, £913.80 (Gamma)	
Annual Comorbidity Resource Use (Excluding Event Costs), Post −Stroke, First Year	£1,270.34	£1016.27, £1524.41 (Gamma)	
Annual Comorbidity Resource Use (Excluding Event Costs), Post −Stroke, Subsequent Years	£880.27	£704.22, £1056.32 (Gamma)	
Cost of Acute Clinical Events (One −Off), MI (Fatal or Non −Fatal)	£3,120.22	£2496.18, £3744.27 (Gamma)	Section B.3.5.2.3
Cost of Acute Clinical Events (One −Off), Stroke (Fatal or Non −Fatal)	£6,089.36	£4871.49, £7307.23 (Gamma)	
Cost of Acute Clinical Events (One −Off), Knee Replacement	£8,186.07	£6548.86, £9823.29 (Gamma)	
Cost of Acute Clinical Events (One −Off), Onset of Angina	£2,172.93	£1738.35, £2607.52 (Gamma)	
Cost of Non −Acute Clinical Events (Annual), OSA	£287.61	£230.08, £345.13 (Gamma)	
Cost of Non −Acute Clinical Events (Annual), NAFLD	£3,108.37	£2486.70, £3730.05 (Gamma)	
Cost of Bariatric Surgery (One −Off), Average Cost	£7,285.92	£5828.74, £8743.10 (Gamma)	
Administration costs			
Administration Costs, First SQ Administration	£24.00	£19.20, £28.80 (Gamma)	Section B.3.5.1.2
Administration Costs, Injection Pen	£0.00	£0.00, £0.00 (Gamma)	

Abbreviations: AE: adverse event; ACS: acute coronary syndrome; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSR: clinical study report; DBP: diastolic blood pressure; eGFR; estimated glomerular rate, FPG: fasting plasma glucose; HDL: high-density lipoprotein; GI: gastrointestinal; ITT: intention-to-treat; OSA: obstructive sleep apnoea; NAFLD: non-alcoholic fatty liver disease; MI: myocardial infarction; SBP: systolic blood pressure; QD: once daily; QW: once weekly; SD: standard deviation; SC: subcutaneous; T2DM: type 2 diabetes mellitus.

Table 101: Summary of base case analysis inputs for mortality applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: DSA bounds (PSA distribution)	Reference to section in submission
Mortality inputs			
BMI-Specific Mortality, HR, <18.5	1.56	1.52, 1.59 (Log Normal)	Section B.3.3.4
BMI-Specific Mortality, HR, 18.5–19.9	1.29	1.27, 1.32 (Log Normal)	
BMI-Specific Mortality, HR, 20.0–22.4	1.11	1.1, 1.12 (Log Normal)	
BMI-Specific Mortality, HR, 22.5–24.9	Reference	-	
BMI-Specific Mortality, HR, 25.0–27.4	0.98	0.97, 0.99 (Log Normal)	
BMI-Specific Mortality, HR, 27.5-29.9	1.01	1, 1.03 (Log Normal)	
BMI-Specific Mortality, HR, 30.0–34.9	1.12	1.1, 1.13 (Log Normal)	
BMI-Specific Mortality, HR, 35.0–39.9	1.36	1.33, 1.38 (Log Normal)	
BMI-Specific Mortality, HR, ≥40.0	1.88	1.83, 1.93 (Log Normal)	
Mortality RR for Patients with Angina or a History of MI	1.30	1.04, 1.56 (Log Normal)	Section B.3.3.4.2
Mortality RR for Patients with a History of Stroke RR, Male, 25–69 Years, >0, ≤1 Years After Stroke	4.64	3.71, 5.57 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, 25–69 Years, >1, ≤5 Years After Stroke	3.01	2.41, 3.61 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, 25–69 Years, >5, ≤10 Years After Stroke	2.75	2.2, 3.3 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, 25–69 Years, >10, ≤15 Years After Stroke	2.50	2, 3 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, ≥70 Years, >0, ≤1 Years After Stroke	3.70	2.96, 4.44 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, ≥70 Years, >1, ≤5 Years After Stroke	1.92	1.54, 2.3 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, ≥70 Years, >5, ≤10 Years After Stroke	1.89	1.51, 2.27 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Male, ≥70 Years, >10, ≤15 Years After Stroke	2.49	1.99, 2.99 (Log Normal)	

Mortality RR for Patients with a History of Stroke RR, Female, 25–69 Years, >0, ≤1 Years After Stroke	9.27	7.42, 11.12 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, 25–69 Years, >1, ≤5 Years After Stroke	3.52	2.82, 4.22 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, 25–69 Years, >5, ≤10 Years After Stroke	3.32	2.66, 3.98 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, 25–69 Years, >10, ≤15 Years After Stroke	2.45	1.96, 2.94 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, ≥70 Years, >0, ≤1 Years After Stroke	5.18	4.14, 6.22 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, ≥70 Years, >1, ≤5 Years After Stroke	2.05	1.64, 2.46 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, ≥70 Years, >5, ≤10 Years After Stroke	1.99	1.59, 2.39 (Log Normal)	
Mortality RR for Patients with a History of Stroke RR, Female, ≥70 Years, >10, ≤15 Years After Stroke	1.67	1.34, 2 (Log Normal)	
Mortality HR for Patients with NAFLD	1.93	1.54, 2.32 (Log Normal)	Section B.3.3.4.1
Case Fatality for MI Events, Probability of Fatality, Male, 30–54 Years	13.80%	11.04%, 16.56% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Male, 55–64 Years	14.20%	11.36%, 17.04% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Male, 65–74 Years	19.50%	15.60%, 23.40% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Male, 75–84 Years	28.00%	22.40%, 33.60% (Beta)	Section B.3.3.4.2
Case Fatality for MI Events, Probability of Fatality, Male, ≥85 Years	37.90%	30.32%, 45.48% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Female, 30–54 Years	13.30%	10.64%, 15.96% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Female, 55–64 Years	17.40%	13.92%, 20.88% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Female, 65–74 Years	25.30%	20.24%, 30.36% (Beta)	
Case Fatality for MI Events, Probability of Fatality, Female, 75–84 Years	35.80%	28.64%, 42.96% (Beta)	

Case Fatality for MI Events, Probability of Fatality, Female, ≥85 Years	45.70%	36.56%, 54.84% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Male, 20–34 Years	11.20%	8.96%, 13.44% (Beta)	Section B.3.3.4.2
Case Fatality for Stroke Events, Probability of Fatality , Male, 35–54 Years	11.50%	9.20%, 13.80% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Male, 55–64 Years	12.50%	10.00%, 15.00% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Male, 65–74 Years	17.10%	13.68%, 20.52% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Male, 75–84 Years	23.40%	18.72%, 28.08% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Male, ≥85 Years	34.30%	27.44%, 41.16% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, 20–34 Years	9.30%	7.44%, 11.16% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, 35–54 Years	11.40%	9.12%, 13.68% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, 55–64 Years	15.00%	12.00%, 18.00% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, 65–74 Years	18.00%	14.40%, 21.60% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, 75–84 Years	25.90%	20.72%, 31.08% (Beta)	
Case Fatality for Stroke Events, Probability of Fatality , Female, ≥85 Years	38.30%	30.64%, 45.96% (Beta)	

Abbreviations: BMI: body mass index; CI: confidence interval; RR: relative risk; NAFLD: non-alcoholic fatty liver disease; MI: myocardial infarction; T2DM: type 2 diabetes mellitus.

B.3.9.2 Assumptions

A summary of the main model assumptions used in the analysis is presented in Table 102.

Table 102: Summary of key assumptions applied in the economic model

Assumption	Justification	Varied in scenario or sensitivity analyses?
Assumptions consistent with TA875		
Development of T2DM was based on QDiabetes	This source was considered more suitable for use in the base case as it has been externally validated, had a larger patient cohort than the Framingham Offspring Study and has been widely used in the UK, given this study was conducted in England (whereas the Framingham Heart Study was based in the US).	Yes; use of the Framingham Offspring Study is explored in scenario analyses
Incidence of initial CVD in patients without T2DM was based on QRisk3	This source has been externally validated, had a larger patient cohort than the Framingham Heart Study and has been widely used in the UK since this study was conducted in England (whereas the Framingham Heart Study was based in the US).	Yes; use of the Framingham Heart Study is explored in scenario analyses
Incidence of recurrent CVD in patients without T2DM was based on Framingham Heart Study	This risk equation was chosen for the base case as it is considered robust and is widely used. This risk equation also explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It also included a larger patient cohort compared with the LIPID study, and has previously been used and accepted in prior TAs for obesity. Although it was developed specifically in a US context, no suitable alternative in a UK context were identified.	Yes; use of the LIPID Study is explored in scenario analyses
Incidence of initial and recurrent CVD in patients with T2DM was based on UKPDS82	This risk equation was chosen for the base case since it explicitly considers the increased risk of recurrent CVD events among patients who have already experienced a CVD event. It has also been externally validated and is widely used in the UK.	No; no appropriate alternative sources identified
Risk of knee replacement based on Wendelboe *et al.* 2003	This study was chosen as no appropriate alternative risk equations were identified. It was also used in the base case of the models presented in TA664 and TA875, and was deemed appropriate by the Committee in these appraisals.	No; no appropriate alternative sources identified

All patients with prediabetes were assumed to have a greater risk of developing T2DM compared with people with normoglycaemia by assuming higher HbA1c (which is a covariate in the risk equations for T2DM) A proportion of patients in all treatment arms experience prediabetes reversal, in which a lower risk of T2DM is applied.	Published risk equations indicate that patients with prediabetes have a higher risk of developing T2DM than those with normal glucose tolerance.[152, 161]	No
Prediabetes reversal was applied in the first cycle (4 weeks) for all interventions	It is expected based on the known efficacy profile of GLP-1 RAs that reversal would occur shortly after pharmacological treatment. Although this same assumption may not be appropriate in the diet and exercise arm since no GLP-1 RA efficacy is being received, no relevant data were identified to inform the dynamics of prediabetes reversal for patients receiving diet and exercise alone. Therefore, it was conservatively assumed that prediabetes reversal would occur over the same timeframe in the diet and exercise arm as for the pharmacological treatments modelled. For both treatment arms this happens in the first cycle, which is aligned with TA875, although it should be noted that the cycle length applied in the current model is shorter (4 weeks) as compared to the TA875 model (3 months).	Yes; several scenarios were explored to investigate the effect of varying the time at which prediabetes reversal occurs in the diet and exercise arm (12 weeks, 24 weeks).
Clinical comorbidity and event disutilities are assumed to be additive.	This approach is aligned with that critiqued and accepted in TA875 and TA664 (Section B.3.4.5.2).[1, 2]	Yes; a multiplicative approach to clinical comorbidities and disutilities is explored in scenario analyses.
Acute event costs and health state costs are assumed to be additive.	Aligned with Ara *et al.* 2012[124] and the approach taken in TA875 and TA664.	No
Bariatric surgery was included in the model as an event occurring in all treatment arms.	Given the positioning of bariatric surgery in the treatment pathway, bariatric surgery was included as a downstream event for all treatment	No
After the duration of trial follow-up, surrogate endpoints were assumed to remain constant for those on active treatment. Surrogate endpoints for patients on diet and	This is a conservative assumption, as treatment benefits are expected to be maintained for a short duration beyond the period of trial follow-up	No; no appropriate alternative scenarios were identified

exercise align with those of the general population after the duration of the trial follow-up		
Following bariatric surgery, patients maintain a reduced weight for their remaining lifetime	Based on the clinical opinion,[131] although this assumption may overestimate the long-term effect of bariatric surgery as it was noted by the patient expert in TA875 that even after bariatric surgery, maintaining weight loss is challenging.[2]	No
Following treatment discontinuation, surrogate endpoints (other than BMI) are assumed to revert to the value of natural progression in diet and exercise at linear rate over the course of three years. Thereafter, they all stay constant until the end of the model time horizon except for weight/BMI, which follows the natural progression from Ara et al 2012[124] (annual BMI increase by gender)	Based on clinical opinion and the results of the STEP-1 trial extension, treatment benefits are not expected to be maintained long-term following treatment discontinuation.[131,177] However, due to lack of equivalent data for tirzepatide, the treatment benefit of tirzepatide was assumed to be lost over the course of three years after discontinuation, aligning with the approach taken in TA875 and TA664.	Scenario analyses have been provided in which the time period over which the treatment benefit of tirzepatide and comparators is lost is explored (1 year, 2 years)
'Baseline' utility values (i.e. not including any disutilities for AEs or comorbidities) are assumed to be BMI-dependent	An appropriate source for BMI-dependent utility values was identified, and the approach was discussed with a clinician[131] This approach is also in line with the approach taken in TA664 and TA875[1, 2]	No; no suitable alternative inputs for utility values were identified
Additional risk of mortality associated with BMI is included in the model	Mortality for patients with obesity is expected to be higher than the general population; this was deemed appropriate by an external expert clinician[131]	No
Additional risk of mortality associated with bariatric surgery, OSA and knee osteoarthritis is not included in the model	Mortality rates directly associated with these events are expected to be low; furthermore, there is a risk that mortality from these events will be double-counted due to application of BMI-specific mortality rates	No
It is assumed that angina does not contribute to increased risk of mortality	Based on clinical opinion, angina would not be considered a direct cause of death for a patient[131]	No
Annual HCRU based on patients' BMI is assumed to align with values reported by Ara *et al.* (2012)	The only other appropriate source identified for these inputs was Le Roux *et al.* 2021; however, the values reported by Le Roux *et al.* were considered to lack face validity due to the high numbers of GP contacts and difficult to quantify from a cost perspective.[172]	No, no other appropriate sources identified.

No uncertainty in the regression parameters in risk equations was incorporated in the PSA	None of the risk equations included in the model report covariance matrices. As all the regression coefficients are intrinsically correlated and therefore varying them independently would be unsuitable for parameterising uncertainty.	No.
Assumptions that differ from TA875		
Comorbidities included in the model: • T2DM • MI • Angina • Stroke • OSA • Knee osteoarthritis • NAFLD	Based on a review of relevant literature and clinical input, these were determined to be the most clinically and economically relevant comorbidities for inclusion in the model. These comorbidities are aligned with TA875, with the exception of NAFLD, given that the omission of modelled benefit on liver disease was noted by the Committee in this appraisal.[2]	The selection of comorbidities was not varied; however, different probabilities of comorbidities are explored through the use of alternative risk equations
It is assumed that tirzepatide will continue to be administered indefinitely, unless patients discontinue treatment due to adverse events	This is in line with the expected use of tirzepatide in clinical practice, given that it is not anticipated that tirzepatide will be isolated to use in SWMS only as per the recommendation for semaglutide and liraglutide. Moreover, based on initial results from SURMOUNT-4 (Appendix M), discontinuation from tirzepatide would be expected to result in weight regain for many patients,[141] potentially limiting the long-term benefits of tirzepatide in reducing the impact of weight-related comorbidities and complications compared to diet and exercise alone.	No; given the anticipated use of tirzepatide in clinical practice it was not considered appropriate to apply discontinuation due to the SWMS limit.
Surrogate endpoints are modelled by assuming a linear rate of change in all surrogate endpoints for the duration of the trial	Surrogate endpoint data were only available from a limited number of timepoints from the relevant trials	No; although the impact on results of changing the rate of change of trial endpoints over the duration of the trial is expected to be minimal
The probability of developing OSA was based on a study by Erridge *et al.* 2021	This source was preferred over the Sleep Heart Study (source used in TA875) due to its larger sample size, UK population, recency, and the granularity of the BMI covariate, particularly between 30–40 BMI kg/m^2 where the majority of the patient population is expected to be upon entering the model.	No.
Following treatment discontinuation in the pharmacological treatment arms, prediabetes reversal is interrupted, and patients return to	While this assumption is largely aligned with TA875, a notable difference in this case is that rather than assuming that patients return to prediabetes gradually at a rate of 33.33% per year over a 3-year period as per TA875, the IPS assumes that all patients return to	Yes; as an inherent part of the scenarios implemented for the time period over which the treatment period is lost

prediabetes in the cycle following the end of the treatment waning period (3 years in the base case).	prediabetes in the cycle following the end of the treatment waning period (3 years in the base case). This difference stems from the fact that prediabetes is implemented as a categorical variable in the IPS model and therefore cannot be gradually waned in the current IPS in an analogous way to the cohort Markov model structure	
For the diet and exercise arm, patients are assumed to return to prediabetes at 2 years.	No discontinuation is assumed to occur for the diet and exercise arm; however, with respect to prediabetes this assumption results in a bias in the model, whereby patients receiving diet and exercise would be modelled to have greater benefits in terms of T2DM prevention compared to those discontinuing from pharmacological treatment. As this was considered to lack face validity, an arbitrary time point is included in the model at which patients receiving diet and exercise are assumed to return to prediabetes.	Yes; alternative time points (3 years, 5 years) are explored as scenario analyses.
Patients with non-diabetic hyperglycaemia are not definitively assumed to develop T2DM after a cardiovascular event.	TA875 assumed that all patients with non-diabetic hyperglycaemia develop T2DM after a cardiovascular event; this was included as a simplifying assumption as the model could only accommodate all or no patients developing T2DM. As this limitation is not required in the current framework (a simulation model), this assumption was not applied.	No; a scenario was not considered appropriate as the modelled method is more realistic than the simplifying assumption in TA875
Appraisal-specific assumptions		
Patients do not titrate between tirzepatide maintenance dose levels based on response or tolerability	Aligns with the available trial data the point of submission, where patients were allocated to one of three maintenance dose levels of tirzepatide. It is noted that future trial data for SURMOUNT-4, to be available in October 2023 will provide some evidence for a “maximum tolerated dose” tirzepatide arm (Appendix M).	No; no data were available at submission to inform a titration scenario. ICERs for each tirzepatide maintenance dose level are provided versus the relevant comparators for each population considered
Probability of developing NAFLD was based on Loomis *et al.* 2016	This source is a retrospective population-based longitudinal cohort study (N= 1,133,525) conducted using THIN database in the UK. Although no internal or external validation was conducted to assess the discrimination or calibration of the models, no suitable alternative sources were identified.	No; no alternative risk equations identified.

Abbreviations: AE: adverse event; BMI: body mass index; CEM: cost-effectiveness model; CVD: cardiovascular disease; DSA: deterministic sensitivity analysis; GP: general practitioner; HbA1c: glycated haemoglobin; HCRU: Health care resource utilisation; HR: hazard ratio; OSA: obstructive sleep apnoea; NAFLD: non-alcoholic fatty liver disease; NMA: network meta-analysis; MI: myocardial infarction; THIN: The Health Improvement Network; T2DM: type 2 diabetes mellitus; US: United States.

B.3.10 *Base-case results*

The population considered in the base case analysis is patients with BMI ≥30 kg/m^2 with at least one weight-related comorbidity. As discussed in Section B.3.2.3.2, the relevant comparators for this population are diet and exercise and semaglutide.

Results for the other populations considered in this submission are presented Section B.3.12.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Probabilistic fully incremental and pairwise analyses for each dose of tirzepatide versus all relevant comparators in this population are presented in Table 103 to Table 105 below. The probabilistic net health benefit base-case results for each dose of tirzepatide versus all relevant comparators are presented in Table 106 to Table 108. For comparison, fully incremental and pairwise deterministic results are presented in Table 109 to Table 111. It should be noted that the probabilistic results presented were generated by running three copies of the model in parallel and therefore the semaglutide 2.4 mg and diet and exercise results vary in the three comparisons to the three tirzepatide doses, as the parameter variation in the PSA analyses is not seeded (see Section B.3.2.2) and therefore exhibits stochastic variation each time they are run (see Section B.3.11.1 for convergence and stability results).

The probabilistic base case ICERs versus diet and exercise were **£11,684/QALY** for tirzepatide 5 mg, **£11,813/QALY** for tirzepatide 10 mg and **£13,203/QALY** for tirzepatide 15 mg.

It should be noted that the ICERs for the comparisons to semaglutide 2.4 mg are anticipated to be artificially high due to the assumption that the price of semaglutide does not vary between the disclosed price of the initial titration doses (0.25 mg, 0.5 mg, 1 mg) and the higher titration dose (1.7 mg) and maintenance dose (2.4 mg), where the price was redacted in TA875 and remains undisclosed at the time of this submission. Nonetheless, even assuming semaglutide prices do not vary across doses, the probabilistic base case ICERs versus semaglutide 2.4 mg were **£14,841/QALY** for tirzepatide 5 mg, **£15,183/QALY** for tirzepatide 10 mg and **£16,293/QALY** for tirzepatide 15 mg.

All three doses of tirzepatide were associated with greater health benefit (in QALYs) and higher total costs (£), compared to both diet and exercise and semaglutide 2.4 mg. The incremental results for costs and health effects indicate that treatment with each dose of tirzepatide was cost-effective compared to both diet and exercise and semaglutide 2.4 mg, with ICERs well below the lower NICE willingness-to-pay threshold of £20,000/QALY.

A comparison of clinical outcomes from the trial and model, and disaggregated cost and quality-adjusted life years (QALYs) results, are presented in Appendix J.

Table 103: Base-case results for tirzepatide 5 mg (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.895	15.992					
Semaglutide (2.4 mg)	[redacted]	18.941	16.145	£111	0.046	0.153	£727	£727
Tirzepatide (5.0 mg)	[redacted]	19.194	16.676	£7,990	0.299	0.684	£11,684	£14,841

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

Table 104: Base-case results for tirzepatide 10 mg (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and exercise	[redacted]	18.895	15.989					
Semaglutide (2.4 mg)	[redacted]	18.941	16.143	£96	0.046	0.154	£622	£622
Tirzepatide (10 mg)	[redacted]	19.164	16.654	£7,849	0.269	0.664	£11,813	£15,183

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

Table 105: Base-case results for tirzepatide 15 mg (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and exercise	[redacted]	18.898	15.999					
Semaglutide (2.4 mg)	[redacted]	18.944	16.152	£118	0.046	0.153	£769	£769
Tirzepatide (15 mg)	[redacted]	19.228	16.769	£10,172	0.330	0.770	£13,203	£16,293

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 106: Net health benefit for tirzepatide 5 mg (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000
Diet and Exercise	[redacted]	15.992			
Semaglutide (2.4 mg)	[redacted]	16.145	£111	0.153	0.147
Tirzepatide (5.0 mg)	[redacted]	16.676	£7,990	0.684	0.284

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life-year.

Table 107: Net health benefit for tirzepatide 10 mg (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000
Diet and Exercise	[redacted]	15.989			
Semaglutide (2.4 mg)	[redacted]	16.143	£96	0.154	0.149
Tirzepatide (10.0 mg)	[redacted]	16.654	£7,849	0.664	0.272

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life-year.

Table 108: Net health benefit for tirzepatide 15 mg (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000
Diet and Exercise	[redacted]	15.999			
Semaglutide (2.4 mg)	[redacted]	16.152	£118	0.153	0.147
Tirzepatide (15.0 mg)	[redacted]	16.769	£10,172	0.770	0.262

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life-year.

Table 109: Base-case results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.986					
Semaglutide (2.4 mg)	[redacted]	18.953	16.153	£131	0.062	0.167	£785	£785
Tirzepatide (5.0 mg)	[redacted]	19.200	16.680	£7,994	0.309	0.695	£11,510	£14,910

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 110: Base-case results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.986					
Semaglutide (2.4 mg)	[redacted]	18.953	16.153	£131	0.062	0.167	£785	£785
Tirzepatide (10.0 mg)	[redacted]	19.162	16.653	£7,856	0.270	0.667	£11,777	£15,454

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 111: Base-case results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.986					
Semaglutide (2.4 mg)	[redacted]	18.953	16.153	£131	0.062	0.167	£785	£785
Tirzepatide (15.0 mg)	[redacted]	19.225	16.767	£9,993	0.334	0.781	£12,792	£16,062

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

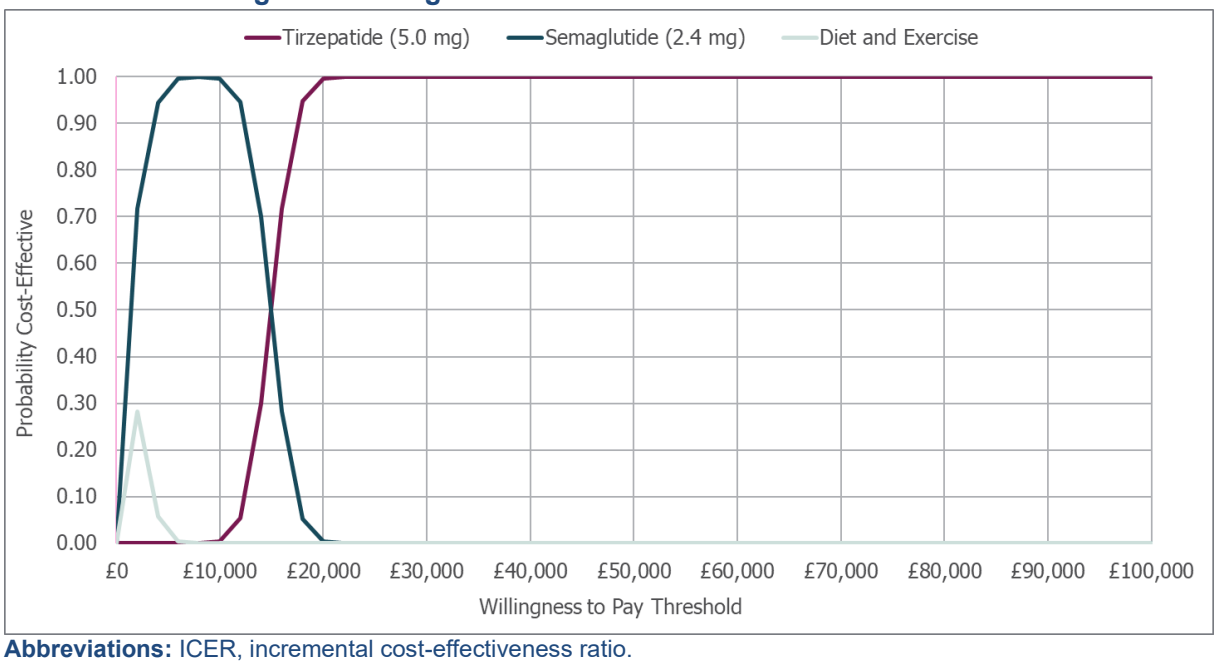
A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the CE model.

Having tested convergence (presented further below), the base case probabilistic results were run with 1,000 simulated patients for 1,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions, with the exception of baseline characteristics which were not varied in the PSA as they are already varied when sampling patients for the modelled cohort. Drug pack prices were also excluded from the PSA as, although comparator confidential prices are not known to Lilly, these parameters are not subject to uncertainty and analyses at the correct prices will be undertaken by the EAG. Where possible the standard error or standard deviation associated with the mean value was used to define the distribution, otherwise it was assumed that the standard error would be 20% of the mean value, with the exception of HbA1c. In the case of HbA1c, assuming random variation for normoglycaemia, prediabetes, and T2DM would lead to them becoming illogically ordered. In TA875 the HbA1c parameters formed part of the health-state definitions and appeared not to have been varied in the sensitivity analyses, therefore each of the three HbA1c parameters was held invariant in the PSA, to constrain logical ordering and to align with TA875. The inputs and distributions used in the PSA are summarised in Section B.3.9.1. As noted in the assumptions table in Section B.3.9.2, coefficients for regression equations (including the risk equations) were not varied in the PSA due to a lack of published covariance matrices.

The average incremental cost-effectiveness results from the PSA were presented as the base case in Section B.3.10. Considering the combined parameter uncertainty in the model, the ICERs for tirzepatide versus diet and exercise and semaglutide 2.4 mg were similar to those reported in the deterministic model results, with variations of a few hundred £/QALY in both directions.

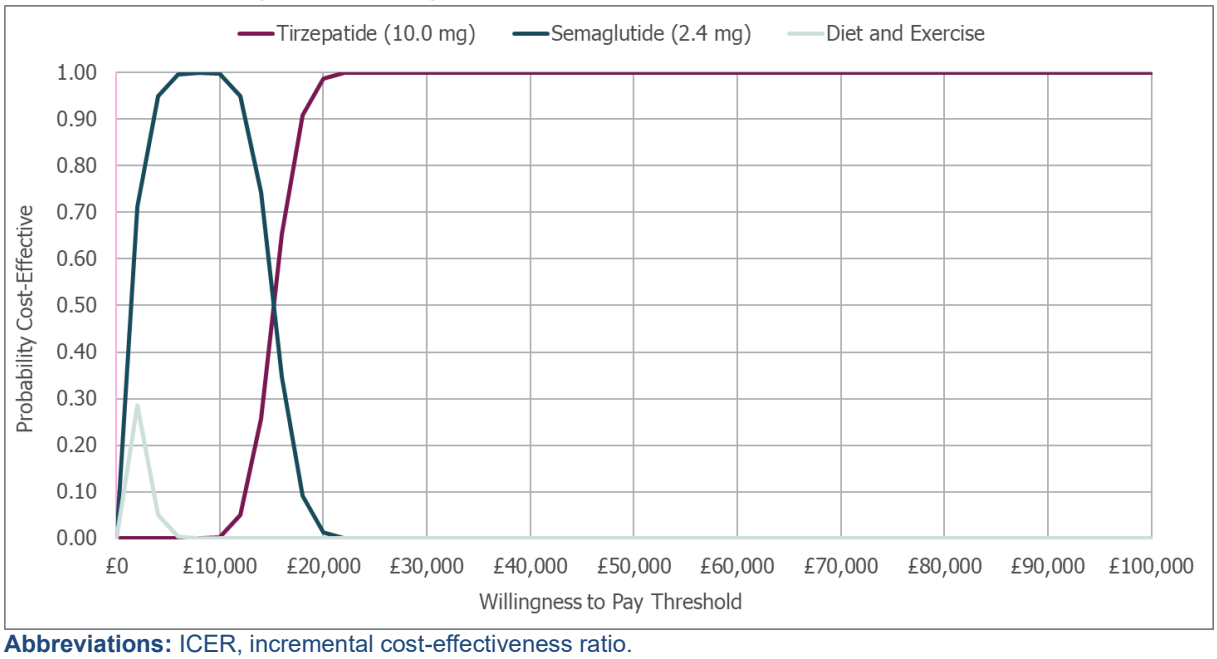
Multi-way cost-effectiveness acceptability curves (CEAC) are presented in Figure 47 to Figure 49. For tirzepatide 5 mg the probability of being the most cost-effective option at £20,000/QALY was 100%, while the next-nearest comparator, semaglutide 2.4 mg was 0% and diet and exercise was 0%. For tirzepatide 10 mg the probability of being the most cost-effective option at £20,000/QALY was 99%, while the next-nearest comparator, semaglutide 2.4 mg was 1% and diet and exercise was 0%. For tirzepatide 15 mg the probability of being the most cost-effective option at £20,000/QALY was 98%, while the next-nearest comparator, semaglutide 2.4 mg was 2% and diet and exercise was 0%.

Figure 47: Cost-effectiveness acceptability curve for tirzepatide 5 mg versus diet and exercise and semaglutide 2.4 mg



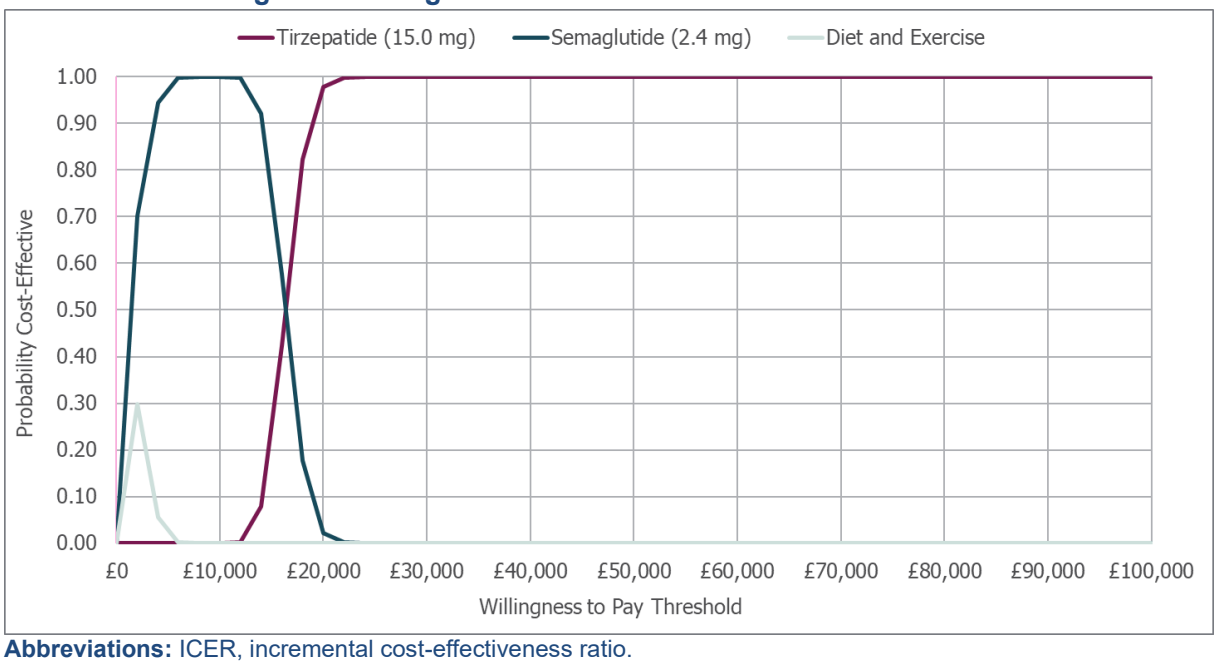
Abbreviations: ICER, incremental cost-effectiveness ratio.

Figure 48: Cost-effectiveness acceptability curve for tirzepatide 10 mg versus diet and exercise and semaglutide 2.4 mg



Abbreviations: ICER, incremental cost-effectiveness ratio.

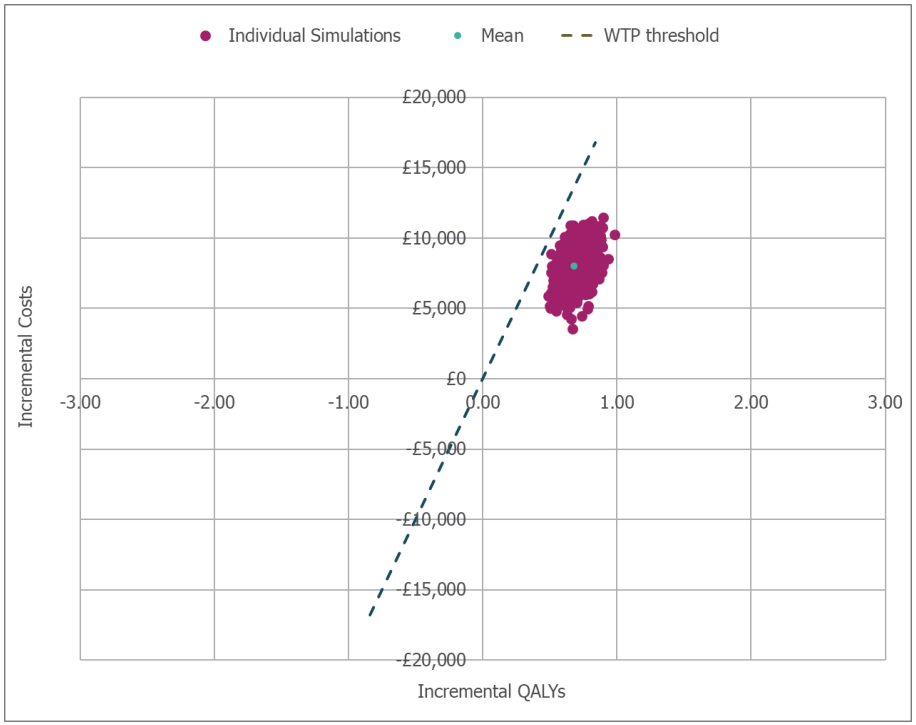
Figure 49: Cost-effectiveness acceptability curve for tirzepatide 15 mg versus diet and exercise and semaglutide 2.4 mg



Abbreviations: ICER, incremental cost-effectiveness ratio.

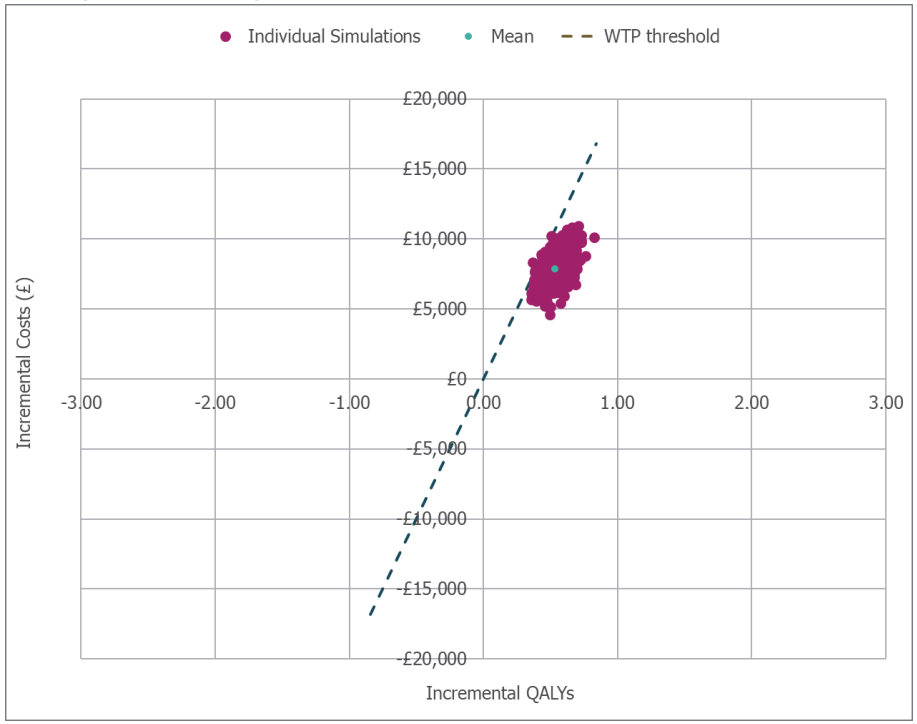
Scatter plots showing the results of each iteration from the PSA on the cost-effectiveness plane are presented in Figure 50 to Figure 55, for each tirzepatide dose versus diet and exercise and semaglutide. In all cases, correlation between costs and QALYs was evident in the cloud shape, and the vast majority of the cloud remained under the £20,000/QALY willingness-to-pay threshold.

Figure 50: Cost-effectiveness plane for tirzepatide 5 mg versus diet and exercise



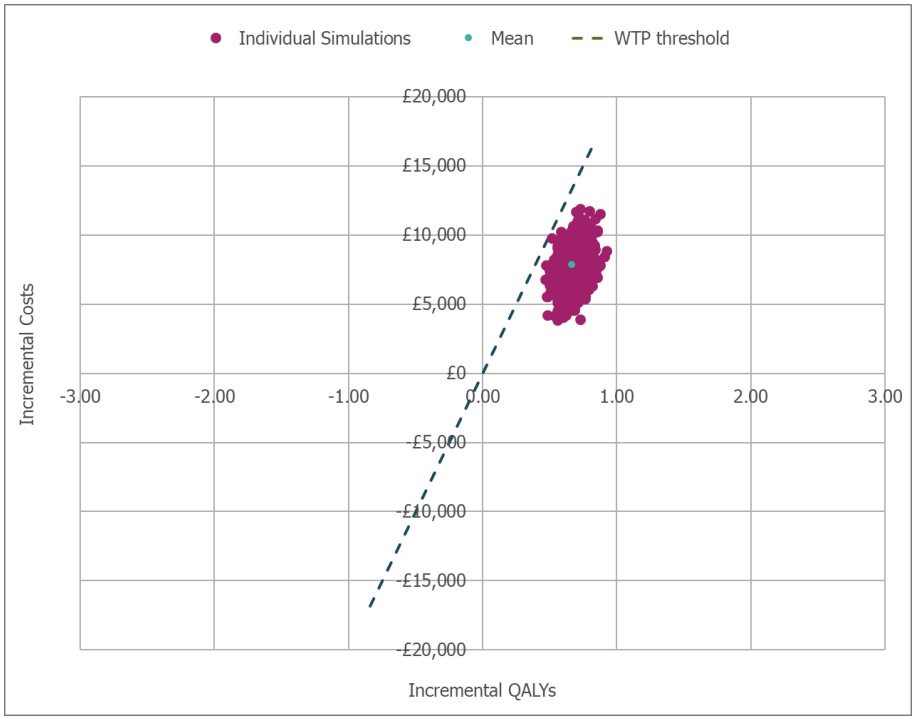
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

Figure 51: Cost-effectiveness plane for tirzepatide 5 mg versus semaglutide 2.4 mg



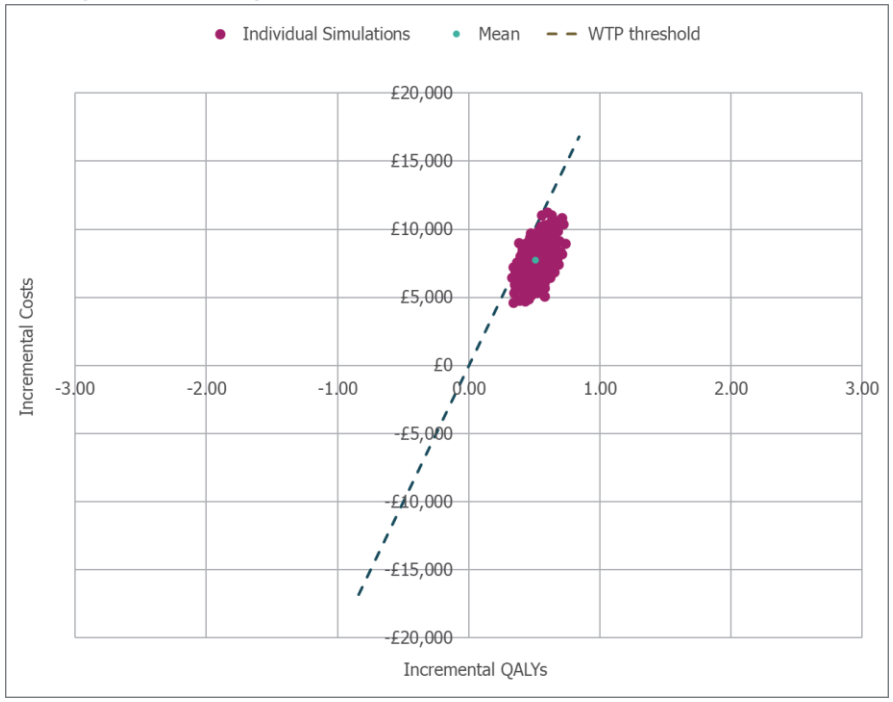
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

Figure 52: Cost-effectiveness plane for tirzepatide 10 mg versus diet and exercise



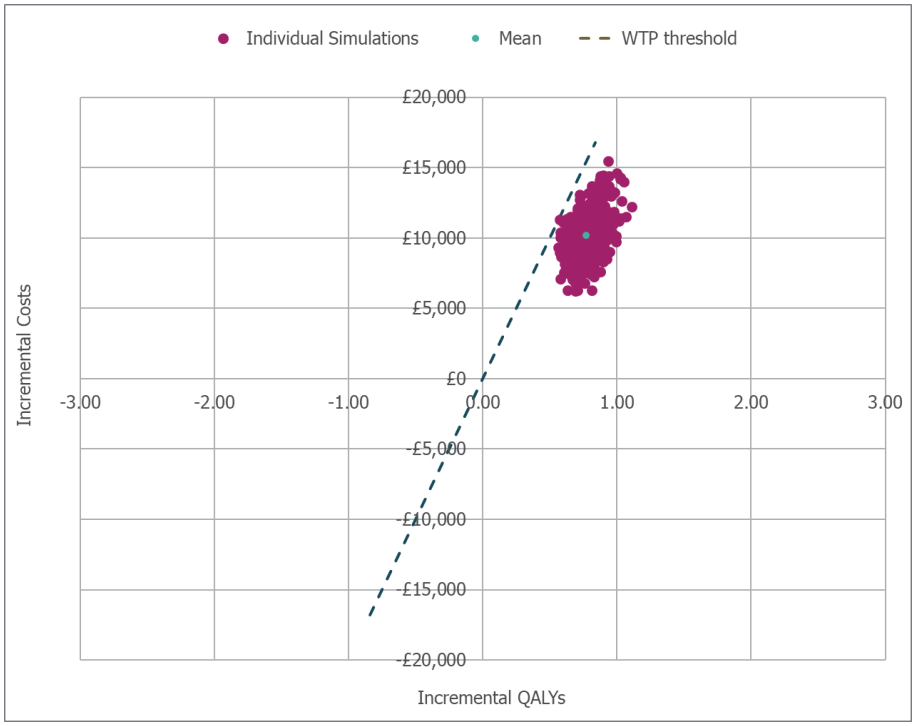
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

Figure 53: Cost-effectiveness plane for tirzepatide 10 mg versus semaglutide 2.4 mg



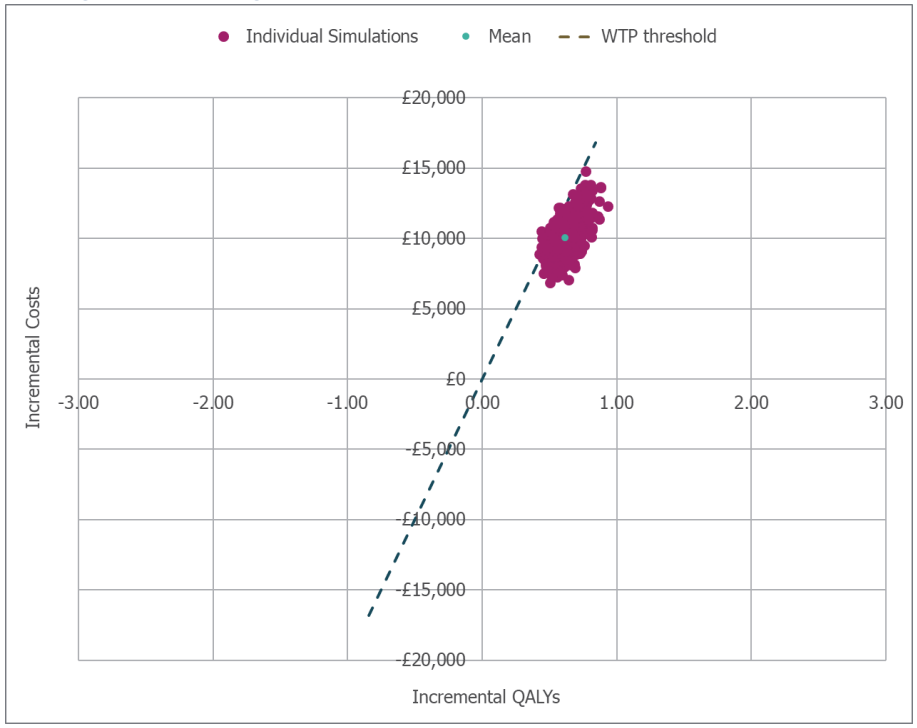
Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

Figure 54: Cost-effectiveness plane for tirzepatide 15 mg versus diet and exercise



Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

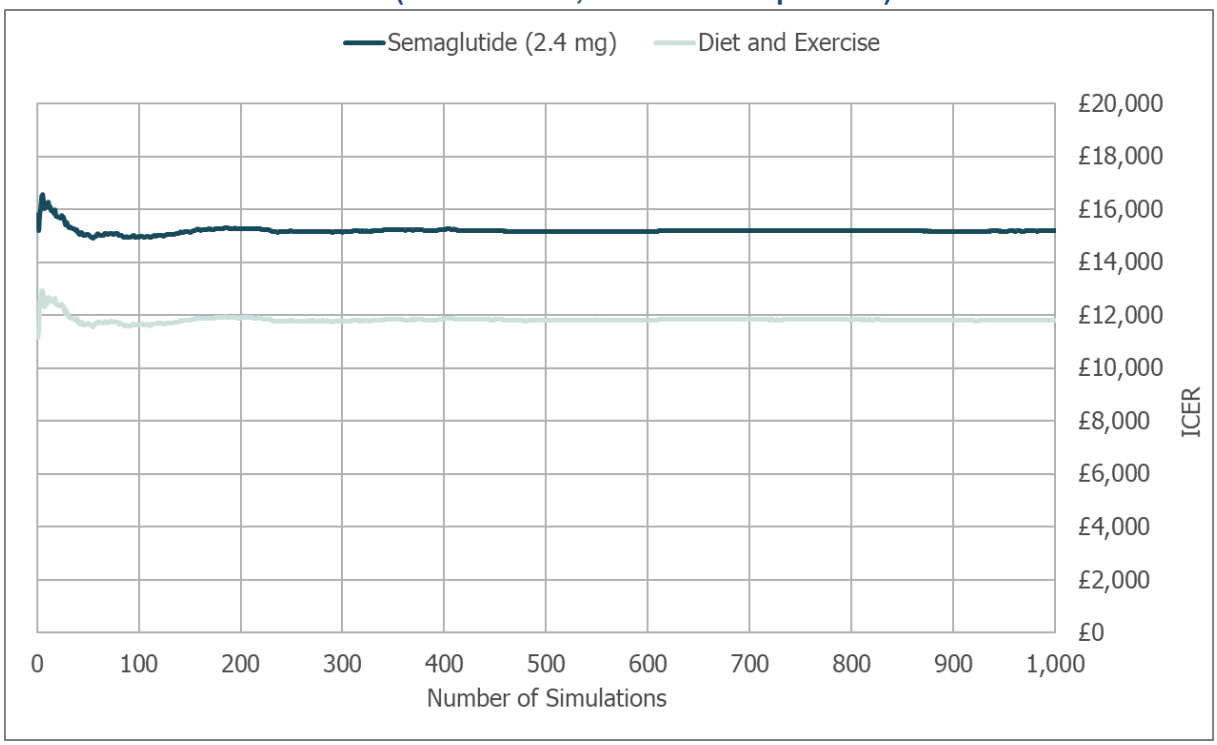
Figure 55: Cost-effectiveness plane for tirzepatide 15 mg versus semaglutide 2.4 mg



Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; WTP: willingness-to-pay.

An ICER convergence plot for the PSA for tirzepatide 10 mg, versus each of semaglutide and diet and exercise, is shown in Figure 56 for a cohort size of 1,000 simulated patients, confirming that the ICER was stable at 1,000 iterations.

Figure 56: PSA ICER convergence plot for tirzepatide 10 mg versus semaglutide 2.4 mg and versus diet and exercise (cohort size 1,000 simulated patients)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis.

B.3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model to the upper and lower limits of the confidence intervals, where 95% CIs were available, whilst keeping all other inputs the same. As with the PSA, baseline characteristics were not varied in the DSA as they are already varied when sampling patients for the modelled cohort. Parameters where CIs were unavailable were varied by ±20% of their mean value, with the exception of HbA1c. In the case of HbA1c, variation by ±20% of their mean value would result in the parameters for normoglycaemia, prediabetes, and T2DM becoming illogically ordered, therefore each of the three HbA1c parameters was varied by ±10% of their mean value, to constrain logical ordering. Coefficients for regression equations (including the risk equations) were not varied in the DSA as it is illogical to vary individual coefficients while holding others unchanged. Drug pack prices were also excluded from the DSA as, although comparator confidential prices are not known to Lilly, these parameters are not subject to uncertainty, and ICERs at the correct prices will be generated by the EAG. The inputs used in the DSA are presented in Section B.3.9.1.

Results from the DSA on the ICER are presented in Table 112 to Table 117 for each dose of tirzepatide in comparison with each of semaglutide and diet and exercise, using a cohort size of 1,000.

Table 112. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 5 mg vs diet and exercise, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£11,510**	**£11,510**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£19,275	£10,251
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£9,555	£14,901
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£12,815	£10,205
Change from Baseline, Weight (%), Tirzepatide (5.0 mg)	−17.78%	−14.05%	£10,351	£12,829
Clinical Event Disutilities, T2DM, Female	−0.07	−0.01	£10,343	£12,336
Change from Baseline, Weight (%), Diet and Exercise	−3.58%	−1.42%	£12,254	£10,984
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (5.0 mg)	2.70%	5.87%	£11,927	£10,888
Clinical Event Disutilities, T2DM, Male	−0.08	−0.03	£11,097	£11,857
Clinical Event Disutilities, NAFLD	−0.16	−0.05	£11,101	£11,847
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£11,223	£11,797

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

Table 113. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 5 mg vs semaglutide 2.4 mg, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£14,910**	**£14,910**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£22,387	£13,420
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£12,887	£18,009
Change from Baseline, Weight (%), Tirzepatide (5.0 mg)	−17.78%	−14.05%	£13,058	£17,098
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£16,031	£13,788
Clinical Event Disutilities, T2DM, Female	−0.07	−0.01	£13,699	£15,735
Change from Baseline, Weight (%), Diet and Exercise	−3.58%	−1.42%	£15,555	£13,779
Clinical Event Disutilities, NAFLD	−0.16	−0.05	£14,231	£15,480
Clinical Event Disutilities, T2DM, Male	−0.08	−0.03	£14,448	£15,295
Change from Baseline, Weight (%), Semaglutide (2.4 mg)	−17.95%	−15.06%	£15,011	£14,215
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£14,628	£15,192

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

Table 114. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 10 mg vs diet and exercise, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£11,777**	**£11,777**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£18,985	£10,420
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£10,733	£14,540
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£13,245	£10,309
Change from Baseline, Weight (%), Tirzepatide (10.0 mg)	-22.57%	-18.84%	£10,662	£13,133
Clinical Event Disutilities, T2DM, Female	-0.07	-0.01	£10,441	£12,745
Change from Baseline, Weight (%), Diet and Exercise	-3.58%	-1.42%	£12,459	£11,279
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (10.0 mg)	5.08%	9.07%	£11,976	£11,020
Clinical Event Disutilities, T2DM, Male	-0.08	-0.03	£11,304	£12,178
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£11,452	£12,102
Reversal of Prediabetes, Tirzepatide (10.0 mg)	90.98%	96.92%	£12,085	£11,682

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

Table 115. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 10 mg vs semaglutide 2.4 mg, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£15,454**	**£15,454**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£22,072	£13,809
Change from Baseline, Weight (%), Tirzepatide (10.0 mg)	−22.57%	−18.84%	£13,704	£17,754
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£14,764	£17,742
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£16,783	£14,124
Clinical Event Disutilities, T2DM, Female	−0.07	−0.01	£13,957	£16,504
Change from Baseline, Weight (%), Diet and Exercise	−3.58%	−1.42%	£15,963	£14,313
Clinical Event Disutilities, T2DM, Male	−0.08	−0.03	£14,890	£15,929
Change from Baseline, Weight (%), Semaglutide (2.4 mg)	−17.95%	−15.06%	£15,560	£14,698
BMI-Specific Mortality, HR, BMI Range: 30.0–34.9	1.10	1.13	£15,494	£14,810
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£15,121	£15,786

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

Table 116. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 15 mg vs diet and exercise, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£12,792**	**£12,792**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£19,232	£11,572
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£12,124	£15,618
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£14,142	£11,443
Clinical Event Disutilities, T2DM, Female	−0.07	−0.01	£11,439	£13,758
Change from Baseline, Weight (%), Tirzepatide (15.0 mg)	−24.17%	−20.41%	£11,995	£14,312
Change from Baseline, Weight (%), Diet and Exercise	−3.58%	−1.42%	£13,478	£12,270
Clinical Event Disutilities, T2DM, Male	−0.08	−0.03	£12,319	£13,192
Ongoing Discontinuation due to AE, % Discontinuation, Tirzepatide (15.0 mg)	4.31%	8.07%	£13,146	£12,450
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£12,508	£13,077
Clinical Event Disutilities, OSA, Female	−0.06	−0.03	£12,552	£12,996

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

Table 117. ICER table from deterministic sensitivity analyses – top 10 parameters (tirzepatide 15 mg vs semaglutide 2.4 mg, cohort size 1000)

Variable	Lower Bound	Upper Bound	ICER (Lower Bound)	ICER (Upper Bound)
Base case:			**£16,062**	**£16,062**
Expected HbA1c for Patients with Prediabetes (%)	5.76%	7.04%	£21,780	£14,652
Change from Baseline, Weight (%), Tirzepatide (15.0 mg)	−24.17%	−20.41%	£14,834	£18,337
Expected HbA1c for Patients with Normoglycaemia (%)	5.13%	6.27%	£15,885	£18,527
Clinical Event Disutilities, T2DM, Female	−0.07	−0.01	£14,617	£17,063
Annual Comorbidity Resource Use (Excluding Event Costs), T2DM	£1,416	£2,125	£17,266	£14,858
Change from Baseline, Weight (%), Diet and Exercise	−3.58%	−1.42%	£16,593	£14,997
Clinical Event Disutilities, T2DM, Male	−0.08	−0.03	£15,529	£16,508
Change from Baseline, Weight (%), Semaglutide (2.4 mg)	−17.95%	−15.06%	£16,149	£15,419
Annual Health Care Resource Costs, BMI Range: 25-29	£187	£280	£15,782	£16,341
Expected HbA1c for Patients with T2DM (%)	6.75%	8.25%	£16,298	£15,760

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; ICER, incremental cost-effectiveness ratio; T2DM: type 2 diabetes mellitus.

In all 6 comparisons, the parameter with the greatest impact on the ICER was the assumed HbA1c value for prediabetes, while the assumed HbA1c value for normoglycaemia ranked in the top four in each comparison, reflecting the importance of developing diabetes on the model outcomes. Three further diabetes parameters were present in the top ten of all 6 comparisons: T2DM comorbidity resource use costs, and T2DM event disutilities for males and females. No ICERs crossed the £20,000/QALY WTP threshold in the comparisons of each dose of tirzepatide versus diet and exercise. For the comparisons of tirzepatide versus semaglutide, the lower extreme of HbA1c in prediabetes crossed the £20,000/QALY WTP threshold in each case. Other parameters in the DSA results included efficacy inputs for change from baseline in weight for each arm, discontinuation due to AE for each tirzepatide arm and BMI-related resource use costs.

Overall, the DSA results show that the model is robust to univariate parameter uncertainty with some sensitivity to the assumed (fixed) HbA1c values for prediabetes and normoglycaemia. It must be noted when interpreting the sensitivity to HbA1c that, in line with the committee-accepted TA875 approach, the base case value for each category is fixed as the top end of each clinical range; consequently, when varied in the DSA, the lower limits tested take the category of prediabetes very close to the value of the normoglycaemia, while the upper limits tested take the values for normoglycaemia and prediabetes into the clinical range of prediabetes and T2DM, respectively. As such, these scenarios represent the testing of extreme values and do not suggest that the model is performing other than would be logically expected in these (clinically implausible) situations. Furthermore, the choice not to explicitly model HbA1c was taken to align with committee-accepted TA875 approach and the non-diabetic nature of the SURMOUNT-1 trial population. However, the DSA results show the assumptions made with respect to normoglycaemia and prediabetes HbA1c are the most individually influential in the model.

Note that any shift from the TA875 approach to HbA1c would need to consider not just the efficacy of prediabetes reversal currently modelled but additionally the clear efficacy on HbA1c seen even in normoglycaemic patients in SURMOUNT-1: thus, any change to the current model assumptions would require the explicit modelling of differential HbA1c in the diet and exercise and tirzepatide arms, with efficacy also applied to semaglutide and liraglutide as applicable. Such a change would then more fully capture the proven glycaemic benefits of tirzepatide but would depart from the previously accepted modelling approach.

B.3.11.3 Scenario analysis

Several scenario analyses were explored altering model assumptions, literature sources or parameters used in the base case. The rationale for each scenario is outlined in Table 118. Deterministic results of the scenario analyses carried out are presented in Table 119 to Table 121, for each dose of tirzepatide vs both semaglutide (where relevant) and diet and exercise.

Table 118: Summary of scenario analyses

#	Scenario analysis	Rationale
1	Time of Prediabetes Reversal for Diet and Exercise (Weeks): 12	To test model sensitivity to the assumption for the time to onset of prediabetes reversal in the diet and exercise arm
2	Time of Prediabetes Reversal for Diet and Exercise (Weeks): 24	To test model sensitivity to the assumption for the time to onset of prediabetes reversal in the diet and exercise arm
3	Time of Return to Prediabetes for Diet and Exercise (Years): 3	To test model sensitivity to the assumption for the time to loss of prediabetes reversal in the diet and exercise arm
4	Time of Return to Prediabetes for Diet and Exercise (Years): 5	To test model sensitivity to the assumption for the time to loss of prediabetes reversal in the diet and exercise arm
5	Model Type for Efficacy Endpoints: Treatment Regimen Estimands	For transparency with respect to the choice of estimand used for efficacy inputs. As explained in Section B.3.3.1, use of the treatment regimen estimand for efficacy in a cost-effectiveness analysis which explicitly models the effect of treatment discontinuation on outcomes is expected to bias the results against active treatments as the effect of discontinuation on cohort level efficacy is applied to patients remaining on treatment in the model
6	Efficacy Waning Period Post-Discontinuation (Years): 1	To test the impact of the assumed waning period of efficacy following treatment discontinuation (base case of 3 years is aligned to TA875)
7	Efficacy Waning Period Post-Discontinuation (Years): 2	To test the impact of the assumed waning period of efficacy following treatment discontinuation (base case of 3 years is aligned to TA875)
8	Approach to Combining Utilities: Multiplicative	Testing an alternative method for combining utilities (base case is aligned to TA875 and the Literature, as discussed in Section B.3.4.5.2)
9	Risk Equation for Development of T2DM: Framingham Offspring Study	Testing alternative sources for risk equations
10	Risk Equation for Initial CVD Event: Framingham Heart Study	Testing alternative sources for risk equations
11	Risk Equation for Recurrent CVD Events: LIPID Study	Testing alternative sources for risk equations
12	Use T2DM-specific Risk Equations for CVD: No	To explore the impact of the use of separate risk equations for cardiovascular events in patients with and without diabetes
13	Source for Natural Weight Regain Post Discontinuation: Iyen et al. 2021[139]	To test an alternative literature source for natural weight gain following treatment discontinuation that was explored by the EAG in TA875; this source did not provide a breakdown by sex, in contrast to the base case source which did provide a breakdown.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 119: Results of scenario analyses – tirzepatide 5 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	£7,863	0.527	£14,910	£7,994	0.695	£11,510
1	£7,863	0.527	£14,910	£7,917	0.691	£11,457
2	£7,863	0.527	£14,910	£7,891	0.693	£11,387
3	£7,863	0.527	£14,910	£8,205	0.697	£11,776
4	£7,863	0.527	£14,910	£8,683	0.692	£12,542
5	£7,938	0.512	£15,515	£8,075	0.647	£12,478
6	£7,736	0.534	£14,474	£8,430	0.665	£12,683
7	£7,595	0.541	£14,043	£8,224	0.685	£12,002
8	£7,863	0.488	£16,112	£7,994	0.654	£12,228
9	£10,733	0.469	£22,863	£12,349	0.599	£20,622
10	£5,477	0.893	£6,135	£4,864	1.073	£4,532
11	£7,842	0.529	£14,833	£7,963	0.697	£11,431
12	£7,894	0.540	£14,613	£8,089	0.730	£11,085
13	£8,020	0.504	£15,919	£8,058	0.651	£12,373

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 120: Results of scenario analyses – tirzepatide 10 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	£7,724	0.500	£15,454	£7,856	0.667	£11,777
1	£7,724	0.500	£15,454	£7,779	0.664	£11,723
2	£7,724	0.500	£15,454	£7,752	0.665	£11,650
3	£7,724	0.500	£15,454	£8,066	0.669	£12,053
4	£7,724	0.500	£15,454	£8,545	0.665	£12,853
5	£7,892	0.461	£17,101	£8,028	0.597	£13,449
6	£7,585	0.501	£15,144	£8,279	0.631	£13,120
7	£7,461	0.511	£14,597	£8,090	0.655	£12,342
8	£7,724	0.495	£15,599	£7,856	0.661	£11,886
9	£10,649	0.444	£23,994	£12,265	0.573	£21,398
10	£5,663	0.858	£6,603	£5,051	1.038	£4,865
11	£7,728	0.502	£15,391	£7,849	0.670	£11,714
12	£7,790	0.529	£14,730	£7,984	0.718	£11,115
13	£7,905	0.485	£16,283	£7,943	0.633	£12,550

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 121: Results of scenario analyses – tirzepatide 15 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	£9,862	0.614	£16,062	£9,993	0.781	£12,792
1	£9,862	0.614	£16,062	£9,916	0.778	£12,751
2	£9,862	0.614	£16,062	£9,890	0.780	£12,686
3	£9,862	0.614	£16,062	£10,204	0.783	£13,025
4	£9,862	0.614	£16,062	£10,682	0.779	£13,713
5	£10,139	0.585	£17,339	£10,276	0.720	£14,268
6	£9,807	0.610	£16,073	£10,501	0.740	£14,185
7	£9,640	0.621	£15,523	£10,269	0.765	£13,417
8	£9,862	0.609	£16,199	£9,993	0.775	£12,902
9	£13,276	0.537	£24,704	£14,892	0.667	£22,334
10	£7,399	1.007	£7,345	£6,786	1.188	£5,713
11	£9,850	0.612	£16,104	£9,971	0.780	£12,790
12	£9,949	0.651	£15,282	£10,143	0.840	£12,069
13	£10,030	0.596	£16,825	£10,068	0.744	£13,540

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Interpretation of Scenario Analyses

Overall, the scenario analyses found the ICERs to be robust to changes in model assumptions, literature sources or parameters, with the majority of ICERs varying by less than £2,000/QALY and only one scenario in each dose table exceeding the £20,000/QALY WTP threshold.

Assumptions on prediabetes reversal in the diet and exercise arm

As discussed in Section B.3.3.2, several assumptions were required regarding the reversal of prediabetes in the diet and exercise arm, and the subsequent return to prediabetes in that arm. These assumptions were tested in Scenarios #1 to #4, and the model results in all comparisons changed in the expected direction, with later onset of reversal of prediabetes lowering the ICER (#1 and #2) while delaying the loss of reversal to later time points increased the ICER (#3 and #4). Reassuring, the effect of these assumptions was found to be modest with the ICER varying by approximately −£120 (#2) to +£1,000 (#4) from the base case ICER across all three doses of tirzepatide.

Efficacy inputs, assumptions, and method of utility combination

When the efficacy inputs were taken from the treatment regimen estimand (Scenario #5) the ICERs increased; this is expected as the treatment regimen estimand captures the cohort level effect of treatment discontinuation on efficacy parameters, which is inconsistent with the model where treatment discontinuation is explicitly modelled and affects both costs and QALYs. Reassuringly, the impact on the ICER of this scenario, which in effect double counts the impact of discontinuation, was moderate.

When the period of treatment waning post-discontinuation was reduced from the 3 years used in the base case (aligned with TA875), to either 1 or 2 years (Scenarios #6 and #7, respectively), the ICERs versus semaglutide improved (by up to ~£750/QALY at most), while those for diet and exercise were increased by between £500 and £1,600/QALY.

Testing an alternative multiplicative method for combining utilities (Scenario #8), which was not supported by the publications the utilities were sourced from and was inconsistent with the EAG-preferred approach in TA875, resulted in increased ICERs, however the magnitude of change was less than £200/QALY for tirzepatide 10 mg and 15 mg versus each of semaglutide and diet and exercise. The magnitude of change was somewhat greater in the comparisons of tirzepatide 5 mg versus each of semaglutide and diet and exercise; inspection of the disaggregated QALY plots showed a greater impact of disutilities in 5 mg than 10 mg and 15 mg and event cumulative incidence plots in these models suggested that earlier incidence of comorbidities resulted in more simulated patients being affected by comorbidities earlier in the simulation, which may explain the relatively greater impact of this scenario on the 5 mg dose.

Risk equations and natural history of weight gain

The scenario exceeding £20,000/QALY was, in each case, use of the Framingham Offspring Study for the risk of developing diabetes (Scenario #9). However, this risk equation was not chosen for the base case because it was based on a US population, was a much older study than the base case risk equation and, most influentially with respect to this scenario result, is based on entirely categorical variables that have limited sensitivity to the surrogate endpoints used in this model (e.g. BMI does not increase modelled risk once it is above 30 kg/m^2).

Use of the alternative risk equations for initial CVD events (Scenario #10) and for recurrent CVD events (Scenario #11) were both associated with lower ICERs versus diet and exercise for all tirzepatide doses, and versus semaglutide for tirzepatide 5 mg and 10 mg; tirzepatide 15 mg ICER became immaterially (~£40) higher versus semaglutide in the scenario changing the recurrent CVD risk

equation. Removal of T2DM-specific risk equations in the model (Scenario #12) led to modest reductions in the ICERs across all comparisons.

Testing an alternative natural weight gain following treatment discontinuation (Scenario #13) led to an increase in ICERs of around ~£750 to ~£1000 across all tirzepatide treatment arms. The annual BMI increase reported in Iyen (0.1060 kg/m^2 per year, irrespective of sex) is lower than the base case values (0.1447 and 0.1747 kg/m^2 per year for males and females, respectively); this leads patients in the diet and exercise arm (after the trial period) and patients modelled to discontinue incretin-based therapies to experience a slower increase in BMI, therefore lessening the comparative efficacy of tirzepatide.

B.3.11.4 First order uncertainty

As IPS models are stochastic, the effect of first-order uncertainty was tested with respect to simulated cohort size, presented in Figure 57 for the comparison of tirzepatide 10 mg versus diet and exercise. From this a cohort size of 1,000 simulated patients was selected for the base-case results.

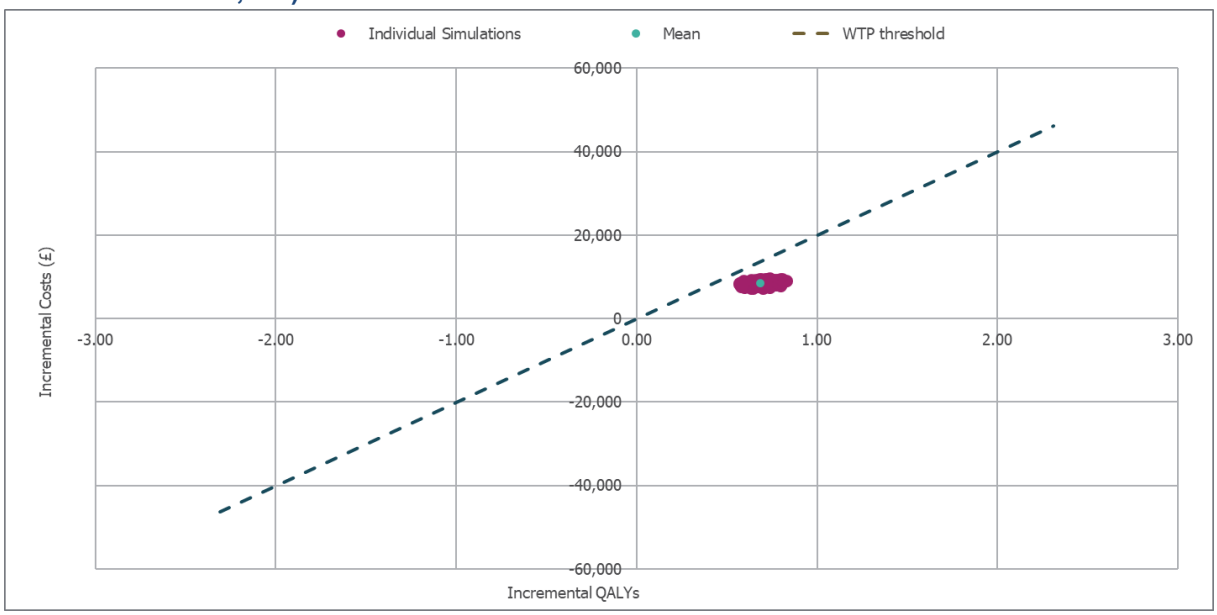
To allow repeatable deterministic results to be generated, the random number generator for the creation of the cohort of simulated patients was seeded. To test the effect of different seeds on the deterministic results, 500 seeds were tested to produce a scatter plot, presented in Figure 58 for the comparison of tirzepatide 10 mg versus diet and exercise.

Figure 57: Cohort convergence plot for tirzepatide 10 mg versus diet and exercise

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio.

Figure 58: Random seed scatter plot for tirzepatide 10 mg versus diet and exercise (cohort iterations set to 1,000)



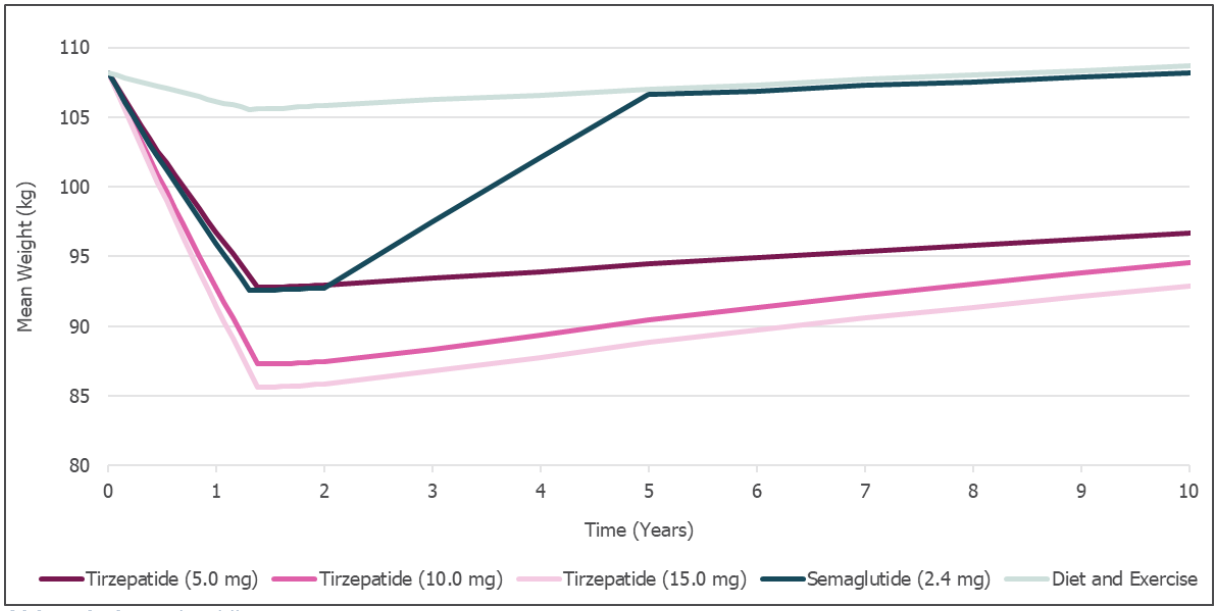
Abbreviations: QALY: quality adjusted life year; WTP: willingness-to-pay.

B.3.11.5 Summary of base-case surrogate endpoint and clinical event results

Projections, from the deterministic model, of modelled surrogate endpoints for all doses of tirzepatide, semaglutide and diet and exercise over the first 10 years of the time horizon are presented in Figure 59 to Figure 62. The figures are presented for the first ten years of the model, as this minimises the effect of mortality on the cohort mean values. Furthermore, as explained in Section B.3.3.1.2, after the initial onset of efficacy, and until discontinuation of treatment, surrogate endpoints either remain constant

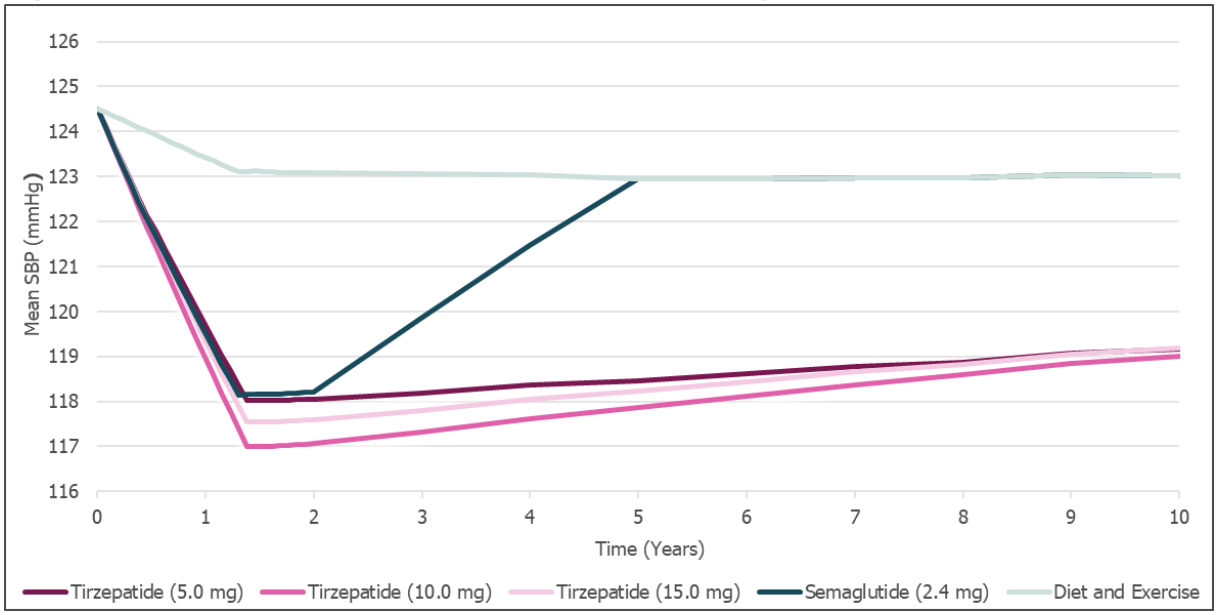
(SBP, total cholesterol, HDL) or increase in line with natural weight gain (weight). The gradual changes seen in the cohort mean values over longer time periods are a result of discontinuation of treatment in some simulated patients within the cohort, as explained in Section B.3.3.3.1. For transparency, figures over longer time periods are available in the model. Tirzepatide 15 mg was associated with the greatest beneficial changes in each biomarker, while tirzepatide 10 mg was associated with greater beneficial changes than semaglutide 2.4 mg in each biomarker except for total cholesterol.

Figure 59: Base-case results for mean weight over first ten years of model (deterministic)



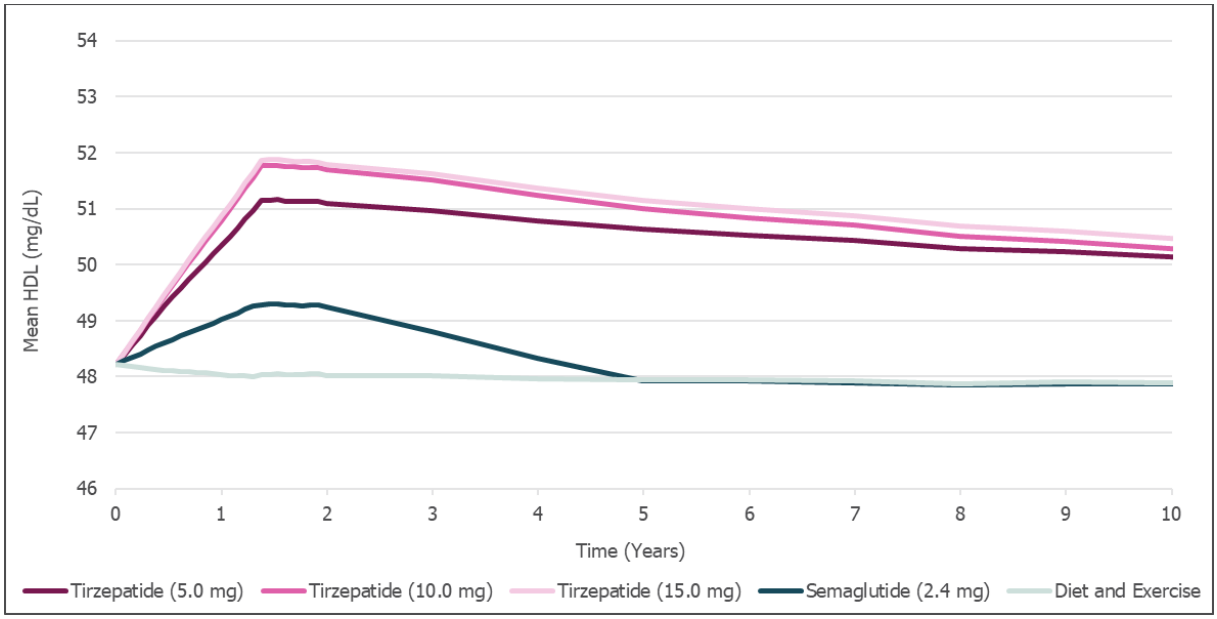
Abbreviations: kg: kilograms.

Figure 60: Base-case results for mean SBP over first ten years of model (deterministic)



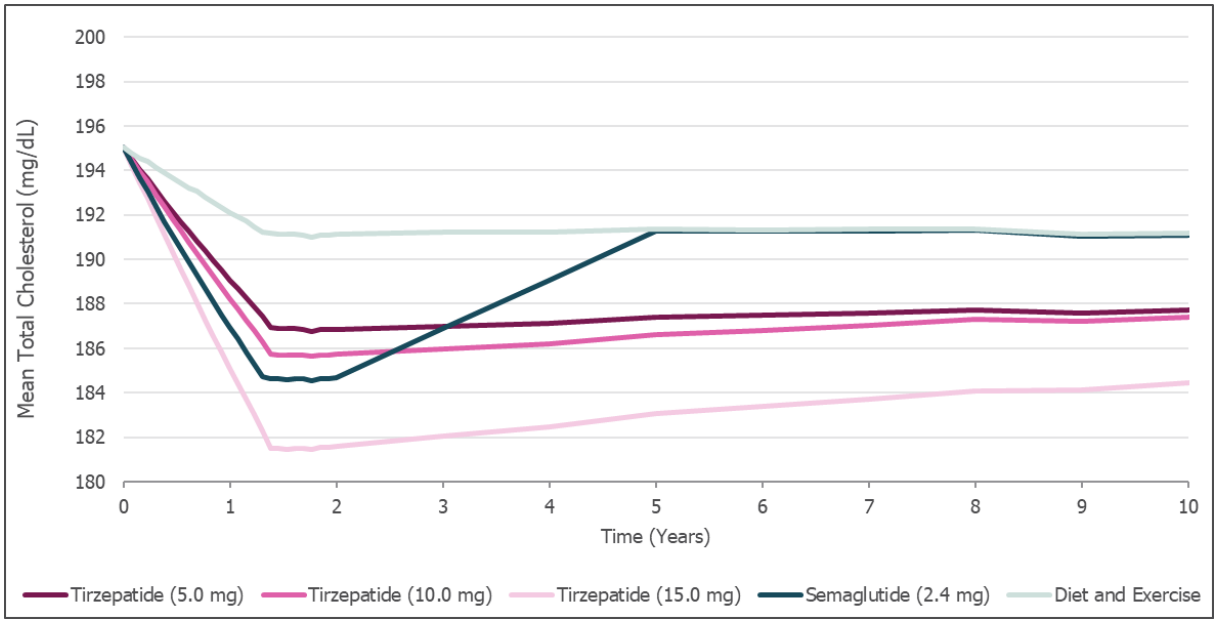
Abbreviations: mmHg: millimetres of mercury; SBP: systolic blood pressure.

Figure 61: Base-case results for mean HDL over first ten years of model (deterministic)



Abbreviations: HDL: high-density lipoprotein; mg/dL: milligrams per decilitre.

Figure 62: Base-case results for mean total cholesterol over first ten years of model (deterministic)



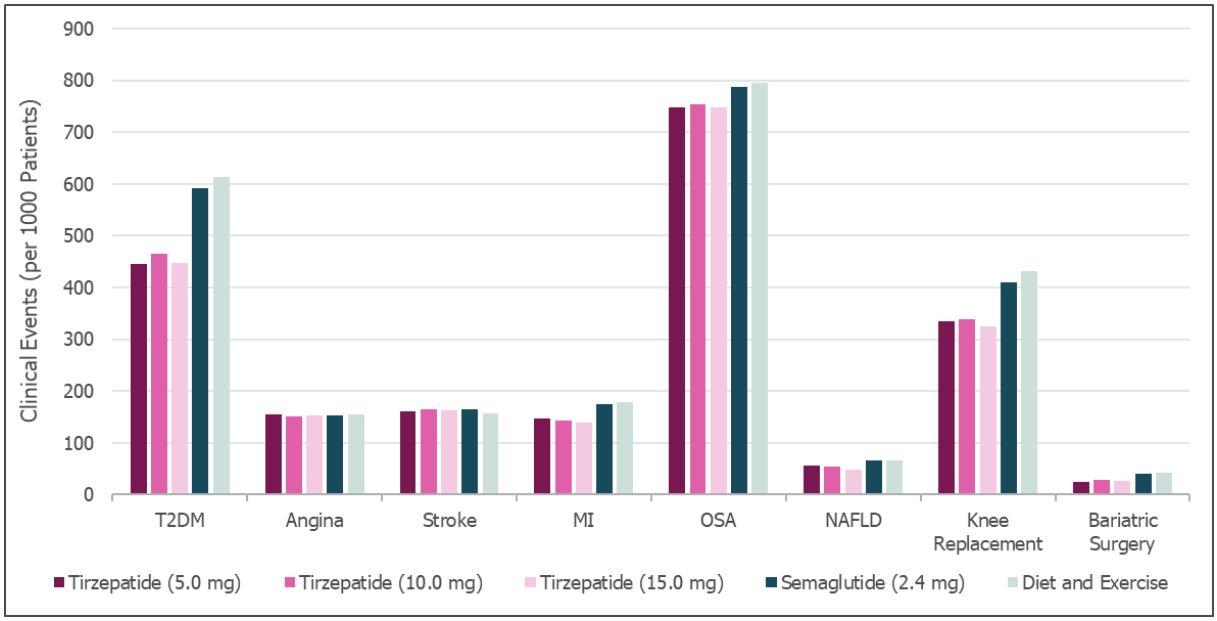
Abbreviations: mg/dL: milligrams per decilitre.

Projected total incidences of clinical events over the model time horizon, from the deterministic model, are presented in Figure 63. Each dose of tirzepatide was associated with fewer total clinical events across the model time horizon than both semaglutide and diet and exercise in the incidence of T2DM, MI, OSA, NAFLD, knee replacement and bariatric surgery. The total cumulative incidence of events was not always associated with a clear pattern between the three tirzepatide doses, because discontinuation rates for each dose to some extent offset gains from efficacy, and also because pre-diabetes reversal results vary by dose: in particular, tirzepatide 10 mg has the highest discontinuation due to AE rate and tirzepatide 5 mg the lowest. Furthermore, tirzepatide 10 mg has the lowest pre-diabetes reversal rate.

No clear trend in total incidence was observed between treatments in the results for angina and stroke, which were similar between all treatments, although inspection of the plots of incidence by time

available in the model (not shown here) showed some small degree of separation in curves between treatments earlier in the time horizon, followed by a convergence at later time points. It was noted however that the TA875 model had also predicted very similar event rates for stroke and angina in the semaglutide and diet and exercise arms of that model. This apparently anomalous result may reflect either a lack of sensitivity of the base case equations to the surrogate endpoints, or it may also reflect an unanticipated interaction between event rates predicted by the different risk equations used in those with and without T2DM. The latter interpretation is supported by the results of Scenario #12 reported in Section B.3.11.4, where a single set of risk equations are used irrespective of diabetes, which does result in a clear benefit of treatment on modelled event rates for both stroke and angina. Notably, the lack of a clear treatment effect on stroke stands at variance with the recently-disclosed top-line results of the SELECT trial of semaglutide 2.4 mg, which stated that all three components of the 3-point MACE composite endpoint (defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) contributed to the 20% reduction in MACE observed in that trial.[178] Given this trial result, it seems likely that the current model base case underpredicts the benefit of pharmacological treatments.

Figure 63: Base-case results for total incidences of clinical events over the model time horizon (deterministic)



Abbreviations: NAFLD: non-alcoholic fatty liver disease; MI: myocardial infarction, OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus.

B.3.12 *Subgroup analysis*

As discussed in Section B.1.3.6, given its unprecedented efficacy, tirzepatide is anticipated to provide substantial clinical benefits to patients who have a BMI of ≥30 kg/m^2 in the presence of at least one weight-related comorbidity and would address a substantial unmet need in this expected eligible population. The availability of a pharmacological treatment that facilitates this magnitude of weight loss could also help alleviate the substantial cost burden of obesity-related events and treatments, and would also contribute to ongoing public health efforts to reduce the prevalence and impact of obesity in the UK.

Nonetheless, tirzepatide is indicated for [redacted]

- [redacted]
- [redacted]

Given this, it is important that the EAG and NICE give consideration to the cost-effectiveness of tirzepatide across its licensed indication, and in wider subgroups of its indication than the target population with greatest unmet need. To facilitate this consideration, sections B.3.12.1, B.3.12.2, B.3.12.3 and B.3.12.4 provide ICERs in the following populations:

1. Population: BMI ≥35 kg/m² + prediabetes + high ASCVD risk (TA664 population)
2. Population: BMI ≥35 kg/m² (irrespective of comorbidities)
3. Population: BMI ≥30 kg/m² (irrespective of comorbidities)
4. Population: Whole SURMOUNT-1 Trial (BMI ≥27 kg/m² + ≥1 comorbidity, or BMI ≥30 kg/m²)

The population in Section B.3.12.1, from TA664, is more restrictive than the target population and each dose of tirzepatide was highly cost-effective versus semaglutide, liraglutide and diet and exercise. Considering the results of each dose of tirzepatide versus the only relevant comparator, diet and exercise, for the populations in Sections B.3.12.2, B.3.12.3 and B.3.12.4, it is apparent that:

- ICERs in Section B.3.12.2, (people living with class 2 or 3 obesity including both those who have not yet developed any weight-related comorbidities and those who have one or more weight-related comorbidity), are mostly slightly higher but are overall notably similar to the base case population. In the case of tirzepatide 10 mg, the ICER is very slightly lower than in the base case. Therefore, consideration could be given to the consequences for decision uncertainty of including this additional subpopulation in any recommendation, which the model results predict to have limited impact on the cost-effectiveness of tirzepatide compared to the base case population.
- ICERs in Section B.3.12.3, which removes the base case requirement for a comorbidity and considers all patients in the SURMOUNT-1 trial with obesity class 1, 2 and 3 (both those who have not yet developed any weight-related comorbidities and those who have one or more weight-related comorbidity) but continues to exclude people with overweight, were higher by £2,000 to £3,000/QALY compared to the base case in all comparisons. This would be expected given the addition of lower risk people who have not yet developed either weight-related comorbidities or class 2 or 3 obesity into the modelled population. The ICERs nonetheless remained well below the £20,000/QALY willingness-to-pay threshold. The consequences for decision uncertainty of including

this additional subpopulation in any recommendation would be expected to be greater than inclusion of population scenario #4.

- ICERs in Section B.3.12.4 consider the whole trial population and are further increased from Section B.3.12.3, being £4,000 to £5,000/QALY higher than the base case, although they nonetheless remain below the £20,000/QALY willingness-to-pay threshold in the overall mixed population. The consequences for decision uncertainty of making a recommendation across the entire indication are expected to be considerable, given this would encompass a large proportion of the adult population of England.

B.3.12.1 BMI ≥35 kg/m^2, prediabetes and high risk for CVD (TA664 population)

This subgroup analysis is included to allow for the comparison of tirzepatide to liraglutide, which was recommended by NICE in TA664. As discussed in Section B.3.2.3.2, the relevant comparators for this population are semaglutide, liraglutide and diet and exercise.

The deterministic base-case results for tirzepatide versus the relevant comparators in this subgroup are presented in Table 122 to Table 124. The incremental results for costs and health effects indicate that treatment with tirzepatide in this highest risk population was highly cost-effective compared to diet and exercise, semaglutide and liraglutide. It should be noted that the reversal of ordering in the results, whereby semaglutide is less costly than diet and exercise, is anticipated to be due to the assumption that the price of semaglutide does not vary between the disclosed price of the initial titration doses and the higher doses, where the price was redacted in TA875 and remains undisclosed at the time of this submission. In addition, TA664 indicates that a confidential PAS discount is available for liraglutide which would affect the fully incremental results and the comparison of tirzepatide versus liraglutide.

Table 122: Pairwise BMI ≥35 kg/m^2, prediabetes and high risk for CVD subgroup results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Semaglutide (2.4 mg)	[redacted]	18.822	15.719					
Diet and Exercise	[redacted]	18.762	15.541	£651	−0.060	−0.178	Dominated	Dominated
Liraglutide (3.0 mg)	[redacted]	18.785	15.628	£3,161	−0.037	−0.091	Dominated	Dominated
Tirzepatide (5.0 mg)	[redacted]	19.128	16.325	£5,811	0.305	0.606	£9,595	£9,595

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 123: Pairwise BMI ≥35 kg/m^2, prediabetes and high risk for CVD subgroup results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Semaglutide (2.4 mg)	[redacted]	18.822	15.719					
Diet and Exercise	[redacted]	18.762	15.541	£651	−0.060	−0.178	Dominated	Dominated
Liraglutide (3.0 mg)	[redacted]	18.785	15.628	£3,161	−0.037	−0.091	Dominated	Dominated
Tirzepatide (10.0 mg)	[redacted]	19.133	16.362	£5,694	0.311	0.642	£8,865	£8,865

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 124: Pairwise BMI ≥35 kg/m^2, prediabetes and high risk for CVD subgroup results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Semaglutide (2.4 mg)	[redacted]	18.822	15.719					
Diet and Exercise	[redacted]	18.762	15.541	£651	−0.060	−0.178	Dominated	Dominated
Liraglutide (3.0 mg)	[redacted]	18.785	15.628	£3,161	−0.037	−0.091	Dominated	Dominated
Tirzepatide (15.0 mg)	[redacted]	19.207	16.480	£8,196	0.385	0.760	£10,778	£10,778

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

B.3.12.2 BMI ≥35 kg/m^2, irrespective of comorbidities

The deterministic base-case results for tirzepatide versus the only relevant comparator, diet and exercise, in this subgroup are presented in Table 122 to Table 124.

Table 125: Pairwise BMI ≥35 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.595	16.440					
Tirzepatide 5 mg	[redacted]	19.955	17.162	£9,150	0.360	0.722	£12,682	£12,682

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 126: Pairwise BMI ≥35 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.595	16.440					
Tirzepatide 10 mg	[redacted]	19.965	17.203	£8,926	0.370	0.763	£11,700	£11,700

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 127: Pairwise BMI ≥35 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.595	16.440					
Tirzepatide 15 mg	[redacted]	20.003	17.311	£11,269	0.408	0.871	£12,940	£12,940

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

B.3.12.3 BMI ≥30 kg/m^2, irrespective of comorbidities

The deterministic base-case results for tirzepatide versus the only relevant comparator, diet and exercise, in this subgroup are presented in Table 122 to Table 124.

Table 128: Pairwise BMI ≥30 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.612	16.702					
Tirzepatide 5 mg	[redacted]	19.952	17.402	£9,627	0.340	0.700	£13,757	£13,757

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 129: Pairwise BMI ≥30 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.612	16.702					
Tirzepatide 10 mg	[redacted]	19.918	17.385	£9,438	0.306	0.683	£13,822	£13,822

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 130: Pairwise BMI ≥30 kg/m^2, irrespective of comorbidities subgroup results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.612	16.702					
Tirzepatide 15 mg	[redacted]	19.950	17.462	£11,844	0.338	0.760	£15,589	£15,589

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

B.3.12.4 SURMOUNT-1 whole trial population

The deterministic base-case results for tirzepatide versus the only relevant comparator, diet and exercise, in this subgroup are presented in Table 122 to Table 124.

Table 131: Pairwise SURMOUNT-1 whole trial population results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.640	16.764					
Tirzepatide 5 mg	[redacted]	19.917	17.393	£9,682	0.277	0.629	£15,386	£15,386

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 132: Pairwise SURMOUNT-1 whole trial population results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.640	16.764					
Tirzepatide 10 mg	[redacted]	19.866	17.351	£9,559	0.226	0.588	£16,265	£16,265

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

Table 133: Pairwise SURMOUNT-1 whole trial population results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	19.640	16.764					
Tirzepatide 15 mg	[redacted]	19.897	17.423	£11,931	0.257	0.659	£18,095	£18,095

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY: quality adjusted life year.

B.3.13 Benefits not captured in the QALY calculation

In TA875, the Committee discussed that, while the long-term benefits of weight loss were modelled, some long-term benefits such as reduced risk of liver disease may not have been captured in the model. As described in Section B.3.2.2.3, to address this, NAFLD has been included in the model for this appraisal.

However, as was discussed in Section B.3.11.5, the base case model does not appear to fully capture the expected benefits of the improvement in surrogate endpoints on all modelled events, notably stroke and angina, as a result of the apparent insensitivity of some of the available risk equations to the modelled surrogate endpoints. In addition, as discussed in Section B.3.11.2, the simplified approach taken with respect to HbA1c (aligned to that accepted in TA875) in the modelled population that is non-diabetic at baseline may also not fully capture the benefit of the significant efficacy of tirzepatide on this endpoint.

The TA875 Committee also discussed that weight loss may have other benefits that may not have been captured in the model. Examples could include:

- a decreased risk of adverse events associated with respiratory infections such as COVID-19
- a reduction in social isolation and stigma associated with obesity, and related improvement in career prospects,
- improvement in fertility or success rate for in vitro fertilisation.

It can be seen from Section B.1.3.2.1, Table 3, that while some of the major comorbidities have been modelled, the majority of comorbidities associated with obesity are not explicitly modelled, including a number of forms of cancer; given this, the ICERs presented in this submission are likely to be overestimated.

The TA875 committee concluded that it was important to consider these uncounted benefits, which may positively affect the cost-effectiveness estimates if they were to be modelled. These additional benefits were also not modelled in the present appraisal and therefore this same conclusion continues to apply to the ICERs presented.

In addition to the direct impact tirzepatide may provide in terms of alleviating the current burden of comorbidities in patients with a BMI ≥30 kg/m^2 and at least one weight-related comorbidity, it may also provide important additional downstream benefits to patients and wider society. Weight loss with tirzepatide may give patients their independence back by allowing them to participate in daily activities, sports and hobbies, by returning to work or improving presenteeism, thereby helping to reduce the significant societal burden and indirect costs associated with obesity. Tirzepatide may also help alleviate the clinical and economic burden associated with postponed or cancelled elective surgeries resulting from obesity,[84] and the increased risks associated with obesity when surgeries do go ahead.[85] Finally, use of this treatment may also reduce the burden of obesity on the healthcare system through reducing the burden of existing comorbidities and preventing additional weight-related comorbidities, thereby reducing weight-related hospitalisations and mortality.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

B.3.14.1.1 *Clinical validation*

The points of uncertainty were validated with an external clinical expert on Tuesday 22nd November 2022 and Wednesday 22nd March 2023.[131] The validation was based on the model specification document, model version and model results available at those times, The job titles of the external clinical expert at the time when they were consulted was as follows:

- Professor of Obesity, Diabetes and Endocrinology [redacted]
- Honorary Consultant
- Clinical Director of Medicine
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The aim of the first validation meeting was to:

- Validate the model approach
- Explore outstanding areas of uncertainty
- Review and validate the model structure, scenario analyses, likely modelling assumptions, and parameter values, including both validity of input sources and suggestions for parameter values in the absence of relevant data

The aim of the second validation meeting was to:

- Validate the clinical relevance of the model results
- Explore the model settings which should be used as the base case or explored in scenarios

The modelling approaches have been adapted to take into account the feedback received by the clinical expert.

[redacted]

B.3.14.1.2 *Internal technical validation*

Once the model was completed, an independent team of Health Economists who were not involved in programming the model performed a full technical quality control check which was conducted by completing two checklists:

- **Quality control checklist**, which involved checking through every cell of the model to ensure that all formulae are correct, that macros have been coded correctly, that everything is

referenced correctly, that there are no spelling or grammar mistakes, and that the formatting is consistent[179]

- **Internal validation checklist**, which involved setting up different scenarios to check that the model responds in the appropriate manner; for example, when all utility values are set to 1, the LYs should equal the QALYs. The model will be pushed to the extremes to ensure that it can handle extreme values as would be expected[180]

Together these checklists provide quality control and internal validation of the model through a documented review process. In addition, an independent analyst has performed a full input quality check, checking all model inputs against their original source.

B.3.14.1.3 *Strategic validation*

Following the internal technical validation, an expert in health technology assessment (HTA) and health economics who had not been involved in the development to date performed a strategic review of the model. The aim was to receive independent advice that could be constructive to the ultimate model development. The expert received the model as well as any related documentation (e.g., model specification document) and provided feedback which was addressed accordingly in the model and its supporting documents.

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of economic results

The base-case results show that all three doses of tirzepatide are cost-effective versus each of semaglutide and diet and exercise in the target population of people with a BMI of ≥30 mg/kg^2 and at least 1 weight-related comorbidity. The multi-way CEACs unambiguously show that each dose of tirzepatide versus semaglutide 2.4 mg and diet and exercise is the most cost-effective option at a willingness-to-pay threshold of £20,000/QALY. The deterministic scenario results reveal that the most influential model drivers relate to assumptions regarding the HbA1c values of simulated patients for normoglycaemia and prediabetes, which each affect the future risk of the development of diabetes; given the significant efficacy on glycaemia seen in the SURMOUNT-1 trial, the model base case assumptions on HbA1c taken from TA875 are likely to underestimate the beneficial effect of tirzepatide on these parameters. Scenario analyses found the model results to be robust to the tested assumptions, literature sources, and inputs, with only a single scenario, of a risk equation that with very limited sensitivity to weight loss, falling above the £20,000/QALY willingness-to-pay threshold.

Subgroup results in other populations revealed that tirzepatide was highly cost-effective in the TA664 population, where liraglutide is available in addition to semaglutide, and further revealed that the ICER in people with a BMI of ≥35 mg/kg^2, both those with and without comorbidities, was very similar to the base case target population, while ICERs including all trial participants with obesity, were above the base case ICER but remained below the £20,000/QALY willingness-to-pay threshold.

Model strengths and limitations

The CEM has both technical and clinical strengths as well as limitations. The technical strengths of the CEM include the comparatively short run time (relative to other simulation models) and the rigorous internal quality control process by independent Health Economists and Statisticians that

were conducted. The model is also highly flexible, with an extensive number of user-adjustable inputs and the ability to test various assumptions. Clinical strengths of the model include its reflection of various patient subgroups relevant to the decision problem with subgroup-specific efficacy inputs and patient characteristics. Further, the ability to track individual patients' history and perform patient-level analyses is a strength of the model, capturing a wide range of possible patient's health statuses and combination of comorbidities and events. Additionally, the choice of risk equations, as well as the model methods, assumptions and results, were thoroughly validated internally, by an independent strategic expert, and externally, by an expert clinician. The strong validation process that the model has undergone further enhances its clinical validity, providing confidence in the results generated by the CEM.

Limitations of the CEM include the extended run time for more complicated functionalities (e.g., sensitivity analyses) and that the risk equations were not derived directly from the population of interest (i.e., patients with obesity). It was also not possible to model the uncertainty around the risk equation coefficients probabilistically due to the lack of published covariance matrices. However, scenarios are available in the model that test alternative risk equations. Relatedly, not all comorbidities relevant to obesity could be incorporated into the model, given the reliance on sourcing appropriate risk equations in the literature; based on external clinical validation and comparison with other models in the indication, it is believed those most important to the estimates of cost-effectiveness have been captured, but it will be the case that some benefits have not been counted. Another key uncertainty is around long-term outcomes for key surrogate endpoints after the end of trial follow-up and following discontinuation. To address these necessary extrapolations, conservative assumptions that are consistent across treatment arms have been chosen, with scenario analyses presented altering them. Similarly, the simulation focusses on modelling surrogate endpoints considered key to obesity and does not fully capture the effect of incretin-based therapies on HbA1c, other than through the categorical presence or absence of prediabetes. Finally, as the price of the semaglutide maintenance dose is not publicly available and the confidential PAS discount for liraglutide is unknown, the true costs of these treatments might not be reflected in the results, although as this is likely to overestimate the ICERs versus semaglutide, the approach taken for that comparison is conservative.

Despite the limitations listed above, the CEM gives a robust indication of the short- and long-term costs and outcomes associated with treatment for patients with obesity. Outcomes have been informed as much as possible by published data, and where assumptions are required, these have been deemed appropriate by a clinician, and steps have been taken to mitigate the resulting uncertainty in the model. Finally, sensitivity and scenario analyses provide a more comprehensive understanding of the potential impacts of various treatment scenarios, reducing the decision uncertainty around whether tirzepatide should be considered a cost-effective use of NHS resources.

Conclusions

Obesity is known to lead to increased rates of many weight-related comorbidities and to reduce both quality of life and life expectancy as a result, yet many factors causing obesity are not fully within the individuals' control.[5, 11, 24, 57] Tirzepatide has demonstrated significant efficacy in obesity, not only on weight loss but also glycaemic control, blood pressure, and cholesterol which are known to be risk factors for many comorbidities that develop in people with obesity.[3, 12, 80, 89] The economic model results show that tirzepatide, adjunct to diet and exercise, is a cost-effective use of NHS resources in the target population of people with a BMI of ≥30 mg/kg^2 and at least one weight-related comorbidity, lowering BMI, SBP, and total cholesterol, while raising HDL

cholesterol and consequently reducing the predicted incidence of the clinical events captured in the model. Furthermore, some elements of the benefit of treatment are not fully captured in the model (Section B.3.12.2) and therefore the true cost effectiveness of tirzepatide is likely to have been underestimated. The subgroup analyses in wider populations that also include those who have not yet developed comorbidities (in addition to those who have) suggest that tirzepatide may be cost effective across its entire licensed indication.

Capacity constraints and geographic variability in access to SWMS have heavily restricted the NHS from providing treatment for obesity,[29, 39, 78] but the recently announced pilot programme for access in primary care initiated by HM Government and the consultation on the NICE Early Value Assessment for digitally-enabled technologies to support treatment with weight-management medication could potentially provide a pathway towards earlier availability of effective therapy than hitherto.[9, 32] In contrast, tirzepatide is a licensed therapy that is about to enter routine used in primary care for the treatment of diabetes.[92]

In summary, tirzepatide, adjunct to diet and exercise, offers the greatest weight loss yet seen in Phase 3 trials for any licensed pharmacological therapy[3] and has been shown to be a cost-effective use of NHS resources, with the economic model predicting lower incidences of many modelled comorbidities and increased quality and length of life as a result. The availability of tirzepatide offers the NHS a paradigm shift from weight management being offered only in capacity-constrained SWMS to being achievable in any setting.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tirzepatide for managing overweight and obesity [ID6179]

Summary of Information for Patients (SIP)

August 2023

File name	Version	Contains confidential information	Date
ID6179_Eli Lilly_Tirzepatide for Obesity_SIP_[NoCON]_22ndAugust2023	Final	No	22/08/2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Tirzepatide; **brand name**: Mounjaro®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adults with obesity who have:

- a body mass index (BMI) of at least 30 kg/m^2, and
- at least one other disease caused by their obesity (known as an 'obesity-related comorbidity').

Please note: Further explanations for some words and phrases are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **green**. References to figures and tables are highlighted in **orange**.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare products Regulatory Agency (MRHA) is reviewing whether tirzepatide should be approved and granted marketing authorisation as a treatment for overweight and obesity. The marketing authorisation for tirzepatide is therefore pending. More information on this can be found in **Document B** in **Section B.1.2**.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Lilly provided sponsorship funding to the following patient group:

Patient Organisation	Project	Financial Support
All About Obesity	Annual corporate membership	£25,000

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is obesity?

Obesity is a condition that is defined as having an excess amount of body fat. The most common method that is used for determining whether someone has obesity is by measuring their BMI. To calculate your BMI, you divide your weight in kilograms (kg) by the square of your height in meters (m). This gives a BMI measurement in kg/m^2 – a BMI of "25" means 25 kg/m^2.[1] Usually, having a BMI of 30 or more would mean that someone has obesity, but for people with some family backgrounds, a lower BMI of 27.5 would mean that they have obesity. Waist circumference is sometimes used as well as BMI because it gives more information about how likely a person is to develop other health conditions.

What causes obesity?

Obesity is a complex issue with many causes. Obesity is caused when energy taken in through food and drink is not balanced with energy used through physical activity.[2] There are lots of different causes which can contribute to this imbalance, which are explained more below.

- **Lifestyle factors:** One of the most important causes of obesity is eating a diet that is high in calories. For example, by eating large amounts of processed or fast food.[2] Lack of physical activity is another important factor related to obesity. This is because if you are not active enough, you do not use the energy provided by the food you eat. This extra energy you consume is stored by the body as fat.[2]
- **Genetics**: There are some genes which are associated with obesity and overweight. In some people, genes can affect how their bodies change food into energy and store fat. Genes can also affect people's lifestyle choices.
- **Medical reasons:** In some cases, medical conditions may contribute to weight gain. For example, conditions that cause abnormal levels of hormones in the body can contribute to obesity. Certain medicines, including some steroids, medications for diabetes, and some medications used to treat mental illness can also contribute to weight gain.[2]

How many people have obesity?

Obesity has become more common over the past 50 years. In England, more than 1 in 4 adults in England had obesity in 2021. This number is predicted to increase in the future, so that more than 1 in 3 people have obesity in 2030.[3]

Obesity is more common in the UK in some groups of people than in others:[4]

- Men are more likely than women to have obesity
- Obesity is more common in the North of England and the Midlands than the South of England
- Obesity is more common in lower income groups compared to higher income groups
- A BMI of greater than 30 is less common in people with Chinese or Asian family backgrounds and is more common in people with Black and White British family backgrounds. However, there is a higher risk of developing obesity-related comorbidities in people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background (**Section 2b**)

How does obesity impact overall health?

Obesity is one of the main causes of death and disability in England and also worldwide.[5] It is estimated that people with a BMI of 30 to 35 live for around 2 to 4 years less than people without obesity. People with a higher BMI of between 40 to 50 are estimated to live for an even shorter time, of around 8 to 10 years less than people without obesity.[6, 7]

People with obesity often do not live as long as people with a normal weight because of their higher risk of developing other serious health conditions that are caused by their

excess body fat. These are sometimes called ‘weight-related’ or ‘obesity-related’ comorbidities.[7] There is a large number of different obesity-related comorbidities, which can affect many different parts of the body. Some of the most common obesity-related comorbidities are explained further below:

Type 2 diabetes

This is a condition where glucose (sugar) levels in the blood become too high. It can cause symptoms like excessive thirst, needing to go to the bathroom a lot and tiredness. It can also increase your risk of getting serious problems with your eyes, heart and **nerves**.[8]

Cardiovascular disease

This is a general term for conditions affecting the heart or blood vessels. Cardiovascular disease can cause complications such as heart failure or stroke.[9]

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is caused by a build-up of fat in the liver. Having NAFLD can eventually lead to liver damage if not detected and managed and is also linked to liver cancer.[10]

What is the cost of obesity to the healthcare system?

Obesity is costly to the healthcare system. This is because obesity-related comorbidities cost money to treat and manage over the short- and long-term. In the UK, it has been estimated that the NHS spent £6.1 billion on obesity-related disease in 2014 to 2015. It is predicted that this spending will increase by up to £9.7 billion by 2050.[11]

What is the impact of obesity on the lives of patients?

Impact on quality of life

Obesity impacts the lives of patients in many ways. Because of this, obesity often has a negative impact on patients’ quality of life. People with obesity often report that they have worse mental wellbeing than people with normal weight.[12, 13] People with obesity also may face challenges with their physical functioning, which can lead to lower quality of life. For instance, people with obesity may struggle to carry out daily activities and move around due to their weight.[12, 13] Studies have also found that people with obesity and certain obesity-related comorbidities have poorer quality of life.[13]

Weight stigma

Many patients with obesity experience stigma because of their weight. For example, in a study of people with overweight and obesity, more than half of the participants said they had experienced stigma because of their weight.[14] People living with obesity can face stigma in education, in the workplace, the mass media, with friends and family, and even in healthcare settings. This can affect education, their careers and self-confidence.[15]

Mental impact

Weight stigma can also have an impact on mental health, leading to depression, anxiety, and lowered self-esteem. Studies have found that anxiety is more common in people with

obesity, and that people with obesity also have a higher risk of depression compared to people with normal weight.[16, 17]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

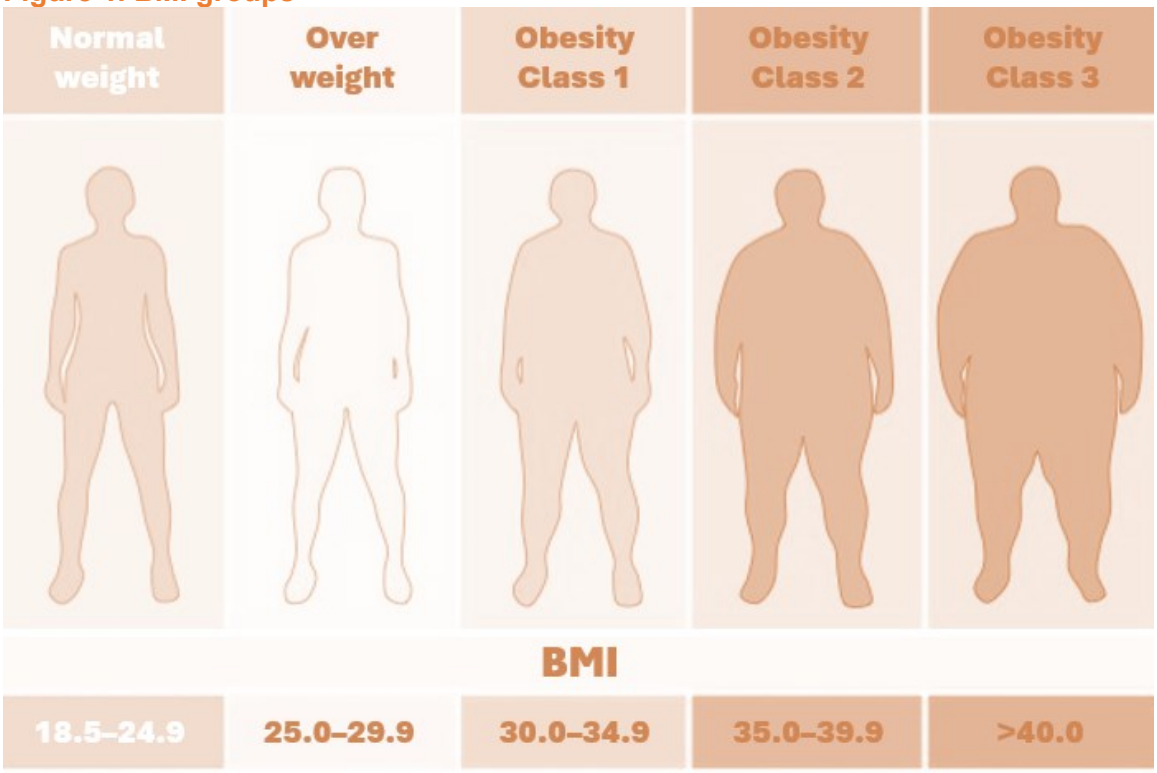
How is obesity diagnosed?

BMI

As described in **Section 2a**, BMI is the most common method that is used to determine whether someone has obesity. If a person has a BMI of 30 or higher, they would usually be considered to have obesity. Patients can also be further divided into various different BMI groups, shown in **Figure 1** below.[1]

There is a higher risk of developing obesity-related comorbidities in people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background. Because of this, a person from one of these family backgrounds would be considered to have obesity at a lower BMI than 30 compared to other ethnic groups. In the UK, a person with a BMI of 27.5 or above would be considered as having obesity if they are from a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background Black, Asian and minority ethnic family backgrounds.[1]

Figure 1. BMI groups



Abbreviations: BMI= body mass index

Other methods

Although BMI is a useful way of determining whether someone has obesity, it is not accurate for everyone. For example, people who are very muscly may have a high BMI, but may not have excess fat. In these cases, it can be more useful to know if a person has excess fat around their abdominal area, or 'increased central adiposity'. Knowing a person's central adiposity can also be more useful than BMI for determining their risk of obesity-related health risks.[7]

There are various methods of measuring central adiposity. The simplest method is by measuring a person's waist circumference. Waist-to-height ratio may also be used, which compares someone's height to their waist circumference. The percentage of body fat that someone has can also be used to indicate central adiposity, which can be measured using various methods, such as skinfold callipers.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

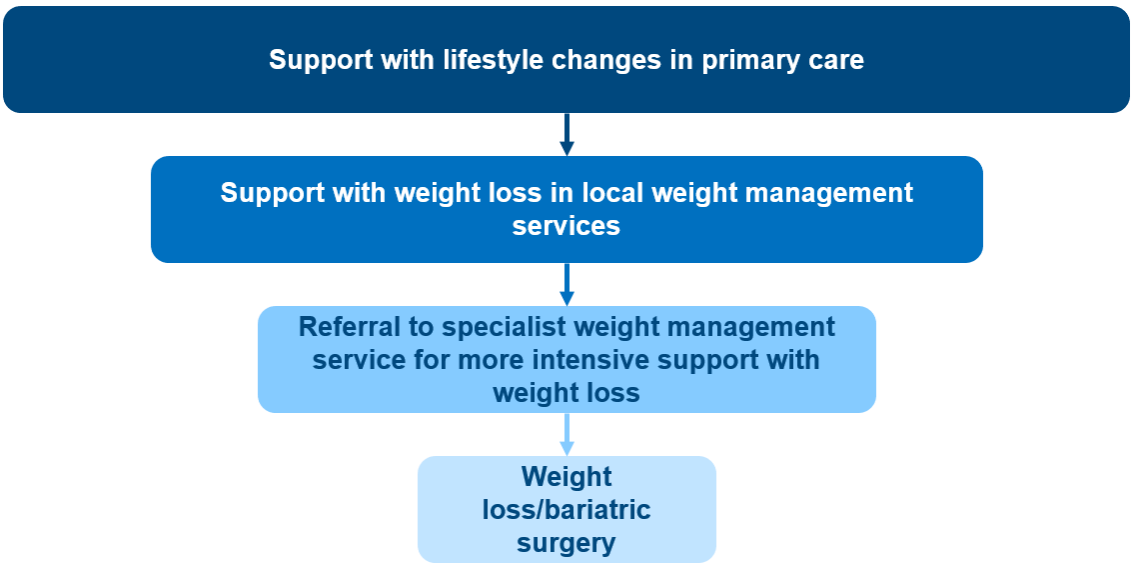
Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

How is obesity managed in the UK?

Within the NHS in England, obesity is managed through a tiered system, shown in **Figure 2**. This means that patients start with the least intensive option for managing their weight. If this does not lead to sufficient weight loss, they then try the next option that is more intensive. The different options are explained more below.

Figure 2. Obesity management in England



Lifestyle changes

The first and most important management option for obesity is lifestyle changes. This involves helping people lose weight through eating a balanced, calorie-controlled diet and by helping them to become more physically active.

In order to make these lifestyle changes, people with obesity usually first get support in primary care by a general practitioner (GP).[18, 19] A GP may also give advice about, or refer people to local weight management services. These services may include weight management programs which provide advice on diet, nutrition, lifestyle and behaviour changes.[2, 18] Usually, these programs are only available to patients for around 12 weeks.[19]

Specialist weight management services

If local weight management services are not successful, then patients might be referred to specialist weight management services (SWMS). In SWMS, patients are assessed by different healthcare professionals. This includes a GP, as well as dieticians, psychologists

and physiotherapists. These teams of healthcare professionals provide more intense management of obesity.

Weight loss surgery

Weight loss surgery, also called bariatric surgery, is used to treat people with severe obesity. In England, it is only available to patients:

- if they have a BMI of 40 or more, or
- if they have a BMI between 35 and 40 and another serious health condition that could be improved with weight loss.

Patients must also be fit enough to have anaesthesia and surgery and must commit to long-term monitoring after the surgery. Surgery is not used very often and is usually considered a last resort.[20, 21] This is because it is carries a number of risks and requires a lot of commitment from patients.[22]

What medicines are available for obesity?

Anti-obesity medicines

If lifestyle changes alone are not successful, patients may also be offered an anti-obesity medicine to help them lose weight. The different types of anti-obesity medicines that are currently available to patients in England are explained below.[1]

Orlistat

Orlistat is a type of oral medicine known as a lipase inhibitor. This means that it works by binding to and removing fat from the body before it is absorbed. Orlistat is only available to patients either if:

- they have a BMI of 30 or more, or
- they have a BMI of 28 or more, as well as other obesity-related comorbidities.

Patients can only continue taking orlistat if they lose at least 5% of their body weight in the first 12 weeks.[7]

Although orlistat is available for these patients, it is not used very often and is prescribed less and less over time.[23] This is most likely because it causes unpleasant **side effects** and is not as effective as other available treatments.[20, 21, 24]

Liraglutide (3 mg)

Liraglutide is a daily injectable glucagon-like polypeptide-1 receptor agonist (GLP-1 RA). It works by mimicking the action of a hormone called glucagon-like polypeptide-1 (GLP-1) in the body. By mimicking this hormone, liraglutide reduces appetite so that people eat and drink less. It also slows down how quickly the stomach digests food and empties, meaning that people feel fuller for longer.

In England, liraglutide is only prescribed in a SWMS. It is only available to patients if they have all three of the following:[20]

- a BMI of 35 or more

- higher than normal blood sugar levels, known as prediabetes
- a high risk of cardiovascular disease.

Semaglutide (2.4 mg)

Semaglutide is a weekly injectable GLP-1 RA, which works in a similar way to liraglutide. In England, semaglutide is recommended for patients if:[21]

- they have a BMI of at least 35, or
- they have a BMI of 30 to 34.9 and are eligible for referral to a SWMS

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Obesity from the patient perspective

Obesity can impact many areas of a patient's life and can be difficult for patients to cope with. In particular, the stigma associated with obesity can make it hard to carry out day-to-day activities, socialise, and perform at work. In studies involving patients with obesity, there were some key topics that patients mentioned were particularly challenging. These included:[25]

Living a limited life

A number of studies have found that patients often feel they are living a limited life because of their obesity. People with obesity report that they experience restrictions in movement, which can lead to them missing out on activities and opportunities.[25] In addition, studies often report that complications of obesity such as diabetes, high blood pressure, and musculoskeletal pain affected people's ability to be active and participate in aspects of daily life.[25]

Studies have also shown that people with obesity may feel socially disconnected and withdraw from life to avoid judgement, stares and comments.[25] For example, a participant in one study said "I notice that I decline invitations when I'm at my worst". [26] Some people with obesity even described their lives as not worth living because of this.[27]

Experiencing stigma, judgment, shame, and blame

In studies of people with obesity, stigma is highlighted as a common challenge, as well as the feelings of shame and worthlessness. Judgment is also mentioned as a common experience, with people explaining how they live under the critical eye of other people.

Feelings of being judged by others as not good enough, not trying hard enough, lazy, and/or undeserving of respect are also common in people with obesity.[25, 28-30]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

About tirzepatide and how it works

Tirzepatide is a novel weekly injectable dual incretin agonist. This means it mimics two different hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1).[31] By mimicking these two different hormones, tirzepatide acts in complementary ways to cause weight loss:[32]

- Firstly, tirzepatide causes the stomach to empty more slowly, so patients feel satisfied with less food. This slowing helps reduce the number of calories that a person eats and drinks.
- Secondly, tirzepatide reduces appetite and hunger, which can also help patients reduce their intake of food and drink.

As well as causing weight loss, tirzepatide also helps to reduce blood glucose (sugar) levels.[31] Tirzepatide is therefore also approved as a treatment for type 2 diabetes.[33]

Another resource that has further information on how tirzepatide works is the Patient Information Leaflet (Package leaflet: Information for the patient | Mounjaro).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Tirzepatide is not intended to be used in combination with other medicines. However, tirzepatide will be given alongside support with lifestyle changes, such as eating a healthy diet with a deficit of 500 calories each day and doing at least 150 minutes of physical activity each week. This is the same way that tirzepatide was used in the SURMOUNT-1 study, which is explained in **Section 3d**.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is tirzepatide taken?

Tirzepatide should be used exactly as the healthcare professional (HCP) has instructed. Tirzepatide is given as an injection once per week, using a pre-filled pen. Tirzepatide should be injected under the skin into the stomach area, upper thigh, or upper arm. A patient can inject themselves in the stomach area or upper leg, but may need some help from someone else if injecting into the upper arm. The area of the body that tirzepatide is being injected into should be rotated each week. The dose can be given at any time of day, with or without meals.[31]

How much medicine do patients take and when?

Tirzepatide is injected once weekly and the dose will be determined by an HCP. Tirzepatide is first started at 2.5 milligrams (mg) each week to help the patient adjust to the treatment. After 4 weeks, the dose is increased to 5 mg per week. If needed, the dose can be increased by 2.5 mg every 4 weeks up to either 5 mg, 10 mg or 15 mg.

The recommended maintenance doses for tirzepatide are 5 mg, 10 mg and 15 mg every week. However, doses of 7.5 and 12.5 mg every week may be given for 4 weeks when changing between the recommended doses. This is to help the patient adjust to the new higher dose. In each case, the HCP will provide instructions on how long each dose should be taken for.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of tirzepatide in obesity

The main clinical evidence that is available for tirzepatide as a treatment for adult patients with overweight and obesity is from a clinical trial was called **SURMOUNT-1**.

The SURMOUNT-1 trial was a Phase 3 clinical trial. It looked at how well tirzepatide worked to treat obesity (its efficacy) and how safe the medicine was compared to placebo. This trial also looked at the impact of tirzepatide on patients' quality of life.

The study included adult patients with overweight and obesity. This meant patients:

- had a BMI of 30 or more (obesity); or
- had a BMI of 27 or more (overweight) as well as at least one obesity-related comorbidity

How was the SURMOUNT-1 trial carried out?

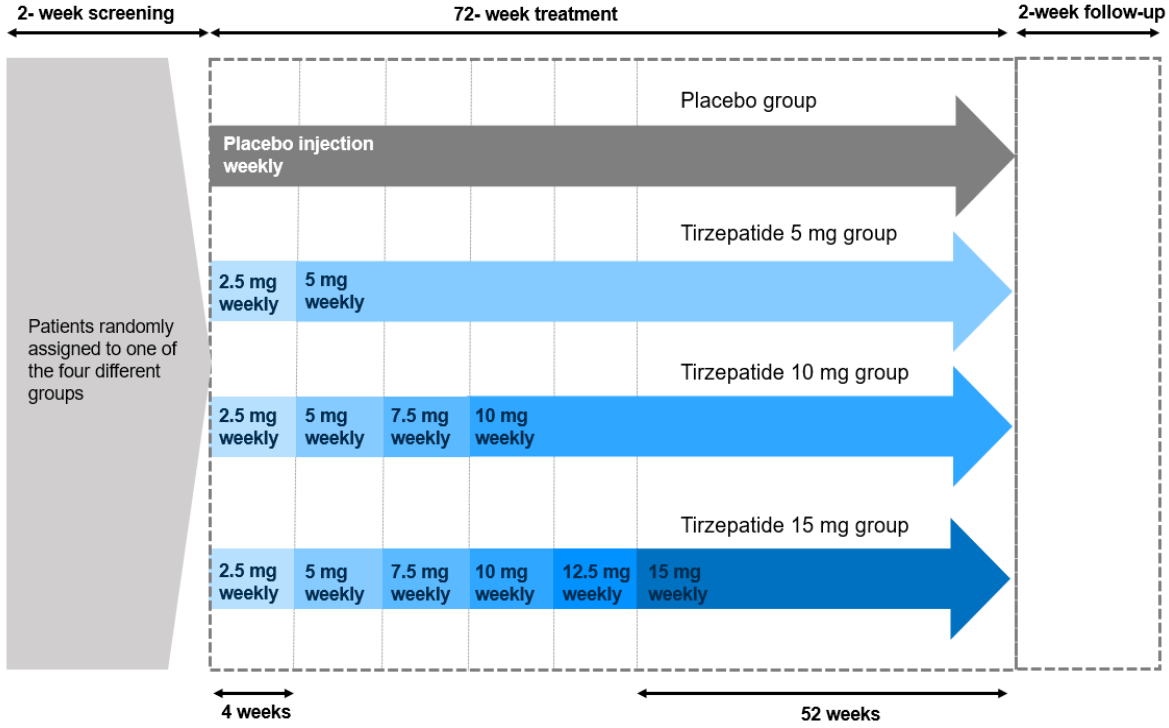
In SURMOUNT-1, all patients were also supported with losing weight through making changes to their lifestyle. This included advice on consuming a reduced calorie diet and doing more exercise.

As SURMOUNT-1 compared three different doses of tirzepatide to placebo, patients were given one of the following options:

1. 5 mg tirzepatide with a reduced calorie diet and increased physical activity
2. 10 mg tirzepatide with a reduced calorie diet and increased physical activity
3. 15 mg tirzepatide with a reduced calorie diet and increased physical activity
4. Placebo with a reduced calorie diet and increased physical activity

A summary of the study design of SURMOUNT-1 is shown in **Figure 3**.

Figure 3. SURMOUNT-1 study design



Note: follow-up and screening are defined in the glossary (**Section 4b**)

A summary of all the other trials studying tirzepatide in obesity is provided in **Table 1**.

Table 1. Trials investigating tirzepatide in obesity

Trial name and number	Location	Patients included	Completion date
SURMOUNT-1 (NCT04184622)	International (United States, Argentina, Brazil, China, India, Japan, Mexico, Puerto Rico, Russian Federation, Taiwan)	2,539	July 2024 (extension completion date)
SURMOUNT-2 (NCT04657003)	International (United States, Argentina, Brazil, India, Japan, Puerto Rico, Russian Federation, Taiwan)	938	April 2023
SURMOUNT-3 (NCT04657016)	International (United States, Argentina, Brazil, Puerto Rico)	806	May 2023
SURMOUNT-4 (NCT04660643)	International (United States, Argentina, Brazil, Puerto Rico, Taiwan)	783	May 2023
SURMOUNT-5 (NCT05822830)	International (United States, Puerto Rico)	700	December 2024
SURMOUNT-CN (NCT05024032)	China	210	December 2022
SURMOUNT-J (NCT04844918)	Japan	267	June 2023
SURMOUNT-OSA (NCT05412004)	International (United States, Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Puerto Rico, Taiwan)	469	March 2024
SURMOUNT-MMO (NCT05556512)	International (United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czechia, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Poland, Puerto Rico, Slovakia, Spain, Taiwan, Turkey, Republic of Korea, Romania, United Kingdom)	15,000	October 2027

More information about SURMOUNT-1 can be found here:

- Jastreboff, 2022 (https://www.nejm.org/doi/full/10.1056/NEJMoa2206038)
- ClinicalTrials.gov (https://www.clinicaltrials.gov/ct2/show/NCT04184622)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How was the efficacy of tirzepatide measured?

In SURMOUNT-1, the efficacy of tirzepatide was measured by looking at how much weight loss patients achieved after 72 weeks of treatment compared to placebo. There were two main ways that this was measured, including:

- The percentage of weight loss that patients achieved in the 10 mg and the 15 mg groups from the beginning of the trial (or 'baseline') to Week 72
- The number of patients who had at least 5% weight loss in the 10 mg and the 15 mg groups from the beginning of the trial to Week 72

In the SURMOUNT-1 trial, two different methods were used to determine how well tirzepatide and the placebo worked to improve weight loss in the participants in the trial. These were:

- The **efficacy estimand**: This was used to determine how well tirzepatide or placebo worked in only the participants who took their treatment for the whole 72-week treatment period
- The **treatment-regimen estimand**: This was used to determine how well tirzepatide or placebo worked in all participants, even if they did not continue to take their treatment for the whole 72-week treatment period

Trial results

Table 2 shows the key results from the efficacy estimand after 72 weeks of treatment with tirzepatide 5 mg, 10 mg and 15 mg and placebo. These results show that all three doses of tirzepatide led to significant improvements in weight loss compared to placebo over 72 weeks.

The SURMOUNT-1 trial also showed that tirzepatide improved many cardiovascular and metabolic risk factors. This means that tirzepatide may reduce the likelihood of patients developing metabolic syndrome and cardiovascular diseases.

More efficacy results can be found in **Document B**, **Section 2.6**.

Table 2. Key efficacy results for SURMOUNT-1 after 72 weeks; efficacy estimand

Parameters	Placebo	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg

Percent change in body weight from baseline to 72 weeks	−2.4%	−16.0%	−21.4%	−22.5%
Participants achieving at least a 5% loss in body weight	27.9%	89.4%	96.2%	96.3%

Indirect treatment comparison

For practical and ethical reasons, clinical trials usually only directly compare a small number of medicines. To compare tirzepatide with all other treatments that people with obesity might receive, indirect comparisons are used. This is a common approach in evaluations of new medicines. An indirect comparison was done in this instance to compare tirzepatide with liraglutide and semaglutide, which are currently used to treat people with obesity. This indirect comparison is explained in further detail in **Document B, Section B.2.9**.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

How was quality of life measured?

The SURMOUNT-1 trial assessed the quality of life of people with obesity through two different questionnaires:[34]

- **The physical functioning domain of the Short-Form-36 Health Survey (SF-36)**: This questionnaire was used to assess the physical functioning of participants in the study.
- **The EuroQol 5-dimensions (EQ-5D) questionnaire**: This looked at the effect of a participant with obesity on their overall quality of life. This questionnaire assessed topics such as mobility, self-care, usual activities, pain and discomfort and anxiety and depression.

- **Impact of Weight on Quality of Life-Lite-Clinical trials (IWQOL-Lite-CT) questionnaire**: This questionnaire was used to assess the physical functioning and emotional and social impacts experienced by participants in the study.

At the start and end of the SURMOUNT-1 trial, patients completed these questionnaires. Comparing the questionnaire scores at the start and the end of the trials showed whether patients thought their physical functioning and quality of life had improved.

Quality of life impact of tirzepatide

Over the 72 weeks of the study, there was an improvement in physical functioning in the tirzepatide 10 mg and 15 mg groups, as well as for people treated with placebo. However, the people treated with tirzepatide 10 mg and 15 mg had a significantly greater improvement in quality of life compared to the placebo group (SF-36).[34]

The SURMOUNT-1 study also showed that all groups in the study had an improvement in their quality of life over the course of the study (EQ-5D). All tirzepatide groups had a greater improvement in their quality of life than the placebo group.[34]

Although there were improvements in quality of life in the SURMOUNT-1 study, the study was not able to measure the long-term benefits of tirzepatide on quality of life as the trial duration was 72 weeks.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own side effects and the same medicine can produce different reactions in different people. In SURMOUNT-1, tirzepatide was generally well tolerated.

Table 3 compares the percentage of patients reporting side effects in the SURMOUNT-1 studies who were taking tirzepatide or placebo. The most common side effects of tirzepatide were gastrointestinal events, including nausea (feeling sick), diarrhoea, vomiting and constipation.[35] Side effects were mostly experienced during the period of time when the dose of tirzepatide was being increased, so they were usually short-term. To reduce these side effects, tirzepatide is started on a lower dose. After 4 weeks, the doses is increased. If needed, dose increases can be made after a minimum of 4 weeks on the current dose until the patient and HCP agree the dose is appropriate.

Many of the side effects experienced by people treated with tirzepatide can be managed by following advice from their HCP.

Table 3. Summary of the most common side effects experienced by patients during SURMOUNT-1[35]

Side effect	Placebo	Tirzepatide		
	(N=643)	5 mg (N=630)	10 mg (N=636)	15 mg (N=630)
Nausea	9.5%	24.6%	33.3%	31.0%
Diarrhoea	7.3%	18.7%	21.2%	23.0%
COVID-19	14.0%	14.9%	15.4%	13.0%
Constipation	5.8%	16.8%	17.1%	11.7%
Acid reflux	4.2%	8.9%	9.7%	11.3%
Vomiting	1.7%	8.3%	10.7%	12.2%
Decreased appetite	3.3%	9.4%	11.5%	8.6%
Headache	6.5%	6.5%	6.8%	6.5%
Abdominal pain	3.3%	4.9%	5.3%	4.9%
Hair loss	0.9%	5.1%	4.9%	5.7%
Dizziness	2.3%	4.1%	5.5%	4.1%
Belching	0.6%	3.8%	5.2%	5.6%
Injection site reaction	0.3%	2.9%	5.7%	4.6%

The proportion of patients who experienced a more serious side effect or stopped their treatment (or "discontinued") because of side effects during SURMOUNT-1 is shown in Table 4. Overall, there were a similar number of serious side effects in patients who were treated with tirzepatide compared with those receiving placebo.

Table 4. Summary of serious side effects and treatment discontinuations during SURMOUNT-1[35]

	Placebo	Tirzepatide		
	(N=643)	5 mg (N=630)	10 mg (N=636)	15 mg (N=630)
Serious side effect	6.8%	6.3%	6.9%	5.1%
Side effect leading to discontinuation	2.6%	4.3%	7.1%	6.2%

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of tirzepatide to patients with obesity include:

Improved weight loss compared to placebo

- Tirzepatide helps people achieve significantly greater weight loss compared to placebo and other medicines used to treat obesity, based on indirect comparisons
- In the SURMOUNT-1 trial, all doses of tirzepatide led to greater reductions in body weight compared with placebo
- The 10 and 15 mg doses of tirzepatide led to more than 20% weight loss on average in the SURMOUNT-1 trial, which is more than any other medicine that has been investigated in a Phase 3 clinical trial[36]

Manageable safety profile

- Tirzepatide is generally well tolerated
- The side effects are likely to be familiar and readily managed by the healthcare community

Positive impact on quality of life

- Tirzepatide leads to greater improvements in quality of life and physical functioning compared with placebo

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Tirzepatide is generally well tolerated and effective in leading to significant weight loss in most patients, however, some things that patients may want to consider before starting treatment include:

Efficacy

Tirzepatide does not work for everyone and some patients might not experience any improvement in weight loss. Patients for whom tirzepatide does not work may still experience side effects, which are detailed further below.

Side effects

Like all medicines, some patients may experience side effects while they are taking tirzepatide. The SURMOUNT-1 trial showed that gastrointestinal events were most common in people with obesity treated with tirzepatide.[35] These side effects can limit the

use of higher doses of tirzepatide in some people with obesity. However, the side effects are likely to be familiar and readily managed by following advice from an HCP.

Administration

Tirzepatide is a medicine which is given by injection.[31] However, semaglutide and liraglutide are both also taken by injection.[37, 38]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

What is the economic model for?

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (tirzepatide) with current treatments for obesity (diet and exercise, semaglutide, liraglutide).

What does the health economic model do?

How the model reflects the obesity

The health economic model simulates people with obesity with characteristics similar to those of people who would receive tirzepatide treatment in the NHS. This includes simulating other health conditions that are linked to obesity, like type 2 diabetes and cardiovascular disease.

The effect of treatment with tirzepatide on obesity and other health conditions was modelled using changes in weight, changes in blood pressure and changes in fats (high-density lipoprotein and cholesterol) in the blood that were seen in the SURMOUNT-1 trial and the indirect comparison.

The model simulates what would happen to patients if they were given different treatments (tirzepatide, semaglutide, liraglutide, or just diet and exercise).

Modelling how much treatments impact patients' lives

As well as direct changes to patient health, the model measured the impact of treatment on patient quality of life; this can include improvements in quality of life due to reduced symptoms or decreases in quality of life due to side effects of treatment.

Tirzepatide treatment helps people lose weight, which can improve quality of life by allowing them to more easily participate in daily activities. This was considered in the model by including an increase in quality of life if weight decreased.

The model also included reductions in quality of life whenever a patient with obesity had a serious obesity-related condition that would affect their health, such as problems with the heart and kidney. Further reductions in quality of life were included when people experienced side effects of tirzepatide treatment, such as nausea and vomiting.

Modelling how the costs of treatment differ with

Various different costs are included in the model for the different obesity treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment
- The costs of other things are also captured, like the cost of healthcare professional time and costs of treating other conditions linked to obesity

Tirzepatide is expected to reduce some costs for the NHS compared to other approved treatments for people with obesity. This is because the improved weight loss and cardiovascular measures from tirzepatide treatment reduce the risk of developing obesity-related complications and comorbidities. This in turn reduces costs associated with treating these complications and comorbidities.

There is some uncertainty in the model

All model results are to some extent uncertain. Key uncertainties in this model are explained below.

- The SURMOUNT-1 trial only lasted for 72 weeks. Therefore, parameters that were measured in the trial (such as weight loss and blood pressure) were used to predict the likelihood that a patient would experience an obesity-related comorbidities or events, such as a heart attack. Because of this, the number of patients experiencing these obesity-related comorbidities or events is uncertain.

However, different ways of predicting these obesity-related comorbidities or events were tested.

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B**, **Section B.3.8.3**.

Cost-effectiveness results from Eli Lilly's analyses

Based on the modelling inputs and assumptions from Eli Lilly, treatment with tirzepatide was associated with higher costs, but also higher benefits (or 'quality-adjusted life years' [QALYs]) than semaglutide and diet and exercise in patients with a BMI ≥30 with at least one obesity-related comorbidity. This resulted in incremental cost-effectiveness ratios (ICERs) for all three doses that were lower than the threshold that the NHS considers to be cost-effective (£20,000 per QALY gained) based on the Eli Lilly's calculations. Liraglutide was not included in this analysis because patients with a BMI ≥30 with at least one obesity-related comorbidity are not eligible for this treatment on the NHS. Instead, a separate analysis was carried out for patients who would be eligible for this treatment (BMI ≥25 with prediabetes and high cardiovascular risk). Based on Eli Lilly's model, this analysis also showed that the ICERs for all three doses of tirzepatide are lower than the threshold that the NHS considers to be cost-effective.

The full cost effectiveness results of the economic analysis are presented in **Document B**, **Section B.3**.

Benefits not captured in the economic model

Weight loss can have many different positive impacts for people with obesity. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example:

- Tirzepatide may make it less likely for people to become seriously ill with respiratory infections like COVID-19[21]
- Weight loss with tirzepatide may make people feel less socially isolated[21]
- Weight loss can also improve fertility and improve the chances of becoming pregnant using in vitro fertilisation[21]
- Weight loss with tirzepatide may give patients their independence back by allowing them to participate in daily activities, sports and hobbies, by returning to work
- Tirzepatide may enable people who require other surgical procedures but who cannot have these due to their high BMI, to lose enough weight to undergo these operations[39]
- Weight loss may reduce the impact of obesity on the healthcare system by reducing the severity of comorbidities and preventing further obesity-related comorbidities

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Tirzepatide is an innovative treatment which would represent an important advancement in the treatment of obesity

Obesity is a condition that can have a significant negative impact on a person's physical health and quality of life. It can lead to many serious health conditions that have a significant cost to patients, society, and the healthcare system. Despite this, there are few treatment options available that have been shown to be effective in patients with obesity.

Tirzepatide is an innovative medicine and the first medicine for obesity which mimics the action of both GIP and GLP-1 hormones. Tirzepatide has strong evidence showing that it causes significant weight loss in people with obesity.[35] The 10 and 15 mg doses of tirzepatide caused more than 20% weight loss in SURMOUNT-1, which is more than any other anti-obesity medicine has shown in a Phase 3 trial.[36] Tirzepatide would therefore give patients the opportunity to experience greater weight loss compared to current treatment options. This would reduce the negative short and long-term impact that obesity has on patients, society and the healthcare system.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are some important inequalities that are associated with treatment of obesity with tirzepatide. These are explained below.

Socioeconomic inequalities:

People who live in lower socioeconomic areas often face challenges with accessing affordable, healthy food and to regularly exercising. This means that obesity is more common in these areas.[11]

Comorbidity risk in different ethnic groups

As explained in **Section 2b,** some ethnic groups have a higher risk of developing obesity-related comorbidities than others.[4] It is therefore recommended that people with a South

Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background should be considered as having obesity at a lower BMI.[1] This is to encourage earlier treatment in these groups to avoid these risk of obesity-related comorbidities developing.

Access inequalities for treatment of other medical conditions

Sometimes, people with obesity cannot access treatments for other disabilities due to their weight. This is because in some hospitals, surgeries are only allowed if a person is below a certain BMI as the risk may be too high if a person has obesity. This means that patients above a certain BMI may have to wait for long periods while losing weight prior to being considered eligible for their surgery.[40]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on obesity:

- Obesity UK: https://www.obesityuk.org.uk/
- NHS website: https://www.nhs.uk/conditions/obesity/
- NICE Guidelines: https://www.nice.org.uk/guidance/cg43

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

4b) Glossary of terms

This glossary explains certain terms in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Abdominal	The belly or tummy area, which contains organs including the stomach.
Anti-obesity medicine	A medicine which is given to patients who have obesity to help them lose weight.
Anaesthesia	A drug that puts you to sleep during surgery.
Body Mass Index (BMI)	A calculation used to work out your weight compared to your height. You can calculate this by dividing your weight (in kg) by your height (in metres squared).
Cardiovascular risk factor	Factors which indicate how much risk a patient has for developing cardiovascular disease.
Cardiovascular disease	A general term for conditions affecting the heart or blood vessels that can lead to events such as heart failure or stroke
Calories	A unit of energy which is used to tell us how much energy different foods contain.
Central adiposity	A measure of how much excess fat around their abdominal area.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Comorbidity	This is when more than one illness or disease is present in one person at the same time.
Complementary	When different things each work better when they are combined together.
Cholesterol	A natural fatty substance in your blood. High cholesterol is when you have too

	much cholesterol in your blood, which can increase the risk of having a heart attack or stroke.
Diabetes	A serious condition where your blood glucose (sugar) level is too high. It can cause symptoms like excessive thirst, needing to urinate a lot and tiredness. It can also increase your risk of getting serious problems with your eyes, heart and nerves.
Dual incretin agonist	A drug which works by acting in the same way as two different types of incretin hormones.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
Follow-up	Continuing to check on a person's health after they have finished treatment.
Gastrointestinal events	Adverse events related to the organs that food and liquids travel through when they are swallowed, digested, absorbed and leave the body (such as the stomach and intestines). An example of a gastrointestinal event is acid reflux.
Gene	A gene is an inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Genetic conditions	A condition that is caused by a problem in a person's genes.
Glucose-dependent insulinotropic polypeptide (GIP)	A hormone which acts in a complementary way to GLP-1 to slow down stomach emptying and reduce hunger.
Glucagon-like polypeptide-1 (GLP-1)	A hormone that reduces appetite so that people eat and drink less. It also slows down how quickly the stomach digests food.

Glucose	The main type of sugar found in the blood. Glucose is the main source of energy for the body's cells.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial.
Healthcare professional (HCP)	A person who provides healthcare services to patients.
Heart failure	A condition where a patient’s heart can’t pump blood around the body as well as it should, causing the body to retain salts and fluids.
High-density lipoprotein	Sometimes called “good” cholesterol. It absorbs cholesterol in the blood and carries it back to the liver to be released from your body
Hormone/s	Chemical substances that carry messages within the body to help coordinate different bodily functions.
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
In vitro fertilisation	A medical procedure where an egg is fertilised by sperm in a test tube or elsewhere outside of the body.
Injection site reaction	When an injection causes pain, itching, swelling or redness around the area of injection.
Lipase inhibitor	A substance which makes the stomach and intestines absorb less fat from foods or drinks.

Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MRHA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
Metabolic risk factors	Factors which can increase a person's risk of other conditions such as diabetes or stroke.
Metabolic syndrome	A combination of conditions, including diabetes, high blood pressure and obesity.
Musculoskeletal	Anything that is related to muscles and bones.
Phase 3 clinical trial	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
Physiotherapist	A professional that helps to restore movement and function when someone is affected by injury, illness or disability.
Physical functioning	The ability to carry out the basic physical activities that are needed in daily life.
Placebo	A treatment that appears real, but has no therapeutic benefit. It is used in clinical trials to compare treatments to.
Prediabetes	When the level of glucose (sugar) in a person's blood is too high, but they do not have diabetes.
Primary care	Primary care services provide the first point of contact for patients in the NHS, such as a general practitioner (GP).

Psychologists	An expert or specialist in the study of the mind and peoples' behaviour.
Quality-adjusted life year (QALY)	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Regulatory bodies	These are legal bodies that review the quality, safety and efficacy of medicines and medical technologies.
Respiratory infection	An infection in the parts of the body involved in breathing, such as the throat or lungs.
Screening (for a clinical trial)	The process where patients are assessed to see whether they are eligible to take part in a clinical trial.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Skinfold callipers	A tool which is used to measure the thickness of skinfolds in order to work out the amount of body fat.
Socioeconomic	Anything which is related to social class or monetary factors, such as education, income and employment.
Specialist weight management services (SWMS)	Healthcare services in which patients are assessed by various different HCPs and are offered specialist help to lose weight.

Steroid hormones	A group of hormones made from cholesterol that act as chemical messengers in the body. The steroid hormones regulate many different bodily functions, including controlling metabolism.
Stigma	Disapproval or discrimination against certain people because of characteristics that separate them from other members of a society.
Stroke	A stroke is where the blood supply to part of the brain is cut off, which can cause brain damage and possibly death.
Waist circumference	The distance around a person's waist, between the rib cage and the hips.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tirzepatide for managing overweight and obesity ID6179

Clarification question responses

October 2023

File name	Version	Contains confidential information	Date
ID6179 Tirzepatide in Obesity_Clarification Question Responses_ 6thOctober2023	Final	Yes	6th October 2023

Section A: Clarification on clinical effectiveness data

A1. The efficacy data in the clinical effectiveness section is in a wider population than the decision problem. The outcomes presented for the narrower population (post hoc subgroup) are the four outcomes used in the NMA / model (% weight; HDL cholesterol; Total cholesterol; SBP). Please provide the other outcomes as stated in the decision problem from this subgroup.

All outcomes specified in the decision problem from SURMOUNT-1 in the patient population with a BMI≥30 kg/m^2 with at least one weight-related comorbidity are summarised in the following sections. All analyses presented were conducted using the efficacy estimand in the efficacy analysis set (EAS). Given the post-hoc nature of these analyses, it should also be noted that p-value results are not controlled for Type 1 error as per the pre-specified primary and key secondary endpoints in SURMOUNT-1, and therefore should be interpreted with caution.

Percentage of patients achieving body weight reduction targets at Week 72

Tirzepatide 5, 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks in the BMI≥30 kg/m^2 with at least one weight-related comorbidity subgroup, consistent with the whole trial population. A summary of the results for the percentage of participants achieving body weight reduction targets at Week 72 is provided in Table 1.

Table 1: Percentage of patients achieving body weight reduction targets at Week 72 in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameters	Placebo ([redacted])	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥5% body weight reduction				
Participants achieving ≥10% body weight reduction (%); imputed values	[redacted]	[redacted]	[redacted]	[redacted]
Participants achieving ≥10% body weight reduction				
Participants achieving ≥10% body weight reduction (%); imputed values	[redacted]	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction				
Participants achieving ≥15% body weight reduction (%); imputed values	[redacted]	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction				
Participants achieving ≥20% body weight reduction (%); imputed values	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of participants in imputed data; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: Imputed data includes observed value and imputed value if endpoint measure is missing. Missing endpoint measures are imputed by predictions using observed data in the efficacy analysis set from the same treatment group through an MMRM analysis model for post-baseline measures.
***p-value <0.001 versus placebo for superiority.

Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_20_subset3a)

Mean change from baseline in BMI from baseline to Week 72

Tirzepatide 5, 10 and 15 mg each achieved superiority compared with placebo for mean change in BMI from baseline to 72 weeks in the BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup, consistent with the whole trial population (Table 2).

Table 2. Mean change from baseline in BMI from baseline to Week 72 in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter (kg/m^2)	Placebo ([redacted])	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of subjects in the population with baseline and post-baseline value at Week 72; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
*** p-Value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi01_taffy_subset3a)

Mean change in waist circumference from baseline to Week 72

Tirzepatide 5, 10 and 15 mg each achieved superiority compared with placebo for mean change in waist circumference from baseline to 72 weeks in the BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup, consistent with the whole trial population. A summary of the results for the mean change from baseline in BMI from baseline to Week 72 is provided in Table 3.

Table 3. Mean change in waist circumference from baseline to Week 72 in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter (cm)	Placebo ([redacted])	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of subjects in the population with baseline and post-baseline value at Week 72; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
*** p-Value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Name: rmwc01_taffy_subset3a)

Mean change in fasting serum glucose (FSG) at Week 72

Tirzepatide 5, 10 and 15 mg each achieved superiority compared with placebo for the mean change in fasting serum glucose from baseline to 72 weeks in the BMI≥30 kg/m^2 with at least one weight-related comorbidity subgroup, consistent with the whole trial population. A summary of the results for the mean change in fasting serum glucose from baseline to Week 72 is provided in Table 4.

Table 4: Mean change in fasting serum glucose (FSG) at Week 72 in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter (mg/dL)	Placebo ([redacted])	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; FSG: fasting serum glucose; N: number of subjects in the population with baseline and post-baseline value at Week 72; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
*** p-Value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_51_subset3a_taffy)

Mean change in HbA1c at Week 72

Tirzepatide 5, 10 and 15 mg each achieved superiority compared with placebo for the mean change in HbA1c from baseline to 72 weeks in the BMI≥30 kg/m^2 with at least one weight-related comorbidity subgroup, consistent with the whole trial population. A summary of the results for the mean change in HbA1c from baseline to Week 72 is provided in Table 5.

Table 5: Mean change in HbA1c at Week 72 in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter (mg/dL)	Placebo ([redacted])	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of subjects in the population with baseline and post-baseline value at Week 72; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
*** p-Value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_49_subset3a_taffy)

Percentage of participants with a change in glycaemic category at Week 72

Table 6 presents the change in glycaemic category from baseline to Week 72 in the BMI≥30 kg/m^2 with at least one weight-related comorbidity subgroup. Of the participants with prediabetes at baseline, a greater proportion in the tirzepatide arms reverted to normoglycaemia at 72 weeks, compared to those with prediabetes at baseline in the placebo arm. In addition, a smaller proportion of participants in the tirzepatide arms with prediabetes at baseline had suspected T2DM at Week 72 compared to the placebo arm. Finally, a smaller proportion in the tirzepatide arms with normoglycaemia at baseline has prediabetes or suspected T2DM at Week 72 compared with the placebo arm, indicating that tirzepatide 5, 10 and 15 mg each provide greater improvements in glycaemic status compared with placebo alone, consistent with the findings in the whole trial population.

Table 6: Percentage of participants with a change in glycaemic category in participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	Total n (%)
Placebo (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 5 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAS: efficacy analysis set; N: number of participants in the population in the specified treatment group; n: number of participants in the specified category; MMRM: mixed model for repeated measures; TZP: tirzepatide.

Footnotes: Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT will be counted in 'Suspected T2DM'. 'Suspected T2DM' will be adjudicated to confirm the diagnosis of T2DM. Participant who meets any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'.

Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_subset3a)

Change in EQ-5D-5DL health index scores from baseline to Week 72

Tirzepatide 5, 10 and 15 mg each achieved a significant improvement from baseline in EQ-5D-5L health index scores from baseline to Week 72, and tirzepatide 15 mg achieved superiority compared to placebo at Week 72, consistent with the whole trial population results. A summary of the results for EQ-5D-5L health index scores from baseline to Week 72 is provided in Table 7.

Table 7. Summary of results for EQ-5D-5L health index scores at baseline and 72 weeks in participants with BMI ≥30 kg/m² with at least one weight-related comorbidity; EAS

Parameters	Placebo (N=[redacted])	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CI: confidence interval; EAS: efficacy analysis set; LOCF: last observation carried forward. N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: The Van Hout value set was used to calculate the index score. LOCF. ANCOVA model for endpoint measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
*** p-value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Names: aceq5d01_taffy_subset3)

Overview of adverse events

In the subgroup with BMI ≥30 kg/m² with at least one weight-related comorbidity, the number of participants experiencing ≥1 TEAE was greater in the tirzepatide groups (between [redacted]) compared with the placebo group ([redacted]), consistent with the whole trial population. The number of participants experiencing SAEs was similar between the placebo group and tirzepatide groups, ranging from [redacted] to [redacted] Overall, the number of participants discontinuing from the study due to an AE was similar across treatment groups. However, there was a higher number of participants discontinuing from study drug due to an AE in the tirzepatide groups ([redacted] compared with the placebo group. Across all treatment groups in this subgroup there were 9 deaths overall, and no imbalance was observed between treatment arms. No other notable differences between tirzepatide dose groups and placebo were observed, consistent with the whole trial population. A summary of adverse events in participants with BMI ≥30 kg/m² with at least one weight-related comorbidity is provided in Table 8.

Table 8. Overview of adverse events in participants with BMI ≥30 kg/m² with at least one weight-related comorbidity; SAS

Category	n (%)				Pairwise p-values		
	Placebo ([redacted])	TZP 5mg ([redacted])	TZP 10mg ([redacted])	TZP 15mg ([redacted])	Placebo vs TZP 5 mg	Placebo vs TZP 10 mg	Placebo vs TZP 15 mg
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TEAE: treatment-emergent adverse event; TZP: tirzepatide.
Footnotes: Subjects may be counted in more than one category. Deaths are also included as serious adverse events and discontinuations due to adverse events. p-values for pairwise treatment comparisons were computed using Fisher's exact test.
Source: Eli Lilly Exploratory Analysis (File Names: smae01_taffy_subset3a)

A2. CS Figure 5 – please provide further details for those discontinuing due to lost follow-up, protocol deviations, withdrawal by participant and 'other', separately for all arms for those discontinuing study drug and discontinuing study.

Unfortunately, the requested details for participants discontinuing due to lost follow-up, withdrawal by participant and 'other' cannot be provided as they are only available in the form of free-text entries in individual patient listings rather than in summary form, and as such cannot be directly shared to protect patient confidentiality. With regards to participants discontinuing due to a protocol deviation, data are only available for participants with *any* protocol deviation, rather than specifically for participants with a protocol deviation that subsequently discontinued treatment; nevertheless, these data are provided in the reference pack for transparency (File Name: SURMOUNT-1 CSR Protocol Deviations Table).

A3. Please provide references or sources for the inputs used in the sample size calculations presented in Table 11 of CS document B.

All inputs for the sample size calculations provided in Table 11 of the CS were based on the two Phase 2 trials for tirzepatide in the T2DM indication: I8F-MC-GPGB (available as a publication: Frias 2018 [provided in response to Question C3]) and I8F-MC-GPGF. CSRs for both trials are provided in the reference pack alongside these responses (File Names: I8F-MC-GPGB CSR, I8F-MC-GPGF CSR). These data informed the sample size calculations for SURMOUNT-1 as no Phase 2 studies were conducted specifically for tirzepatide in the obesity indication; instead, the weight loss findings in the T2DM Phase 2 studies warranted further investigation for tirzepatide in the treatment of obesity in the Phase 3 SURMOUNT-1 studies.[1]

A4. Please provide baseline characteristic tables of participants in SURMOUNT-1 populations, by treatment arm for:

- BMI ≥30 + weight-related comorbidity
- BMI ≥35 + prediabetes + high CVD risk

The baseline demographic and clinical characteristics, comorbidities and concomitant medication use of participants in SURMOUNT-1 with BMI ≥30 kg/m^2 with at least one weight-related comorbidity are presented in Table 9–Table 12. The baseline demographic and clinical characteristics, comorbidities and concomitant medication use of participants in SURMOUNT-1 with BMI of ≥35 kg/m^2 with prediabetes and high CV risk are presented in Table 12–Table 14.

Overall, the clinical and demographic characteristics for these subgroups were broadly aligned with the whole trial population for characteristics outside the subgroup definitions, and no substantial imbalances were observed between trial arms for any subgroup.

Table 9: Summary baseline demographic characteristics of participants with BMI ≥30 kg/m^2 with at least one weight-related comorbidity in SURMOUNT-1

Attribute	Placebo (N=435)	TZP 5 mg (N=423)	TZP 10 mg (N=433)	TZP 15 mg (N=414)	Total (N=1,705)
Age (years), mean ± SD	47.0 ± 12.2	48.1 ± 12.0	47.1 ± 11.8	47.4 ± 11.9	47.4 ± 12.0
Female, n (%)	289 (66.4)	281 (66.4)	285 (65.8)	274 (66.2)	1129 (66.2)
Age Category 1, n (%)					
<65	405 (93.1)	379 (89.6)	406 (93.8)	386 (93.2)	1576 (92.4)
≥65	30 (6.9)	44 (10.4)	27 (6.2)	28 (6.8)	129 (7.6)
Age Category 2, n (%)					
<75	432 (99.3)	423 (100.0)	432 (99.8)	411 (99.3)	1698 (99.6)
≥75	3 (0.7)	0	1 (0.2)	3 (0.7)	7 (0.4)
Country/Region, n (%)					
Argentina	67 (15.4)	63 (14.9)	60 (13.9)	66 (15.9)	256 (15.0)
Brazil	42 (9.7)	45 (10.6)	40 (9.2)	38 (9.2)	165 (9.7)
China	4 (0.9)	5 (1.2)	5 (1.2)	5 (1.2)	19 (1.1)
India	3 (0.7)	1 (0.2)	3 (0.7)	2 (0.5)	9 (0.5)
Japan	20 (4.6)	19 (4.5)	16 (3.7)	17 (4.1)	72 (4.2)
Mexico	60 (13.8)	61 (14.4)	67 (15.5)	54 (13.0)	242 (14.2)
Russian Federation	23 (5.3)	22 (5.2)	23 (5.3)	19 (4.6)	87 (5.1)
Taiwan	8 (1.8)	6 (1.4)	9 (2.1)	10 (2.4)	33 (1.9)
The United States	208 (47.8)	201 (47.5)	210 (48.5)	203 (49.0)	822 (48.2)
Race, n (%)					
American Indian or Alaska Native	32 (7.4)	37 (8.7)	41 (9.5)	32 (7.7)	142 (8.3)
Asian	41 (9.4)	36 (8.5)	40 (9.2)	38 (9.2)	155 (9.1)
Black or African American	42 (9.7)	35 (8.3)	34 (7.9)	36 (8.7)	147 (8.6)
Multiple	6 (1.4)	9 (2.1)	5 (1.2)	6 (1.4)	26 (1.5)
Native Hawaiian or Other Pacific Islander	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	8 (0.5)
White	312 (71.7)	304 (71.9)	311 (71.8)	300 (72.5)	1227 (72.0)
Ethnicity, n (%)					
Hispanic or Latino	195 (44.8)	199 (47.0)	191 (44.1)	183 (44.2)	768 (45.0)
Not Hispanic or Latino	211 (48.5)	195 (46.1)	212 (49.0)	203 (49.0)	821 (48.2)
Missing	29 (6.7)	29 (6.9)	30 (6.9)	28 (6.8)	116 (6.8)

Education (year), mean ± SD	13.9 ± 4.4	14.1 ± 3.8	14.2 ± 3.8	13.8 ± 4.0	14.0 ± 4.0

Abbreviations: BMI: body mass index; SD: standard deviation; TZP: tirzepatide.
Source: Eli Lilly Exploratory Analysis (File Names: gphk_8_4_subset3a_taffy)

Table 10: Summary baseline clinical characteristics of participants with BMI ≥30 kg/m² with at least one weight-related comorbidity in SURMOUNT-1

Attribute	Placebo (N=435)	TZP 5 mg (N=423)	TZP 10 mg (N=433)	TZP 15 mg (N=414)	Total (N=1705)
Weight (kg), mean ± SD	106.5 ± 21.7	104.9 ± 21.1	108.5 ± 23.5	108.3 ± 23.5	107.1 ± 22.5
Height (cm), mean ± SD	165.6 ± 9.8	165.7 ± 9.2	166.4 ± 9.1	166.1 ± 9.9	165.9 ± 9.5
BMI (kg/m²), mean ± SD	38.8 ± 6.9	38.2 ± 6.6	39.0 ± 6.9	39.1 ± 6.8	38.8 ± 6.8
BMI Categories, n (%)					
<30	N/A	N/A	N/A	N/A	N/A
≥30 to <35	150 (34.5)	171 (40.4)	150 (34.6)	134 (32.4)	605 (35.5)
≥35 to <40	134 (30.8)	119 (28.1)	126 (29.1)	122 (29.5)	501 (29.4)
≥40	151 (34.7)	133 (31.4)	157 (36.3)	158 (38.2)	599 (35.1)
Waist Circumference (cm), mean ± SD	115.7 ± 15.0	114.8 ± 14.4	117.0 ± 15.6	116.7 ± 15.6	116.1 ± 15.2
Prediabetes, n (%)	260 (59.8)	234 (55.3)	248 (57.3)	239 (57.7)	981 (57.5)
Duration of obesity (year), mean ± SD	15.1 ± 11.5	15.4 ± 11.3	16.1 ± 11.8	15.9 ± 11.2	15.6 ± 11.4
SBP (mmHg), mean ± SD	124.2 ± 12.7	125.0 ± 12.3	125.3 ± 13.2	124.5 ± 12.9	124.8 ± 12.8
DBP (mmHg), mean ± SD	80.43 ± 7.7	79.9 ± 8.3	80.4 ± 8.4	79.7 ± 8.1	80.1 ± 8.1
Pulse rate (bpm), mean ± SD	73.1 ± 9.6	72.4 ± 10.1	71.7 ± 9.9	72.4 ± 9.7	72.4 ± 9.9
HbA1c (%) ± SD	5.7 (0.4)	5.7 (0.3)	5.6 (0.4)	5.6 (0.4)	5.6 (0.4)
Lipid levels (mg/dL), geometric mean (% coefficient of variation)					
Total cholesterol	189.6 (20.6)	189.4 (20.9)	192.5 (20.2)	188.7 (20.5)	190.08 (20.5)
HDL cholesterol	46.3 (27.2)	47.5 (25.4)	47.2 (26.9)	47.4 (25.9)	47.1 (26.4)
LDL cholesterol	111.2 (31.1)	109.6 (31.1)	112.8 (31.6)	109.3 (30.9)	110.8 (31.2)
Triglycerides	133.1 (50.5)	135.8 (51.0)	132.7 (51.3)	133.9 (47.8)	133.9 (50.1)
eGFR (mL/min/1.73 m²), mean ± SD	95.7 ± 18.3	94.3 ± 17.6	96.0 ± 18.4	95.7 ± 17.7	95.4 ± 18.0
eGFR Categories, n (%)					
≥30 to <45	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)	5 (0.3)
≥45 to <60	6 (1.4)	7 (1.7)	10 (2.3)	13 (3.1)	36 (2.1)
≥60 to <90	146 (33.6)	178 (42.1)	139 (32.1)	128 (30.9)	591 (34.7)
≥90	282 (64.8)	237 (56.0)	283 (65.4)	271 (65.5)	1073 (62.9)

Abbreviations: BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HDL; high density lipoprotein; LDL; low density lipoprotein; SBP: systolic blood pressure; SD: standard deviation; TZP: tirzepatide.
Sources: Eli Lilly Exploratory Analysis (File Names: gphk_8_5_subset3a_taffy, gphk_8_6_subset3a,

gphk_8_49_subset3a_taffy)

Table 11: Baseline comorbidities and concomitant medications of participants with BMI ≥30 kg/m2 with at least one weight-related comorbidity in SURMOUNT-1

Comorbidities†	n (%)				
	Placebo (N=435)	TZP 5 mg (N=423)	TZP 10 mg (N=433)	TZP 15 mg (N=414)	Total (N=1705)
Hypertension	193 (44.4)	187 (44.2)	181 (41.8)	181 (43.7)	742 (43.5)
Dyslipidaemia	169 (38.9)	175 (41.4)	165 (38.1)	160 (38.6)	669 (39.2)
ASCVD	20 (4.6)	15 (3.5)	18 (4.2)	18 (4.3)	71 (4.2)
PCOS	7 (2.4)	4 (1.4)	9 (3.2)	3 (1.1)	23 (2.0)
OSA	58 (13.3)	41 (9.7)	47 (10.9)	45 (10.9)	191 (11.2)
Osteoarthritis	54 (12.4)	60 (14.2)	62 (14.3)	62 (15.0)	238 (14.0)
Depression	44 (10.1)	47 (11.1)	42 (9.7)	35 (8.5)	168 (9.9)
NAFLD	9 (2.1)	4 (0.9)	9 (2.1)	4 (1.0)	26 (1.5)
Asthma	64 (14.7)	46 (10.9)	52 (12.0)	41 (9.9)	203 (11.9)
COPD	5 (1.1)	8 (1.9)	3 (0.7)	4 (1.0)	20 (1.2)
Gout	6 (1.4)	8 (1.9)	6 (1.4)	10 (2.4)	30 (1.8)
Participants using corticosteroids	8 (1.8)	7 (1.7)	10 (2.3)	7 (1.7)	N/A
Participants using statins	84 (19.31)	86 (20.33)	65 (15.01)	69 (16.67)	N/A

Footnotes: † Comorbidities were assessed through review of medical history.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; COPD: chronic obstructive pulmonary disease; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; PCOS: polycystic ovary syndrome; TZP: tirzepatide.
Source: Eli Lilly Exploratory Analysis (File Names: gphk_8_5_subset3a_taffy, gphk_8_11_subset3a_taffy, smcm_subset3a)

Table 12: Summary baseline demographic characteristics of participants with BMI of ≥35 kg/m^2 with prediabetes and high CV risk in SURMOUNT-1

Attribute	Placebo (N=157)	TZP 5 mg (N=114)	TZP 10 mg (N=143)	TZP 15 mg (N=131)	Total (N=545)
Age (years), mean ± SD	46.1 ± 11.7	48.1 ± 13.1	46.0 ± 11.4	46.7 ± 11.4	46.6 ± 11.8
Female, n ()	109 (69.4)	78 (68.4)	91 (63.6)	84 (64.1)	362 (66.4)
Age Category 1, n (%)					
<65	148 (94.3)	98 (86.0)	138 (96.5)	122 (93.1)	506 (92.8)
≥65	9 (5.7)	16 (14.0)	5 (3.5)	9 (6.9)	39 (7.2)
Age Category 2, n (%)					
<75	155 (98.7)	114 (100.0)	143 (100.0)	131 (100.0)	543 (99.6)
≥75	2 (1.3)	0	0	0	2 (0.4)
Country/Region, n (%)					
Argentina	31 (19.7)	26 (22.8)	30 (21.0)	32 (24.4)	119 (21.8)
Brazil	15 (9.6)	8 (7.0)	13 (9.1)	11 (8.4)	47 (8.6)
China	2 (1.3)	1 (0.9)	0	2 (1.5)	5 (0.9)
India	2 (1.3)	0	0	0	2 (0.4)

Japan	2 (1.3)	1 (0.9)	0	2 (1.5)	5 (0.9)
Mexico	19 (12.1)	16 (14.0)	18 (12.6)	22 (16.8)	75 (13.8)
Russian Federation	10 (6.4)	10 (8.8)	10 (7.0)	8 (6.1)	38 (7.0)
Taiwan	2 (1.3)	0	1 (0.7)	2 (1.5)	5 (0.9)
The United States	74 (47.1)	52 (45.6)	71 (49.7)	52 (39.7)	249 (45.7)
Race, n (%)					
American Indian or Alaska Native	9 (5.7)	9 (7.9)	11 (7.7)	12 (9.2)	41 (7.5)
Asian	8 (5.1)	4 (3.5)	4 (2.8)	6 (4.6)	22 (4.0)
Black or African American	15 (9.6)	9 (7.9)	12 (8.4)	8 (6.1)	44 (8.1)
Multiple	120 (76.4)	90 (78.9)	114 (79.7)	105 (80.2)	429 (78.7)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.7)	0	1 (0.2)
White	120 (76.4)	90 (78.9)	114 (79.7)	105 (80.2)	429 (78.7)
Ethnicity, n (%)					
Hispanic or Latino	77 (49.0)	60 (52.6)	70 (49.0)	68 (51.9)	275 (50.5)
Not Hispanic or Latino	75 (47.8)	53 (46.5)	71 (49.7)	57 (43.5)	256 (47.0)
Missing	5 (3.2)	1 (0.9)	2 (1.4)	6 (4.6)	14 (2.6)
Education (year), mean ± SD	14.0 ± 3.8	13.7 ± 3.8	14.3 ± 3.6	13.5 ± 3.7	13.9 ± 3.7

Abbreviations: SD: standard deviation; TZP: tirzepatide.
Source: Eli Lilly Exploratory Analysis (File Names: gphk_8_4_subset4_taffy)

Table 13: Summary baseline clinical characteristics of participants with BMI of ≥35 kg/m^2 with prediabetes and high CV risk in SURMOUNT-1

Attribute	Placebo (N=157)	TZP 5 mg (N=114)	TZP 10 mg (N=143)	TZP 15 mg (N=131)	Total (N=545)
Weight (kg), mean ± SD	117.0 ± 20.6	115.3 ± 20.3	120.1 ± 22.2	118.1 ± 23.3	117.7 ± 21.6
Height (cm), mean ± SD	165.3 ± 10.5	165.9 ± 9.3	167.3 ± 9.1	165.9 ± 10.8	166.1 ± 10.0
BMI (kg/m^2), mean ± SD	42.8 ± 6.4	41.8 ± 5.8	42.8 ± 6.4	42.8 ± 6.5	42.6 ± 6.3
BMI Categories, n (%)					
<30	N/A	N/A	N/A	N/A	N/A
≥30 to <35	N/A	N/A	N/A	N/A	N/A
≥35 to <40	59 (37.6)	53 (46.5)	57 (39.9)	61 (46.6)	230 (42.2)
≥40	98 (62.4)	61 (53.5)	86 (60.1)	70 (53.4)	315 (57.8)
Waist Circumference (cm), mean ± SD	123.1 ± 14.7	121.9 ± 13.9	124.5 ± 14.8	122.6 ± 15.9	123.1 ± 14.9
Prediabetes, n (%)	157 (100.0)	114 (100.0)	143 (100.0)	131 (100.0)	545 (100.0)
Duration of obesity (year), mean ± SD	16.7 ± 11.7	17.0 ± 11.7	17.5 ± 10.7	17.0 ± 10.9	17.0 ± 11.2
SBP (mmHg), mean ± SD	125.1 ± 13.2	127.9 ± 13.1	126.9 ± 13.9	126.3 ± 13.4	126.5 ± 13.4
DSP (mmHg), mean ± SD	81.3 ± 7.8	81.6 ± 8.9	81.0 ± 9.1	81.5 ± 8.5	81.3 ± 8.5
Pulse rate (bpm), mean ± SD	73.5 ± 9.4	74.5 ± 9.7	72.5 ± 9.5	74.5 ± 10.8	73.7 ± 9.8

HbA1c (%) ± SD	5.8 (0.3)	5.8 (0.3)	5.8 (0.3)	5.8 (0.5)	5.8 (0.4)
Lipid levels (mg/dL), geometric mean (coefficient of variation)					
Total cholesterol	188.4 (22.6)	191.9 (21.9)	191.3 (19.1)	186.5 (21.7)	189.4 (21.3)
HDL cholesterol	43.5 (24.0)	45.0 (23.7)	44.5 (25.7)	43.4 (23.5)	44.0 (24.3)
LDL cholesterol	112.0 (33.3)	113.3 (32.7)	113.9 (27.8)	108.9 (31.1)	112.0 (31.2)
Triglycerides	141.8 (44.5)	145.6 (44.2)	141.6 (44.7)	148.3 (47.0)	144.1 (45.0)
eGFR (mL/min/1.73 m^2), mean ± SD	97.6 ± 18.9	95.6 ± 18.9	95.4 ± 19.7	97.2 ± 16.5	96.5 ± 18.6
eGFR Categories, n (%)					
≥30 to <45	1 (0.6)	1 (0.9)	1 (0.7)	1 (0.8)	4 (0.7)
≥45 to <60	3 (1.9)	1 (0.9)	5 (3.5)	4 (3.1)	13 (2.4)
≥60 to <90	44 (28.0)	46 (40.4)	48 (33.6)	32 (24.4)	170 (31.2)
≥90	109 (69.4)	66 (57.9)	89 (62.2)	94 (71.8)	358 (65.7)

Abbreviations: BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HDL; high density lipoprotein; LDL; low density lipoprotein; SBP: systolic blood pressure; SD: standard deviation; TZP: tirzepatide.
Source: Eli Lilly Exploratory Analysis (File Names: gphk_8_5_subset4_taffy, gphk_8_6_subset4, gphk_8_49_subset4_taffy)

Table 14: Baseline comorbidities and concomitant medications of participants with BMI of ≥35 kg/m^2 with prediabetes and high CV risk in SURMOUNT-1

Comorbidities†	Placebo (N=157)	TZP 5 mg (N=144)	TZP 10 mg (N=143)	TZP 15 mg (N=131)	Total (N=545)
Hypertension	58 (36.9)	50 (43.9)	61 (42.7)	53 (40.5)	222 (40.7)
Dyslipidaemia	48 (30.6)	37 (32.5)	35 (24.5)	37 (28.2)	157 (28.8)
ASCVD	6 (3.8)	4 (3.5)	5 (3.5)	6 (4.6)	21 (3.9)
PCOS	2 (1.8)	1 (1.3)	1 (1.1)	0 (0)	4 (1.1)
OSA	19 (12.1)	10 (8.8)	15 (10.5)	8 (6.1)	52 (9.5)
Osteoarthritis	17 (10.8)	15 (13.2)	19 (13.3)	11 (8.4)	62 (11.4)
Depression	12 (7.6)	14 (12.3)	14 (9.8)	6 (4.6)	46 (8.4)
NAFLD	4 (2.5)	1 (0.9)	5 (3.5)	0 (0)	10 (1.8)
Asthma	19 (12.1)	7 (6.1)	13 (9.1)	8 (6.1)	47 (8.6)
COPD	2 (1.3)	3 (2.6)	1 (0.7)	2 (1.5)	8 (1.5)
Gout	3 (1.9)	1 (0.9)	1 (0.7)	4 (3.1)	9 (1.7)
Participants using corticosteroids	1 (0.64)	3 (2.63)	4 (2.80)	2 (1.53)	N/A
Participants using statins	20 (12.74)	21 (18.42)	7 (4.90)	21 (16.03)	N/A

Footnotes: † Comorbidities were assessed through review of medical history.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; COPD: chronic obstructive pulmonary disease; NAFLD: non-alcoholic fatty liver disease; OSA: obstructive sleep apnoea; PCOS: polycystic ovary syndrome; TZP: tirzepatide.
Source: Eli Lilly Exploratory Analysis (File name: gphk_8_11_subset4_taffy, smcm_subset4)

A.5 Please correct the values in Table 21.

The data previously presented in Document B Table 21 has been corrected and presented in Table 15 below.

Table 15: Mean changes in FSG from baseline to Week 72; EAS

Parameters	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Baseline (mg/dL)	95.8	95.4	95.5	95.2
Baseline (mmol/L)	5.3	5.3	5.3	5.3
Change from baseline at 72 weeks (mg/dL)	0.9	−7.7†††	−9.7†††	−10.6†††
Change from baseline at 72 weeks (mmol/L)	0.1	−0.4†††	−0.5†††	−0.6†††
Change difference from placebo at 72 Weeks (95% CI) (mg/dL)	N/A	−8.6*** (−10.0, −7.2)	−10.6*** (−12.0, −9.2)	−11.4*** (−12.8, −10.0)
Change difference from placebo at 72 Weeks (95% CI) (mmol/L)	N/A	−0.5*** (−0.6, −0.4)	−0.6*** (−0.7, –0.5)	−0.6*** (−0.7, −0.6)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; FSG: fasting serum glucose; MMRM: mixed model for repeated measures; N: number of participants who were randomly assigned and received at least 1 dose of study drug; N/A: not applicable; TZP: tirzepatide.
Footnotes: MMRM analysis for postbaseline measures. ANOVA model for baseline measures. Shown are least-squares means.
***p-value <0.001 versus placebo for superiority.
†††p-value <0.001 versus baseline.
Source: SURMOUNT-1 CSR.[2]

A6. PRIORITY: Are the CIC clinical effectiveness estimates for the subgroups within Document B Tables 22, 23, 24 and 25 on a mITT basis or an EAS basis? If on a mITT basis, please provide additional analyses for the subgroups on an EAS basis, while if on an EAS basis please provide additional analyses for the subgroups on a mITT basis.

As per Table 12 in the CS, the definition for the modified intention to treat (mITT) population is 'all randomly assigned participants who took at least 1 dose of study drug. In the event of a treatment error, participants were analysed according to the treatment they were randomised to'. In other words, the mITT pertains to the selection of **participants**. In contrast, the efficacy analysis set (EAS) pertains to the selection of **data** from relevant participants, aligned with the estimand definitions used; specifically, the EAS relates to the efficacy estimand and uses 'data obtained during the treatment period from the mITT population, excluding data after discontinuation of study drug (last dose + 7 days)'.

Given the above definitions, the Company would like to clarify that the data presented in the CS in Tables 22–25 is conducted using the EAS (within the mITT) and that it is therefore not possible to provide additional analyses on an 'mITT basis' as requested by the EAG. However, it should be noted that equivalent data for the full analysis set (FAS; defined as all available data obtained during the treatment period from the mITT population, regardless of adherence to study drug) is presented in Appendix E, Tables 67–70.

As detailed in Document B, Section B.2.4.1, both estimands used in SURMOUNT-1 were based on the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 (R1) draft addendum on estimands and sensitivity analysis in clinical trials (available here: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf). This document provides further explanation and context for each estimand considered in SURMOUNT-1, and discusses the importance of "defining both the population of subjects to be included in the estimation of that treatment effect" (the mITT in the case of SURMOUNT-1) and "the observations from each subject to be included in the analysis considering the occurrence of intercurrent events" (the EAS or FAS in SURMOUNT-1).

A7. The subgroup analysis results presented in CS Document B Table 22 differ to the results of Table 68 in Appendix E despite having the same number of people in each treatment group and overall. Please confirm that those in the EAS differ to the FAS. If not, why do the numbers differ? Please give an illustrative explanation.

It is assumed that the EAG mean to refer to Table 23 in the CS (data from the population with a BMI ≥35 kg/m^2 with prediabetes and high CV risk i.e. the same population as Table 68 in the Appendices). Provided this is the case, the Company would like to clarify that the n number presented in the CS for each arm is the number of participants with a baseline value, which were the same for both analysis sets. In contrast, there were a different number of participants in the EAS and FAS with a post-baseline value at Week 72 in these datasets (driven by the differences in definitions for these analysis sets), which is why the efficacy data differ. For transparency, the number of participants with a post-baseline value at Week 72 included in the EAS and FAS analyses for the subgroup of people with a BMI of ≥35 kg/m^2 with prediabetes and high CV risk is provided in Table 16 and Table 17, respectively.

Table 16: Key efficacy endpoints for the subgroup of people with a BMI of ≥35 kg/m^2 with prediabetes and high CV risk, EAS (Table 23 in the CS)

	TZP 5 mg	TZP 10 mg	TZP 15 mg	Placebo
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CS: company submission; CV: cardiovascular; EAS: efficacy analysis set; HDL: high-density lipoprotein; N: number of subjects in the population with baseline and post-baseline value at Week 72; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure.

Footnotes: †As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.

Table 17: Key efficacy endpoints for the subgroup of people with a BMI of ≥35 kg/m^2 with prediabetes and high CV risk, FAS (Table 68 in the Appendices)

	TZP 5 mg	TZP 10 mg	TZP 15 mg	Placebo
Body weight, % (SE)	[redacted]	[redacted]	[redacted]	[redacted]
HDL cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Total cholesterol, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
SBP, mmHg (SE)†	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CS: company submission; CV: cardiovascular; FAS: full analysis set; HDL: high-density lipoprotein; N: number of subjects in the population with baseline and post-baseline value at Week 72; mITT: modified intent-to-treat; SE: standard error; SBP: systolic blood pressure.

Footnotes: †As CfB SPB was analysed as a safety endpoint in SURMOUNT-1 within the safety dataset, separate treatment regimen and efficacy estimand data are not available for this endpoint.

A8. CS Table 12 – all analysis sets have total N=2,539. Please explain.

Please refer to Question A6 which provides further details on the definition for each population/analysis set and their relationship to each other. Of note, the mITT and EAS/FAS have the same N because the FAS and EAS both refer to analyses sets based on the mITT population.

A9. Please present the equivalent of Document B Table 20 for the baseline values.

Table 20 in the CS already presents the baseline values; these are shown in the 'Total' column. For instance, for the placebo row (shown in Table 18 for reference, with some minor edits to the table configuration for clarity), the table shows that overall there were [redacted] participants with normoglycaemia at baseline. Of these, [redacted] transitioned to normoglycaemia at Week 72, while [redacted] transitioned to prediabetes, [redacted] transitioned to suspected T2DM and [redacted] had an undetermined glycaemic status at Week 72.

Table 18: Glycaemic status from baseline to 72 weeks (Table 20 in CS)

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total N (%)
		Normoglycemia N (%)	Prediabetes N (%)	Suspected T2DM N (%)	Undetermined N (%)	
Placebo (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HbA1c: glycated haemoglobin; N: number of participants in the population in the specified treatment group; n: number of participants in the specified category; OGTT: 2-hour oral glucose tolerance test; TZP: tirzepatide; T2DM: type 2 diabetes mellitus.

Footnotes: Percentage values refer to the total patients in each treatment arm. Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT was counted in 'Suspected T2DM'. 'Suspected T2DM' was adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT was counted in 'Undetermined'.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01; Dated: 14th July 2023)

A10. To the extent available, please present market share data for Wegovy, Saxenda and Orlistat.

Please find the market share data for Wegovy, Saxenda, and Orlistat in Table 19 for patients with BMI ≥30 kg/m^2 + ≥1 comorbidity, and Table 20 for patients with BMI ≥35 kg/m² + ≥1 comorbidity (aligned with TA875), sourced from the NICE Resource impact template for TA875, assuming a world without tirzepatide.

Table 19: Market shares for patients with BMI ≥35 kg/m^2 with at least one weight-related comorbidity

Treatment	Market Share (current year)	Source
Wegovy	[redacted]	National Institute for Health and Care Excellence (NICE). Resource impact template. 2023 [TA875]
Saxenda	[redacted]	
Orlistat	[redacted]	

Abbreviations: BMI: body mass index; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

Table 20: Market shares for patients with BMI ≥30 kg/m^2 with at least one weight-related comorbidity

Treatment	Market Share (current year)	Source
Wegovy	[redacted]	Adjusted to account for wider population compared to Table 19 from: National Institute for Health and Care Excellence (NICE). Resource impact template. 2023 [TA875]
Saxenda	[redacted]	
Orlistat	[redacted]	National Institute for Health and Care Excellence (NICE). Resource impact template. 2023 [TA875]

Abbreviations: BMI: body mass index; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

A11. Please describe the process (number of reviewers) for the feasibility assessment / eligibility assessment for the NMA.

A team of up to four statisticians working on the NMA summarised the studies identified in the clinical SLR (Appendix D), extracting details of study design, treatments received, eligibility criteria and patient baseline characteristics.

Eligibility criteria for the NMA were subsequently devised based on this review of study details by the same team of statisticians and through repeated feasibility assessment review meetings with the wider Company team (comprising one statistician, two scientists and up to four medical colleagues). Based on the eligibility criteria, and through considering the summarised study

characteristics from the clinical SLR, the list of eligible studies was narrowed. A subsequent detailed review of each individual study then took place (from both the NMA and wider Company teams) to arrive at a final list of eligible studies.

A12. CS Figure 15 states there was an NMA comparing AEs. Please provide the NMA details and results.

CS Figure 15 shows the timepoints at which **safety outcomes** (including SBP) were reported which were investigated as part of the scoping process of the feasibility assessment, rather than stating that an NMA for AEs was conducted. Moreover, since AE data were not available for any subgroup explored in the cost effectiveness model (AE data are only available for comparators for the whole trial population), it was considered more appropriate that a consistent approach was taken between the whole trial population and subgroups, whereby individual trial data were used to inform AE inputs in the CEM.

A13. Please clarify if the efficacy inputs for tirzepatide inputted to the NMA are estimated on a mITT basis or an EAS basis. Please also clarify this for the efficacy inputs to the NMA for semaglutide and for liraglutide.

All SURMOUNT-1 efficacy estimand inputs for the NMA were on an EAS basis. Please refer to the response for Question A6, which clarifies that the EAS is based on the mITT population. The population definitions for all studies included in the NMA are summarised in Table 31, Section B.2.9.3.6 of the CS, and a more granular summary of the analysis sets and estimand used for each specific NMA analysis is provided in response to Question A21.

A14. Dyslipidaemia, hypertension and cardiovascular disease are described as treatment effect modifiers on CS p74, but are not included in CS Table 28 as specific comorbidities (as they are in CS Table 10). Please provide details of these at baseline in each of the studies included in the NMA.

The Company wishes to clarify that dyslipidaemia, hypertension and cardiovascular disease are not described as treatment effect modifiers in the CS, as the question states; the CS noted that these comorbidities were discussed as *potential* effect modifiers in the ongoing company submission for TA875.[3]

Nevertheless, for transparency, details of baseline dyslipidaemia, hypertension and cardiovascular disease are provided for each of the studies included in the NMA in Table 21. It should be noted that the data in Table 21 pertain to the whole trial population in each trial, not to the two populations where the NMA results are used in the CEM, as these data are not reported for the subgroups. Given that the definitions of two populations relevant to the NMA comparisons (BMI ≥30 kg/m^2 with at least one weight-related comorbidity; and BMI of ≥35 kg/m^2 with prediabetes and high CV risk) each incorporate an element of selection by comorbidity, the baseline comorbidities in each population considered in the economic analysis will differ from those presented below.

Table 21: Comorbidities at baseline for each study included in the NMA

Study Name	Dyslipidaemia, %	Hypertension, %	CVD, %
O'Neil, 2018	NR	NR	NR
SCALE Obesity and Prediabetes	29.3	35.1	8.6
STEP 1	37	36	NR
STEP 5	35.2	38.8	NR
STEP 8	47.6	42	NR
SURMOUNT-1	29.8	32.2	3.1

Abbreviations: CVD: cardiovascular disease; NMA: network meta-analysis; NR; not reported.
Sources: O'Neil et al. (2018), Pi-Sunyer et al. (2015), Wilding et al. (2021), Garvey et al. (2022), Rubino et al. (2022), Jastreboff et al. (2022)[1, 4-8]

A15. In Table 29 of CS document B, the summary of STEP 5 is 'Diet + Exercise', however a lifestyle intervention is described in the form of individual dietary counselling. Therefore, should the summary of STEP 5 be 'Diet + Exercise + Lifestyle'?

The Company would like to confirm that there was a typographical error in Table 29 of CS Document B. We agree that the summary of STEP 5 should be 'Diet + Exercise + Lifestyle' due to the individual dietary counselling.

A16. PRIORITY: Please provide the raw data of the central estimates used in the NMA for all of the studies, for all NMAs conducted.

Please find all NMA input data in the reference pack accompanying these responses [File Names: BMI S3a EE, BMI S3a TR, BMI S4 EE, BMI S4 TR, Whole Pop EE and Whole Pop TR]. Separate tabs are provided for each outcome, along with the indices required for labelling of treatments.

Please note that these files are identical to the input data provided for A20.

A17. PRIORITY: Please provide the central estimates for the comparator group (placebo) for all of the studies included in the NMA.

Please find the reported mean values and standard errors for the placebo group for all studies for each outcome in the reference pack accompanying these responses [File Name: Placebo Response Table].

A18. CS B.2.9.3.1 states 'based on clinical opinion the following were also considered to be potential treatment effect modifiers: OSA, background therapy (principally diet and exercise), concomitant medication and physical functional as measured by component of HRQoL questionnaires such as SF-36 and IWQOL-Lite-CT'. Please describe how expert opinion was elicited.

The clinical opinion above refers to the opinion of Lilly's internal Medical team. This was elicited

in an informal way through regular correspondence, in which the team of Statisticians conducting the feasibility assessment and NMA requested input from Lilly's Medical team on which variables should be initially explored as potentially clinically relevant characteristics for the NMA.

A19. CS Table 29 described background therapy (diet and exercise) from the studies included in the NMA – please provide details of concomitant medications received for the included studies, by treatment arm.

Concomitant medications were generally poorly reported across the included studies in the NMA. However, the percentage of patients receiving anti-hypertensive medication and the percentage of patients receiving lipid lowering medication were reported in both STEP 1 and SCALE for the whole trial population (BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with a least one weight-related comorbidity); available data for concomitant medication use in this population for studies that reported these data are summarised in Table 22 below.

Table 22: Summary of concomitant medication use in studies included in the NMA

Study	Arm	N	Anti-hypertensive Medication (%)	Lipid-Lowering Medication (%)
SCALE Obesity and Prediabetes	Liraglutide 3.0 mg QD	2,487	30.9	15.8
	Placebo	1,244	33.0	14.9
STEP 1	Semaglutide 2.4 mg QW	1,306	23.8	19.1
	Placebo	655	23.2	17.4
SURMOUNT-1	Tirzepatide 5 mg QW	630	31.1	18.4
	Tirzepatide 10 mg QW	636	30.0	15.6
	Tirzepatide 15 mg QW	630	30.0	15.7
	Placebo	643	28.1	17.9

Abbreviations: NMA: network meta-analysis; QD: once daily; QW: once weekly.
Sources: Pi-Sunyer et al. (2015), Wilding et al. (2021), Jastreboff et al. (2022)[1, 5, 6]

A20. Please provide the outcome data that were used in the NMAs from the other included trials for:

- BMI ≥30 +weight-related comorbidity
- BMI ≥35 + prediabetes + high CVD risk
- Whole trial population: without diabetes, BMI 30, or BMI ≥27 + weight-related comorbidity

Please refer to the response to A16, where all NMA input data have been provided.

A21. PRIORITY: Please provide the following data for all of the studies included in the NMA (and for each outcome where appropriate):

- **All the timepoints that were analysed (follow-up period)**
- **The timepoint where the primary analysis was analysed**
- **The geographic locations of participants from all the studies, frequency and percentages**
- **The disease area**
- **The population that was analysed (full trial cohort or a subgroup such as BMI < 35, etc)**
- **The analysis set that was analysed (ITT, mITT, PP, EAS, etc)**
- **What type of blinding was implemented**
- **The number of participants in each of the treatment groups**
- **Study design and phase (such as phase III RCT)**

The timepoint, population, analysis set and number of participants in each treatment group for all analyses in the NMA are summarised in an Excel file in the reference pack [File Name: Analysis Information].

When interpreting the table, it should be noted that the analysis set provided is aligned with the terminology reported in the study primary publications. However, the Company would suggest that it is of greater relevance to consider the *estimand* used when determining the homogeneity of populations analysed for this NMA rather than the analysis set, since each estimand addresses a distinct research question and the reported analysis set terminology may not necessarily correspond with the estimand used. Specifically, the efficacy estimand addresses efficacy in patients who adhered to their randomised treatment and the treatment regimen estimand addresses efficacy regardless of adherence to treatment. Please refer to the CS Section B.2.9.3.6 for how homogeneity of estimands were considered as part of the NMA. Given the importance of considering the homogeneity of estimands across studies, these details have additionally been provided as part of the Analysis Information file in the reference pack.

Please also find a table of study details in the reference pack [File Name: Study Details] for all studies included in the NMA. This table includes details of the study design, study phase, type of blinding and geographic location of participants. Additionally, studies reporting on whole populations which had a comorbidity which did not align with SURMOUNT-1 were excluded. In particular, studies requiring inclusion of patients with T2DM (e.g. STEP-2), binge eating disorder, chronic obstructive pulmonary disease, gastrectomy, gastric bypass, heart failure, knee osteoarthritis, non-alcoholic fatty liver disease, psychosis and schizophrenia were excluded. All studies included in the NMA had 0% T2DM patients, as detailed in Section B.2.9.3.4 of the CS.

A22. PRIORITY: Discontinuation due to adverse effects, discontinuation due to primary treatment failure, and reversal of prediabetes were used in the

economic model but not included in the NMA. Please explain why (for examples, were these NMAs unfeasible?).

Although comparator discontinuation and prediabetes reversal were available in the whole trial population in comparator studies (as detailed in response to Question A22), comparator discontinuation data were not available for any subgroup considered in the economic analysis, and comparator prediabetes data for subgroups were only available as model inputs or ITC results in TA875 Appendix O,[3] rather than as raw data results from clinical trials that would be suitable to include in an NMA. Therefore, to ensure the consistency of the approach between the whole trial population and the subgroups, NMAs were not conducted for discontinuations or reversal of prediabetes, and individual trial data were used to inform inputs in the CEM.

A23. The heterogeneity assessment does not assess the proportions who were prediabetic at baseline. Please present the data, to the extent available, on the proportions who were prediabetic at baseline.

The percentage of patients who were prediabetic at baseline in the studies included in the NMA are presented in Table 23 for the whole trial populations.

Table 23: Percentage of patients who were prediabetic at baseline for whole trial populations in the studies included in the NMA

Study Name	Study Population, N	Prediabetes, %
O'Neil, 2018	239	NR
SCALE Obesity and Prediabetes	4,974	61.2
STEP 1	1,961	43.7
STEP 5	304	46.4
STEP 8	338	36.1
SURMOUNT-1	2,539	40.7

Abbreviations: NMA : network meta-analysis; NR: not reported
Sources: O'Neil et al. (2018), Pi-Sunyer et al. (2015), Wilding et al. (2021), Garvey et al. (2022), Rubino et al. (2022), Jastreboff et al. (2022)[1, 4-8]

A24. For the trials' active treatments and placebo, i.e. all arms, please present the data, to the extent available, on (1) discontinuations for any reason together with their relevant time point alongside the data on discontinuations due to AEs together with their relevant time point and (2) reversal of pre-diabetes. Please present this separately for the relevant subgroups of (A) the TA875 base case population subgroup (SURMOUNT and STEP trials) as used for the comparison with semaglutide and (B) the TA664 population subgroup (SURMOUNT, SCALE and O'Neil) as used for the comparison with liraglutide. Why were discontinuations and reversals of pre-diabetes not included in the NMA?

Table 24 present the proportion of participants discontinuing from treatment both due to AEs and overall, while Table 21 presents the proportion of participants experiencing pre-diabetes reversal

for all studies included in the NMA for the whole trial population.

Please refer to the response to Question A22 for a further explanation of why discontinuations and prediabetes reversal were not included in the NMA.

Table 24: Percentage of patients who discontinued for the whole trial populations in the studies included in the NMA

Study Name	Arm	Follow-up Time	All Cause Treatment Discontinuation, %	Treatment Discontinuation due to AEs, %
O'Neil, 2018	Liraglutide 3.0 mg QD	Week 52	16.5	9.0
	Placebo	Week 52	24.3	3.0
SCALE Obesity and Prediabetes	Liraglutide 3.0 mg QD	Week 56	28.1	9.6
	Placebo	Week 56	35.7	3.6
STEP 1	Semaglutide 2.4 mg QW	Week 68	17.1	7.0
	Placebo	Week 68	22.4	3.1
STEP 5	Semaglutide 2.4 mg QW	Week 104	13.2	6.6
	Placebo	Week 104	27.0	4.6
STEP 8	Semaglutide 2.4 mg QW	Week 75	14.3	3.2
	Liraglutide 3.0 mg QD	Week 75	27.6	12.6
	Placebo	Week 75	17.6	3.5
SURMOUNT-1	Tirzepatide 5 mg QW	NR	14.3	4.3
	Tirzepatide 10 mg QW	NR	16.4	7.1
	Tirzepatide 15 mg QW	NR	15.10	6.2
	Placebo	NR	26.40	2.6

Abbreviations: AE, adverse effect; NMA : network meta-analysis; NR: not reported

Table 25: Percentage of patients who were prediabetic at baseline and achieved normoglycaemia for the whole trial populations in the studies included in the NMA

Study Name	Arm	Reversal of Prediabetes, %
O'Neil, 2018	Liraglutide 3.0 mg QD	NR
	Placebo	NR
SCALE Obesity and Prediabetes	Liraglutide 3.0 mg QD	NR
	Placebo	NR

STEP 1	Semaglutide 2.4 mg QW	84.1
	Placebo	47.8
STEP 5	Semaglutide 2.4 mg QW	79.7
	Placebo	37.0
STEP 8	Semaglutide 2.4 mg QW	NR
	Liraglutide 3.0 mg QD	NR
	Placebo	NR
SURMOUNT-1 (Efficacy Estimand)	Tirzepatide 5 mg QW	94.7
	Tirzepatide 10 mg QW	94.3
	Tirzepatide 15 mg QW	96.8
	Placebo	61.9
SURMOUNT-1 (Treatment Regimen Estimand)	Tirzepatide 5 mg QW	93.5
	Tirzepatide 10 mg QW	92.4
	Tirzepatide 15 mg QW	93.7
	Placebo	61.9

Footnote: Data values for both estimands were reported for SURMOUNT-1, whilst for the other studies, the treatment regimen estimand has been reported.
Abbreviations: NMA: network meta-analysis; NR: not reported

A25. Please present the Kaplan Meier (KM) time to treatment discontinuation data of SURMOUNT-1, separately by arm including placebo, and if possible also present this for time to treatment discontinuation due to AEs.

The KM time to treatment discontinuation data both overall and for AEs specifically for SURMOUNT-1 per treatment arm are provided in the reference pack alongside these responses (Files Names: grdis01 and grdis02).

A26. Please tabulate the interim effectiveness data of SURMOUNT-4 as mean weight (kg) and as weight change from baseline (%) values.

All SURMOUNT-4 data beyond the top-line results presented in Appendix M.6 were embargoed and therefore could not be presented at the time of writing these responses. However, these data were disclosed at the European Association for the Study of Diabetes (EASD) conference the evening before submission of these responses and subsequently will be available in the form of a CSR. Once the CSR is available (estimated to be completed by 10th October 2023 at the earliest), the Company will share a response to this question with the EAG.

A27. PRIORITY: Please tabulate the number of patients with (A) CV Disease, (B) Hypertension, (C) CHF, (D) family history of diabetes, (E) smoking at baseline and (F) NGT for those with baseline age 20-40, 41-50, 51-60, 61-70, 71-80 and 80+ separately for all patients and the subset with T2DM at baseline (2 tables).

The number of participants with atherosclerotic cardiovascular disease (ASCVD), hypertension (HT), congestive heart failure (CHF), smoking and normal glucose tolerance (NGT) at baseline in

SURMOUNT-1 is presented for the whole trial population and for participants with BMI ≥30kg/m^2 with at least one weight-related comorbidity below in Table 26 and Table 27, respectively. Family history of type 2 diabetes mellitus (T2DM) is not reported as these data were not collected in SURMOUNT-1. Accordingly, as detailed in the CS Section B.3.2.1., these data were obtained from the relevant risk equation source (Hippisley-Cox *et al.* 2017 [QDiabetes])[9] for use in the economic model rather than being derived from SURMOUNT-1.

Table 26. Proportion of participants in SURMOUNT-1 with CVD, HT, CHF, family history of T2DM, smoking and normal glucose tolerance at baseline by age; randomised population (BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with at least one weight-related comorbidity)

Characteristic, n (%)	Baseline Age					
	≤ 40 [redacted]	41–50 [redacted]	51–60 [redacted]	61–70 [redacted]	71–80 [redacted]	≥ 81 [redacted]
ASCVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHF*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NGT†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHF: congestive heart failure; HT: hypertension; N: number of participants in the population in the specified age group; n = number of participants with the specified characteristics; NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus.
Footnotes: *MedDRA Preferred Term (Cardiac failure congestive]. † Normal glucose tolerance at baseline is defined as having Glucose Value at Time 0 During OGTT <100 mg/dL Glucose Value at Time 120 mins During OGTT < 140 mg/dL at the baseline visit.
Source: Eli Lilly Exploratory Analysis (File Name: smdem06)

Table 27. Participants with CVD, HT, CHF, family history of T2DM, smoking and normal glucose tolerance at baseline by age overall and in BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup

Characteristic, n (%)	Baseline Age					
	≤ 40 [redacted]	41–50 [redacted]	51–60 [redacted]	61–70 [redacted]	71–80 [redacted]	≥ 81 [redacted]
ASCVD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHF*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NGT†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHF: congestive heart failure; HT: hypertension; N: number of participants in the population in the specified age group; n = number of participants with the specified characteristics; NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus.
Footnotes: *MedDRA Preferred Term (Cardiac failure congestive]. † Normal glucose tolerance at baseline is defined as having Glucose Value at Time 0 During OGTT <100 mg/dL Glucose Value at Time 120 mins During OGTT < 140 mg/dL at the baseline visit.
Source: Eli Lilly Exploratory Analysis (File Name: smdem06_subset3a)

A28. PRIORITY: Please provide reasons that this population is generalisable to England and Wales. CS p136 says: Limitations of the SURMOUNT-1 trial include

the absence of any trial sites in the UK or Europe. However, given the global nature of the trial, the large sample size and high completion rate, the results still remain generalisable to UK clinical practice. In addition, the consistently significant results observed across the population suggest that this limitation is unlikely to be important point within this evaluation. Please also provide details as to how the healthcare systems and standard of care arm are generalisable to England and Wales.

Although SURMOUNT-1 did not include centres in UK and European countries, the findings should be considered generalisable to England and Wales, as detailed below.

Subgroup analysis results

Firstly, results from the subgroup analyses by race, region of enrolment (both presented in Appendix E2), and country of enrolment[10] demonstrate that tirzepatide consistently leads to substantial and clinical meaningful body weight reduction:

- Firstly, the effect of tirzepatide for the co-primary endpoints was consistent across the participants' race subgroups (Appendix E2).[2] Notably, 71% of participants in SURMOUNT-1 were White, and White is the predominant ethnic group in the UK population (82% white; 74% white British).[11] Moreover, the trials included a robust representation of patients from other race groups, which is important when considering the multi-racial diversity of the UK population and the prevalence of obesity across race groups in the UK.[12]
- In addition, subgroup analyses by region of enrolment indicate that for the co-primary endpoints, the benefit of tirzepatide was consistent for participants enrolled in the US versus those enrolled outside of the US.[2]
- Finally, an exploratory post hoc subgroup analysis for percent change in body weight by enrolment country indicated that despite the diversity between the included countries in terms of race, ethnicity, nutrition, lifestyle, and health care systems, tirzepatide consistently led to substantial and clinically meaningful body weight reduction in participants from all the countries.[10]

Given these subgroup analysis results it is expected, by association, that a similar effect of tirzepatide on body weight reduction should also be observed in UK patients. It is also worth noting that SURMOUNT-1 included 44.9% of participants from the US,[2] and tirzepatide substantially reduced body weight in this cohort across all races and ethnicities. Although Lilly acknowledges the uniqueness of every country, it is likely that the effects of tirzepatide observed in the US participants are particularly generalisable to UK patients given the ancestry, socioeconomics, racial demographics, post-industrial Western culture and lifestyle shared by these two countries.

Generalisability of healthcare systems and standard of care arm

The diet and exercise arm in SURMOUNT-1 should also be considered generalisable to clinical practice in England and Wales because it closely reflects the CG189 clinical guidelines.[13] In SURMOUNT-1, patients were advised to adhere to a hypocaloric diet (with a 500-calorie deficit that was individually calculated) and to increase their physical activity to at least 150 minutes per week. This closely reflects the CG189 guidelines for obesity, which recommend that people with

obesity adhere to a 600 kcal/day deficit for sustainable weight loss, and that they should accumulate at least 150 minutes of physical activity per week, as per the recommendations in the UK Chief Medical Officers' Physical Activity Guidelines.[13, 14]

With regards to the generalisability of the healthcare systems in which SURMOUNT-1 trial sites were operating to NHS England, the Company would highlight that regardless of the country in which participants were enrolled, the same lifestyle modification was provided, as per the SURMOUNT-1 study protocol.[15] Given the lifestyle modification provided in SURMOUNT-1 was closely aligned with the standard of care for obesity management in England and Wales (as highlighted above), the Company therefore do not consider the healthcare systems in which the support was provided to be of importance when considering the generalisability of the trial data to clinical practice in England and Wales.

Supporting data from SURPASS programme

As detailed in the CS, tirzepatide is also being investigated in the SURPASS programme. In these Phase 3 clinical studies, including 86% of participants with BMI ≥27 kg/m^2, tirzepatide consistently reduced body weight (an alpha-controlled secondary endpoint), irrespective of T2DM duration and background medication. Importantly, in SURPASS-2, -3, -4, and -5, there were 1,558 participants from the EU, including UK, enrolled, which comprised a considerable proportion of the trial populations (4.1% in SURPASS-2; 53.9% in SURPASS-3; 29.0% in SURPASS-4 and 79.1% in SURPASS-5).[16-19]

Importantly these studies indicated that participant characteristics at baseline (such as body weight, BMI, and HbA1c) were comparable between participants within the US and outside the US, and that the efficacy of tirzepatide was consistent within the US and outside the US, as indicated by the subgroup analysis of weight change by region in each aforementioned SURPASS studies.[16-19]

A29. Additional question raised during the clarification meeting on 2nd October: Please explain why CfB SBP, HDL and total cholesterol are reported for pooled tirzepatide 5/10/15 mg in B.2.6.2.

In SURMOUNT-1, specific endpoints were reported for pooled tirzepatide 5/10/15 mg as per the pre-specified analyses set out in the protocol. For SBP and lipid parameters (including total cholesterol and HDL), tirzepatide doses were pooled because it was hypothesised that all three doses would improve cardiometabolic parameters in a similar magnitude, and therefore that it was unnecessary to analyse these data by tirzepatide arm.[1]

While SBP, HDL and total cholesterol were pooled in pre-specified analysis in SURMOUNT-1, by-arm data were also analysed to inform the NMA. These by-arm data are reported below in Table 28–Table 30.

Table 28. Change from baseline in SBP at 72 Weeks; SAS

Parameter (mmHg)	Placebo (N=245)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline	125.9 (0.7)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	−2.0 (0.7)††	[redacted]	[redacted]	[redacted]

Change difference from placebo at 72 weeks (95% CI)	N/A	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; CI: confidence interval; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; SAS: safety analysis set; SBP: systolic blood pressure; TZP: tirzepatide.
Footnotes: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. MMRM model for post-baseline measures. ANOVA model for baseline measures.
***p-value <0.001 versus placebo for superiority.
†† p-value <0.01 versus baseline.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_124_subset1_taffy.rtf)

Table 29. Change form baseline in HDL at 72 Weeks; EAS

Parameter	Placebo (N=312)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	46.4	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	−0.2	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	−0.5	[redacted]	[redacted]	[redacted]
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; CI: confidence interval; EAS: efficacy analysis set; HDL: high density lipoprotein; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. MMRM model for post-baseline measures. ANOVA model for baseline measures.
***p-value <0.001 versus placebo for superiority.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_subset3a_taffy)

Table 30. Change form baseline in total cholesterol at 72 Weeks; EAS

Parameter	Placebo (N=312)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	188.6	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	−3.9	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	−2.1	[redacted]	[redacted]	[redacted]
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; CI: confidence interval; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at

Week 72;: tirzepatide.
Footnotes: MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
***p-value <0.001 versus placebo for superiority.
**p-value <0.01 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_subset3a_taffy)

Section B: Clarification on cost-effectiveness data

B1. PRIORITY: Given the primary efficacy stopping rule at six months within the model, please present the SURMOUNT-1 effect estimates for each of the four arms for BMI percentage change, proportions losing the various BMI %s, SBP, HDL, TC, discontinuations due to AEs and pre-diabetes reversal restricted to those patients achieving primary efficacy, separately for each of the economic analysis groups of Document B Sections B.3.10, B.3.12.1, B.3.12.2, B.3.12.3 and B.3.12.4.

Given the draft SmPC states that [redacted], it would be anticipated that response to tirzepatide would be assessed in clinical practice at different timepoints depending on the dose, since the three doses have different titration periods (as detailed in Document B, Section B.2.3.1.1). Specifically, response to tirzepatide would be assessed after 30 weeks for tirzepatide 5 mg, after 38 weeks for tirzepatide 10 mg and after 46 weeks for tirzepatide 15 mg. However, these SmPC-defined timepoints at which response to tirzepatide should be assessed do not align with the timepoints that weight was measured in SURMOUNT-1 (weight was only measured at Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60 and 72).[15] For this reason, it is not possible to determine the exact number of patients who met the SmPC-defined primary efficacy criteria in SURMOUNT-1 and subsequently to provide efficacy estimates for these patients.

The Company have therefore provided the requested responder analyses for patients reaching ≥5% weight loss in SURMOUNT-1 at the closest trial timepoint after the primary efficacy criteria period. This approach was taken as it was considered to reflect what would happen in clinical practice, with any surplus time beyond 6 months post-titration reflecting the wait for appointments in NHS clinical practice. Assessment of response to tirzepatide (achievement of ≤5% weight loss) was therefore performed at Week 36 weeks for 5 mg tirzepatide and Week 48 for 10 and 15 mg tirzepatide. The results for these analyses for the requested endpoints are presented separately by arm in Table 31 to Table 70 for each population considered in the economic analysis. It should be noted that percentage change in BMI has not been presented as this is not considered to be a clinically relevant measure and as such was not measured as an endpoint in SURMOUNT-1; instead, mean change in BMI and % change in body weight are presented. Additionally, it should be noted that all reported p-values for these analyses are not controlled for Type 1 error given they are post-hoc in nature.

BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup (base case population; Section B.3.10)

Table 31. Mean percent change from baseline in body weight at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameters	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline (kg)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-Value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_18_wlge5_subset3a)

Table 32. Mean change in BMI from baseline to 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameters (kg/m^2)	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi01_wlge5_subset3a_taffy)

Table 33: Percentage of patients achieving body weight reduction targets at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameters, n(%);	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥10% body weight reduction			
Participants achieving ≥10% body weight reduction; observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction			
Participants achieving ≥15% body weight reduction; observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction			
Participants achieving ≥20% body weight reduction; observed values	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of participants with baseline value and at least one non-missing post-baseline value; n: number of participants achieving target in observed data;

TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Only participants with valid baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Statistical summary and inference for baseline uses observed values.
Source: Eli Lilly Exploratory Analysis (File Name: fqwgt01_wlge5_subset3a)

Table 34. Change from baseline in SBP at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; SAS

Parameter (mmHg)	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI; body mass index; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; SAS: safety analysis set; SBP: systolic blood pressure; TZP: tirzepatide
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_124_wlge5_subset3a)

Table 35. Change from baseline in HDL at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA = analysis of variance; BMI; body mass index; EAS: efficacy analysis set; HDL-C = high-density lipoprotein cholesterol; MMRM = mixed model repeated measures; N = number of subjects in the population with baseline and post-baseline value at Week 72; TZP = tirzepatide
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_wlge5_subset3a_taffy)

Table 36. Change from baseline in total cholesterol at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI; body mass index; EAS: efficacy analysis set; MMRM: mixed

model repeated measures; N: number of subjects in the population with baseline and post-baseline value at the specified time point; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_wlge5_subset3a_taffy)

Table 37: Percentage of participants with a change in glycaemic category in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; EAS

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total n (%)
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	
TZP 5 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI; body mass index; EAS: efficacy analysis set; HbA1c; haemoglobin A1c; N; number of participants in the population in the specified treatment group; n; number of participants in the specified category; OGTT; 2-hour oral glucose tolerance test; TZP; tirzepatide; T2DM; type 2 diabetes mellitus.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Suspected T2DM'. 'Suspected T2DM' were adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_wlge5_subset3a)

Table 38. Proportion of participants discontinuing study or study intervention due to an AE in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2 with at least one weight-related comorbidity; SAS

Category, n (%)	TZP 5 mg ([redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BMI: body mass index; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Subjects may be counted in more than one category.
Source: Eli Lilly Exploratory Analysis (File Name: smae01_wlge5_subset3a_taffy)

BMI ≥35 kg/m^2 with prediabetes and high CVD risk (Section B.3.12.1)

Table 39. Mean percent change from baseline in body weight at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2 with prediabetes and high CVD risk; EAS

Parameters	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline (kg)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_18_wlge5_subset4)

Table 40. Mean change in BMI from baseline to 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2 with prediabetes and high CVD risk; EAS

Parameters (kg/m^2)	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi01_wlge5_subset4_taffy)

Table 41: Percentage of patients achieving body weight reduction targets at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m² with prediabetes and high CVD risk; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥10% body weight reduction			
Participants achieving ≥10% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction			
Participants achieving ≥15% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction			
Participants achieving ≥20% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; N: number of participants with baseline value and at least one non-missing post-baseline value; n: number of participants achieving target in observed data; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Only participants with valid baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Statistical summary and inference for baseline uses observed values.
Source: Eli Lilly Exploratory Analysis (File Name: fqwgt01_wlge5_subset4)

Table 42. Change from baseline in SBP at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m² with prediabetes and high CVD risk; SAS

Parameter (mmHg)	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; SBP; systolic blood pressure; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_124_wlge5_subset4)

Table 43. Change from baseline in HDL at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m² with prediabetes and high CVD risk; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; HDL-C; high-density lipoprotein; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.

Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_wlge5_subset4_taffy)

Table 44. Change from baseline in total cholesterol at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2 with prediabetes and high CVD risk; AS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; MMRM; mixed model repeated measures; n; number of subjects in the population with baseline and post-baseline value at the Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_wlge5_subset4_taffy)

Table 45: Percentage of participants with a change in glycaemic category at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2 with prediabetes and high CVD risk; EAS

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total n (%)
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	
TZP 5 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI; body mass index; CVD: cardiovascular disease; EAS: efficacy analysis set; HbA1c; haemoglobin A1c; N; number of participants in the population in the specified treatment group; n; number of participants in the specified category; OGTT; 2-hour oral glucose tolerance test; TZP; tirzepatide; T2DM; type 2 diabetes mellitus.
Footnotes: Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Suspected T2DM'. 'Suspected T2DM' was adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'. Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_wlge5_subset4)

Table 46. Proportion of participants discontinuing study or study intervention due to an AE in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2 with prediabetes and high CVD risk; SAS

Category, n (%)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BMI: body mass index; CVD: cardiovascular disease; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Subjects may be counted in more than one category.
Source: Eli Lilly Exploratory Analysis (File Name: smae01_wlge5_subset4_taffy)

BMI ≥35 kg/m^2 (irrespective of comorbidities)

Table 47. Mean percent change from baseline in body weight at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline (kg)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; EAS: efficacy analysis set; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_18_wlge5_subset5)

Table 48. Mean change in BMI from baseline at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; EAS

Parameters (kg/m^2)	TZP 5 mg (N[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; EAS: efficacy analysis set; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi_wgle5_subset5_taffy)

Table 49: Percentage of patients achieving body weight reduction targets at Week 72 in BMI ≥35 kg/m^2 subgroup; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥10% body weight reduction			
Participants achieving ≥10% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction			
Participants achieving ≥15% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction			
Participants achieving ≥20% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; BMI; body mass index; EAS: efficacy analysis set; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Only participants with valid baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Statistical summary and inference for baseline uses observed values.
Source: Eli Lilly Exploratory Analysis (File Name: fqwgt01_wlge5_subset5)

Table 50. Change from baseline in SBP at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; SAS

Parameter (mmHg)	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15mg (N=[redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; SBP; systolic blood pressure; SAS: safety analysis set; TZP; tirzepatide
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_124_wlge5_subset5)

Table 51. Change from baseline in HDL at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA = analysis of variance; HDL-C = high-density lipoprotein cholesterol; MMRM = mixed model repeated measures; N = number of subjects in the population with baseline and post-baseline value at the Week 72; TZP = tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_wlge5_subset5_taffy)

Table 52. Change from baseline in total cholesterol at 72 weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_wlge5_subset5_taffy)

Table 53: Percentage of participants with a change in glycaemic category in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; EAS

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total n (%)
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	
TZP 5 mg (N=314)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=363)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=369)	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HbA1c; haemoglobin A1c; N; number of participants in the population in the specified treatment group; n; number of participants in the specified category; OGTT; 2-hour oral glucose tolerance test; TZP; tirzepatide; T2DM; type 2 diabetes mellitus.
Footnotes: Participant who meets any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Suspected T2DM'. 'Suspected T2DM' were adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'. Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_wlge5_subset5)

Table 54. Proportion of participants discontinuing study or study intervention due to an AE in responders (≥5% body weight reduction) from subgroup with BMI ≥35 kg/m^2; SAS

Category, n (%)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BMI: body mass index; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Subjects may be counted in more than one category.
Source: Eli Lilly Exploratory Analysis (File Name: smae01_wlge5_subset5_taffy)

BMI ≥30 kg/m^2 (irrespective of comorbidities)

Table 55. Mean percent change from baseline in body weight at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline (kg)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; SD; standard deviation; SE; standard error; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-Value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_18_wlge5_subset2)

Table 56. Mean change in BMI from baseline to 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; EAS

Parameters (kg/m^2)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi01_wlge5_subset2_taffy)

Table 57: Percentage of patients achieving body weight reduction targets at Week 72 in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥10% body weight reduction			
Participants achieving ≥10% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction			
Participants achieving ≥15% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction			
Participants achieving ≥20% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; EAS: efficacy analysis set; N: number of participants in imputed data; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Only participants with valid baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Statistical summary and inference for baseline uses observed values.
Source: Eli Lilly Exploratory Analysis (File Name: fqwgt01_wlge5_subset2)

Table 58. Change from baseline in SBP at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; SAS

Parameter (mmHg)	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; SAS: safety analysis set; SBP; systolic blood pressure; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_wlge5_subset2_taffy)

Table 59. Change from baseline in HDL at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; EAS; efficacy analysis set; HDL-C; high-density lipoprotein cholesterol; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip02a_wlge5_subset2_taffy)

Table 60. Change from baseline in total cholesterol at 72 Weeks in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m^2; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA; analysis of variance; EAS; efficacy analysis set; MMRM; mixed model repeated measures; N; number of subjects in the population with baseline and post-baseline value at Week 72; TZP; tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_wlge5_subset2_taffy)

Table 61: Percentage of participants with a change in glycaemic category

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total n (%)
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	
TZP 5 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HbA1c = haemoglobin A1c; N = number of participants in the population in the specified treatment group; n = number of participants in the specified category; OGTT = 2-hour oral glucose tolerance test; TZP = tirzepatide; T2DM = type 2 diabetes mellitus.
Footnotes: Participant who met any two of conditions such as, HbA1c ≥ 6.5%, fasting glucose >= 126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Suspected T2DM'. 'Suspected T2DM' was adjudicated to confirm the diagnosis of T2DM. Participant who met any one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'. Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg.
Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_wlge5_subset2)

Table 62. Proportion of participants discontinuing study or study intervention due to an AE in responders (≥5% body weight reduction) from subgroup with BMI ≥30 kg/m²; SAS

Category, n (%)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BMI: body mass index; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Subjects may be counted in more than one category.
Source: Eli Lilly Exploratory Analysis (File Name: smae01_wlge5_subset2_taffy)

Whole trial population (BMI ≥30 kg/m², or BMI ≥27 kg/m² with at least one weight-related comorbidity)

Table 63. Mean percent change from baseline in body weight at Week 72 in responders (≥5% body weight reduction) from whole trial population; EAS

Parameters	TZP 5 mg (N=[redacted])	TZP 10 mg (N=[redacted])	TZP 15 mg (N=[redacted])
Baseline (kg)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-Value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: gphk_8_18_wlge5)

Table 64. Mean change in BMI from baseline to 72 Weeks in responders (≥5% body weight reduction) from whole trial population; EAS

Parameters (kg/m²)	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; BMI: body mass index; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
††† p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmbmi01_wlge5_taffy)

Table 65: Percentage of patients achieving body weight reduction targets at Week 72 in responders (≥5% body weight reduction) from whole trial population; EAS

Parameters	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Participants achieving ≥10% body weight reduction			
Participants achieving ≥10% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥15% body weight reduction			
Participants achieving ≥15% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]
Participants achieving ≥20% body weight reduction			
Participants achieving ≥20% body weight reduction (%); observed values	[redacted]	[redacted]	[redacted]

Abbreviations: EAS: efficacy analysis set; N: number of participants in imputed data; MMRM: mixed model for repeated measures; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Only participants with valid baseline value and at least one non-missing post-baseline value of the response variable were included in analysis. Statistical summary and inference for baseline uses observed values.
Source: Eli Lilly Exploratory Analysis (File Name: fqwgt01_wlge5)

Table 66. Change from baseline in SBP at 72 Weeks in responders (≥5% body weight reduction) from whole trial population; SAS

Parameter (mmHg)	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; SBP: systolic blood pressure; SD: standard deviation; SE: standard error; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
[†††]p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (file name: gphk_8_124_wlge5)

Table 67. Change from baseline in HDL at 72 Weeks in responders (≥5% body weight reduction) from whole trial population; EAS

Parameter	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15mg [redacted]
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; EAS: efficacy analysis set; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
[†††]p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (file name: rmlblop02a_wlge5_taffy)

Table 68. Change from baseline in total cholesterol at 72 Weeks in responders (≥5% body weight reduction) from whole trial population; EAS

Parameter	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15mg ([redacted])
Baseline (mg/dL)	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks (mg/dL)	[redacted]	[redacted]	[redacted]
Percent change from baseline at 72 weeks (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ANOVA: analysis of variance; EAS: efficacy analysis set; MMRM: mixed model repeated measures; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. MMRM model for post-baseline measures. ANOVA model for baseline measures.
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Name: rmlblip04a_wlge5_taffy)

Table 69: Percentage of participants with a change in glycaemic category at 72 Weeks; EAS

Treatment	Glycaemic status at baseline	Glycaemic status at Week 72				Total n (%)
		Normoglycemia n (%)	Prediabetes n (%)	Suspected T2DM n (%)	Undetermined n (%)	
TZP 5 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 10 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZP 15 mg (N=[redacted])	Normoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAS: efficacy analysis set; HbA1c: haemoglobin A1c; N: number of participants in the population in the specified treatment group; n: number of participants in the specified category; OGTT: 2-hour oral glucose tolerance test; TZP: tirzepatide; T2DM: type 2 diabetes mellitus.

Footnotes: Participant who met any two of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT was counted in 'Suspected T2DM'. 'Suspected T2DM' was adjudicated to confirm the diagnosis of T2DM. Participants who met one of conditions such as, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, fasting glucose ≥126 mg/dL obtained alone at time = 0 min during an OGTT, fasting glucose ≥200 mg/dL obtained alone or at time = 120 min during an OGTT were counted in 'Undetermined'. Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg.

Source: Eli Lilly Exploratory Analysis (File Name: shgly_bmi01_wlge5)

Table 70. Proportion of participants discontinuing study or study intervention due to an AE in responders (≥5% body weight reduction) from whole trial population; SAS

Category, n (%)	TZP 5 mg ([redacted])	TZP 10 mg ([redacted])	TZP 15 mg ([redacted])
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BMI: body mass index; N: number of subjects in the analysis population; n: number of subjects with at least one adverse event per event type; SAS: safety analysis set; TZP: tirzepatide.
Footnotes: Primary efficacy was assessed from baseline to 36 weeks for TZP 5 mg, 48 weeks for TZP 10 mg and TZP 15 mg. Subjects may be counted in more than one category.
Source: Eli Lilly Exploratory Analysis (File Name: smae01_wlge5_ taffy)

B2. Please clarify if the semaglutide 10% primary efficacy failure estimate is trial data and if so from which trial(s), Lilly/Costello expert opinion or TA875 Novo Nordisk expert opinion.

As per Table 74 in the CS, the 10% primary treatment failure estimate for semaglutide was informed clinical expert opinion obtained by the Company.[20] This was necessary as the semaglutide primary treatment failure estimate was redacted in TA875 (see TA875 Company Submission Table 21).[3]

B3. PRIORITY: Please present the EQ-5D health state index data of Appendix M Table 126 separately for each of the economic analysis groups of Document B Sections B.3.10, B.3.12.1, B.3.12.2, B.3.12.3 and B.3.12.4. Please also present this and Table 126 on an EAS basis.

EQ-5D health state index data from SURMOUNT-1 for the subgroup with a BMI ≥30 kg/m^2 with ≥1 comorbidity (Section B.3.10) is already presented in response to Question A1, and EQ-5D data for the whole trial population is presented in Appendix M, Table 126. EQ-5D data for the other requested subgroups are presented in Table 71–Table 73.

Table 71: Summary of results for EQ-5D-5L health index scores at baseline and 72 weeks in participants with BMI ≥35 kg/m^2, prediabetes and high risk for CVD; EAS

Parameters	Placebo [redacted]	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CI: confidence interval; EAS: efficacy analysis set; LOCF: last observation carried forward. N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: The Van Hout value set was used to calculate the index score. LOCF. ANCOVA model for endpoint

measures. ANOVA model for baseline measures.
†† p-value <0.01 versus baseline.
††† p-value <0.001 versus baseline.
** p-value <0.01 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Names: aceq5d01_taffy_subset4)

Table 72: Summary of results for EQ-5D-5L health index scores at baseline and 72 weeks in participants with BMI ≥35 kg/m^2; EAS

Parameters	Placebo [redacted]	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CI: confidence interval; EAS: efficacy analysis set; LOCF: last observation carried forward; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: The Van Hout value set was used to calculate the index score. LOCF. ANCOVA model for endpoint measures. ANOVA model for baseline measures.
†† p-value <0.01 versus baseline.
††† p-value <0.001 versus baseline.
** p-value <0.01 versus placebo for superiority.
*** p-value <0.001 versus placebo for superiority.
Source: Eli Lilly Exploratory Analysis (File Names: aceq5d01_taffy_subset5)

Table 73: Summary of results for EQ-5D-5L health index scores at baseline and 72 weeks in participants with BMI ≥30 kg/m^2; EAS

Parameters	Placebo [redacted]	TZP 5 mg [redacted]	TZP 10 mg [redacted]	TZP 15 mg [redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; CI: confidence interval; EAS: efficacy analysis set; LOCF: last observation carried forward; N: number of subjects in the population with baseline and post-baseline value at Week 72; TZP: tirzepatide.
Footnotes: The Van Hout value set was used to calculate the index score. LOCF. ANCOVA model for endpoint measures. ANOVA model for baseline measures.
***p-value <0.001 versus placebo.
** p-value <0.01 versus placebo.
†† p-value <0.01
†††p-value <0.001 versus baseline.
Source: Eli Lilly Exploratory Analysis (File Names: aceq5d01_taffy_subset2)

B4. The SURMOUNT-1 CSR Table GPHK.3.4 notes patient reported outcomes of SF-36v2 acute form, IWQOL-Lite-CT, EQ-5D-5L and PGIS. Appendix M Table 126 provides EQ-5D-5L health state index values valued using the Van Hout value set for

baseline and change from baseline. Section B.3.4.1 states that SURMOUNT-1 assessed HRQoL using SF-36 and IWQOL-Lite-CT and that these are not aligned with the NICE reference case hence the need to take baseline values from the literature. Please provide a fuller account of this to augment Section B.3.4.1.

The Company would like to clarify that contrary to what is stated in the CS, the EQ-5D data collected in SURMOUNT-1 do align with the NICE reference case, since they were collected using EQ-5D and valued using the Van Hout value set.[21] However, this does not negate the use of utilities derived from the literature rather than using EQ-5D from SURMOUNT-1; the justification for the use of literature-derived values to inform baseline utility in the model is four-fold:

- Unlike the trial-based utilities, the utility values used in the model (derived from Søltoft *et al*. 2009)[22] enable each individual sampled patient to be assigned a utility value based on their sex, age and BMI. Each utility value is also adjusted for baseline comorbidities, meaning that these data truly reflect a 'baseline' utility value
    - In contrast, use of trial-based utilities would require the use of either an average value or a regression analysis using the IPD to mimic the dataset from Søltoft *et al*.; both approaches are limited by the sample size in SURMOUNT-1 compared to the dataset in Søltoft *et al*., and as such it is likely that these approaches would produce less accurate values
- Additionally, while not collected from the trial directly, the utilities reported in Søltoft *et al.* were derived from patients in England and therefore likely to be generalisable to the population who would receive tirzepatide in NHS England clinical practice if it is recommended
- The same source for baseline utilities was used and accepted by the Committee in TA875[3]
- Finally, use of Søltoft *et al.* over the trial-based utilities means that there is alignment between the source used for the baseline utilities and several of the utility decrements modelled for the various comorbidities (the utility decrements for T2DM, knee replacement and OSA are also taken from Søltoft *et al*.)

B5. Please clarify if discontinuations due to adverse events apply only for a given duration while on treatment, and if so for how long, or are these reapplied every model cycle that the patient remains on treatment.

Discontinuation due to adverse events is applied in every cycle that patients remain on treatment, in line with the way adverse events are modelled. This can be seen in lines 990–998 of the Model_Simulation VBA code.

B6. Please provide the source of the mortality data together with the relevant ICD10 codes and the method of removing CVD deaths; i.e. how to calculate the model Mortality cells I79:L82 with full referencing to enable its replication. The EAG is more familiar with data reported in 5-year age bands for this type of calculation.

The proportion of overall deaths caused by MI and stroke, stratified for patient sex and age

category (35–49, 50–64, 65–79 and 80+) are calculated from the ONS Leading Causes of Death, UK dataset, available online here: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/datasets/leadingcausesofdeathuk using the latest available year (2018). Deaths attributable to MI are based on ICD codes I20–I25 (ischaemic heart diseases) and deaths attributable to stroke are based on ICD codes I60–K69 (cerebrovascular diseases).

The proportions are calculated by dividing the number of patients in the relevant age and sex category with deaths corresponding to the ICD codes of interest (Table 5 in the referenced source) divided by the total number of deaths in that age and sex category (Table 6 in the referenced source). Please note that the correct age and sex category must be selected in cells B12 and B13 to view the relevant data in Table 5. A copy of the ONS spreadsheet, with the values used in the model highlighted in yellow, is provided in the supplementary file in the reference pack, named 'B6 ONS Cause of Death' for clarity.

The general population mortality is reweighted within the economic model to 'remove' cardiovascular events as follows, ensuring these are not double-counted:

1. The overall proportion of deaths caused by CV events in each age and sex category is calculated as a sum of the proportion of deaths which are caused by MI and stroke respectively (M79:N82 in the Mortality sheet of the model)

2. The general population mortality for each corresponding age and sex (I88:J170 in the Mortality sheet of the model) is adjusted by multiplying by 1 minus the proportion of deaths caused by CV events:

$$GPM(without\ CV\ death) = GPM\ (overall) \times (1 - proportion\ of\ deaths\ caused\ by\ CV\ events)$$

B7. The QDiabetes risk function model B apparently requires FPG rather than the HbA1c of model C. Please outline the assumed evolution of FPG within the model.

Further details are provided below in response to Question B8 regarding the patient characteristics that are updated during the simulation and those that remain constant. FPG is a variable that is held constant at the patient's baseline value throughout the model time horizon. However, the Company would also like to note that the QDiabetes Model B is not used in the model (base case or scenario) but is included for completeness and reference only; Model C was preferred over Model B for the modelling of diabetes due to the inclusion of HbA1c, as detailed in Appendix N.3.1.1. This approach is aligned with prior appraisals in obesity, including TA875 and TA664.[3, 23] FPG is therefore only relevant in a scenario analysis, when the Framingham Offspring Study is used to estimate the incidence of T2DM.

B8. Please outline how various elements within the QDiabetes, QRisk3, MI and OSA risk functions are modelled at baseline and as the model progresses for an individual patient: Townsend Score, smoking and its evolution, hypertension, treated hypertension, gestational diabetes, PCOS, CKD stage 3-5, SLE, RA, AF, eGFR<60, WBC, macroalbuminuria, hyperlipidaemia, COPD, GERD, CKD, hyperthyroidism, acromegaly, benzodiazepines and bariatric surgery.

At baseline, a patient is simulated and assigned a unique set of patient characteristics. As

described in B.3.2.1 of the CS, in order to generate patient characteristics for individual patients simulated in the cohort, parameter values are sampled with the appropriate corresponding distributions, aligned with the mean (and standard deviation [SD], if appropriate) of the distributions observed in the relevant population from SURMOUNT-1.

At each model cycle, a number of patient characteristics are updated for each simulated patient and used in the risk equations. Specifically, the following variables are updated for each simulated patient during the modelled time horizon: age, weight, BMI, SBP, total cholesterol, HDL, LDL, HbA1c, prior CVD, T2DM, and bariatric surgery. All other variables (e.g. Townsend score, smoking, hypertension, treated hypertension, gestational diabetes, hyperlipidaemia, COPD, GERD, CKD, hyperthyroidism, acromegaly, benzodiazepines, amongst others) were assumed to remain constant over the patient's modelled time horizon and are held constant at their baseline value. It is acknowledged that some of these variables would be expected to change (due to ageing and other events included in the model); however, in the absence of trial data to inform this and to avoid adding further complexity, a simplifying assumption was made. This approach is aligned with prior appraisals in obesity, including TA875 and TA664.[3, 23]

B9. To what extent is bariatric surgery considered within the model as a function of the patient's BMI during each model cycle?

Bariatric surgery incidence is calculated in each model cycle based on an annual probability. Only patients with a BMI ≥40 kg/m^2, or with a BMI between 35–40 kg/m^2 in addition to any weight-related comorbidities are eligible for bariatric surgery, in line with the NICE quality standard QS127.[24] These criteria are implemented in lines 1,099–1,106 of the Model_Simulation module in the VBA, and looks at eligibility based on a patient's current BMI (not baseline BMI). In lines 3,122–3,135 of the Model_Simulation module, the annual incidence rate of 0.20% (see cell I38 in the Efficacy tab) is applied, determining whether each patient receives surgery or not on a per-cycle basis; for 4-week cycles the probability is adjusted accordingly.

As stated in Section B.3.3.2.3. of the Company Submission, patients experience weight reduction following surgery, the extent of which varies based on the specific type of surgery received. On the basis of clinician input, it was assumed that this weight loss initially reduces a patient's BMI after the surgery, which remains constant thereafter.[20] Reduction in body weight as a result of bariatric surgery was informed by recent data from the National Bariatric Surgery Registry (NBSR)[25] and can be found in Table 71 of the Company Submission.

B10. In order to better understand the modelling it would be appreciated if an excel spreadsheet with the relevant formulae and workings in the excel (not in the VBA) could be presented that derives the evolutions of the risk factors BMI, HDL, TC, SBP and pre-diabetes status from baseline to 20 years, with the first 2 years split into the 4 weekly model cycles, separately for (A) the base case comparison of (1) diet and exercise, (2) semaglutide, (3) tirzepatide 5mg, (4) tirzepatide 10mg and (5) tirzepatide 15mg and (B) the scenario comparison of (1) diet and exercise, (2) liraglutide, (3) tirzepatide 5mg, (4) tirzepatide 10mg and (5) tirzepatide 15mg. Please present these

separately applying the company base case and liraglutide scenario clinical effectiveness inputs for the following patients at baseline.

- a male, age 45, BMI 33, no T2DM, not prediabetic
- a male, age 45, BMI 33, no T2DM, prediabetic
- a male, age 45, BMI 33, with T2DM
- a female, age 45, BMI 33, no T2DM, not prediabetic
- a female, age 45, BMI 33, no T2DM, prediabetic
- a female, age 45, BMI 33, with T2DM

For the following scenarios:

- not applying the 2 year stopping rules for liraglutide and semaglutide and assuming patients remain on treatment for 10 years at which point all patients on all treatments discontinue treatment
- applying the base case 2 year stopping rules for semaglutide, liraglutide and tirzepatide, but assuming no other treatment discontinuations
- assuming all patients ceases treatment due to lack of primary efficacy, but assuming no other treatment discontinuations

Please provide full cell referencing to the cost effectiveness model for the required inputs to these calculations. Within this please assume that the patients experience no events such as CVD, diabetes incidence or death during the 20-year period. Note that the EAG understands that there is no T2DM at baseline but asks for the above for the sake of simplicity.

The Company has provided the requested formulae and workings in Excel, in a new 'B10. Surrogate Endpoints' tab in the cost-effectiveness model, with full cell referencing to inputs within the model. As subgroups A and B have different efficacy and baseline characteristics, these are used accordingly (with the exception of age and BMI, which have been specified as part of the question). Results for (A) are found in Columns N:AL and results for (B) are found in Columns AM:BK. Figures are also included which plot the evolution of risk factors, for ease of interpretation.

The following instructions should be followed to view results for each of the requested patients and scenarios:

- Age and BMI are already set to the specified 45 and 33 respectively, however can be changed in Cell I11 and I12.
- Male and female can be selected in Cell I15.
- T2DM status can be changed between T2DM, No T2DM or Prediabetes in Cell I16.

- The three discontinuation scenarios can be observed as follows:
    - Scenario 1 (not applying the 2 year stopping rules for liraglutide and semaglutide and assuming patients remain on treatment for 10 years at which point all patients on all treatments discontinue treatment): Change all Discontinuation time points (K11:K15) to 10.
    - Scenario 2 (applying the base case 2 year stopping rules for semaglutide, liraglutide and tirzepatide, but assuming no other treatment discontinuations): Change all Discontinuation time points (K11:K15) to 2.
    - Scenario 3 (assuming all patients ceases treatment due to lack of primary efficacy, but assuming no other treatment discontinuations): Change all Discontinuation time points (K11:K15) to the treatment-relevant time point for evaluating primary efficacy (K57:K61 on the Efficacy tab, converted to years as detailed in Table 74 below).

Table 74. Discontinuation timepoint for primary treatment failure

Treatment	Discontinuation time point (weeks; as quoted in Table 74 in the CS)	Discontinuation time point (years*; to be implemented as part of Scenario 3)
Tirzepatide (5.0 mg)	30.00	0.58
Tirzepatide (10.0 mg)	38.00	0.73
Tirzepatide (15.0 mg)	46.00	0.88
Liraglutide (3.0 mg)	16.00	0.31
Semaglutide (2.4 mg)	26.00	0.50

Footnotes: *the timepoint in weeks has been converted into years by dividing the number of weeks by the average number of weeks in a year (52.18 [365.25 days in a year]).

The following should be noted:

- Weight is provided as the risk factor rather than BMI, as the efficacy inputs (derived from the NMA) and model are based around weight not BMI. Patient weight has been calculated for each cohort based on the provided BMI (33 kg/m^2) and subgroup-specific height.
- In line with the question, the only discontinuation reflected in the calculations is a one-off discontinuation (this can be used to represent a stopping rule or all patients ceasing treatment due to lack of primary efficacy; see instructions above); ongoing discontinuation, such as that from AEs is not reflected.
- As these calculations do not incorporate risk equations (e.g. predicting onset of T2DM), the 'prediabetes' columns are only relevant for a patient who has prediabetes at baseline. If the patient is 'not prediabetic' or 'with T2DM' then these columns will be N/A.
    - Relatedly, prediabetes is shown for an average cohort specified rather than a single patient, so will be 100% at baseline if a patient has prediabetes and then be a proportion between 0% and 100% based on the prediabetes reversal for that treatment. At return to prediabetes, this will by definition revert to 100%.

As validation, it should be noted that graphs illustrating the trajectory of surrogate endpoints over time directly from the IPS/simulated cohort (i.e. reflecting all discontinuation and risk equations) can be found on the 'Secondary Deterministic Results' tab from Row 54. These show a similar trajectory to those generated in response to this question (slight variations are expected, given the provided patient characteristics from EAG and simplifications around discontinuation/other events).

B11.(a) In order to better understand the model it would be appreciated if two excel spreadsheets with the relevant formulae and workings in the excel (not in the VBA) could be presented that derive (A) the total annual mortality risk and (B) the patient quality of life for both options “additive” and “multiplicative”, with full cell referencing to the cost effectiveness model for the required inputs to these calculations, for:

- a male, age 45, BMI33, no T2DM, no prior CVD event, no NAFLD
- a male, age 45, BMI33, no T2DM, prior stroke, no other prior CVD event, no NAFLD
- a male, age 45, BMI33, no T2DM, prior MI, no other prior CVD event, no NAFLD
- a male, age 45, BMI33, no T2DM, prior MI, prior stroke, no NAFLD
- a male, age 45, BMI33, no T2DM, MI event that year, prior stroke, no NAFLD
- a female, age 45, BMI33, no T2DM, no prior CVD event, no NAFLD
- a male, age 45, BMI33, no T2DM, no prior CVD event, with NAFLD
- a male, age 45, BMI33, no T2DM, prior stroke, no other prior CVD event, with NAFLD
- a male, age 45, BMI33, no T2DM, prior MI, no other prior CVD event, with NAFLD
- a male, age 45, BMI33, no T2DM, prior MI, prior stroke, with NAFLD
- a male, age 45, BMI33, no T2DM, MI event that year, prior stroke, with NAFLD
- a female, age 45, BMI33, no T2DM, no prior CVD event, with NAFLD
- a male, age 45, BMI33, with T2DM, no prior CVD event, no NAFLD
- a male, age 45, BMI33, with T2DM, prior MI, prior stroke, no NAFLD
- a male, age 45, BMI33, with T2DM, MI event that year, prior stroke, no NAFLD
- a male, age 45, BMI33, with T2DM, no prior CVD event, with NAFLD
- a male, age 45, BMI33, with T2DM, prior MI, prior stroke, with NAFLD
- a male, age 45, BMI33, with T2DM, MI event that year, prior stroke, with NAFLD.

The Company has provided the requested formulae and workings in Excel, in a new 'B11. Mortality and Utilities' tab in the cost-effectiveness model, with full cell referencing to inputs within the model. Age and baseline BMI, set at 45 years old and 33 kg/m² respectively as per the request, apply uniformly to all calculations and are user-definable. The assumed years after patient experiences prior stroke, which is assumed to be 5 years, is another user-adjustable input which applies uniformly to all calculations. Additionally, there are individual patient-specific inputs for sex, whether the patient has an MI in the current year and the patient’s T2DM, prior stroke, prior MI and NAFLD status.

The calculations yield mortality risk and quality of life estimates for a single year, constituting one long cycle in the model. It is assumed that the patient's characteristics remain constant throughout the year, and they do not experience any other health events aside from those aforementioned.

B11.(b) In order to better understand the modelling it would be appreciated if an excel spreadsheet with the relevant formulae and workings in the excel (not in the VBA) could be presented that derives the down adjustment to the 10 year risk of CVD events from Appendices Tables 147 using the inputs of Appendices Table 148, together with an intuitive account of the arithmetic and full referencing.

The 'down adjustment' for the 10-year risk of CVD is derived from the proportions of different categories of CV events reported in the two Framingham risk equation publications presented in the CS Appendix, Table 148 (D'Agostino *et al.* 2000 and D'Agostino *et al.* 2008).[26, 27] It is noted that there is a minor discrepancy (at the second decimal place) between the values presented in Table 148 and those on the Risk Equations tab of the economic model (I249:J252). It should be noted that the values in the economic model are correct, and a corrected table is therefore presented below (Table 75) – the Company apologise for the inconsistency here.

A full account of calculations, including intuitive explanations and references, is provided in the supplementary Excel spreadsheet in the reference pack [File name: B11 Derivation of CV Event Weighting]. The same approach was used in TA875 which had similar values (differing by less than 0.1%), based on the reported weightings from Table 63 of TA875.[3]

Table 75: Adjustment of CVD events for Framingham Heart Study for initial CVD events

Event	% CVD (Males)	% CVD (Females)	Source
MI	41.63%	23.10%	D'Agostino et al. 2000[26]
Angina	29.14%	34.37%	
Stroke	15.90%	23.85%	D'Agostino et al. 2008[27]
Total	86.68%	81.33%	

Abbreviations: CVD: cardiovascular disease; MI: myocardial infarction.

B12. PRIORITY: Unfortunately, due to the model structure and the risk of undoing EAG changes to the model by inadvertently running subroutines such as Reset_AllDefaults() the EAG will have to amend elements of the Data_Store worksheet. The EAG would be grateful if the company could briefly review the implementation of changes as per the EAG worksheet, with full cell referencing to the Data_Store elements, and associated EAG VBA module to check whether there are any issues with this implementation within the supplied ID6179 Tirzepatide v0.1 22082023 EAG amended 2023-09-12 workbook. Note that a number of message boxes have been commented out in the VBA in order to permit the model to run, possibly repeatedly, without user input. Searching the VBA project for "EAG" will identify these. In a similar vein, if the EAG wishes to revise the main clinical inputs to the model is it sufficient to revise the relevant Subgroup_Data and is there any risk of these changes being overwritten by the VBA? Note that if it eases matters and cell referencing spreadsheets could be

inserted into the EAG amended model with the calculations requested under the previous "In order to better understand the model…" questions.

Firstly, the Company would like to thank the EAG for identifying and rectifying the error in the T2DM disutility values within the Trace tabs; the company agrees with the correction and has incorporated it into the model base case with a negligible change in results. The Company also identified an error in line 2,836 of the VBA code within the Model Simulation module. The MI mortality for patients ≥85 years old was incorrectly employing the input for the stroke mortality for patients in the same age group. The correction has minimal impact on results and can be toggled on and off in cells A35:F35 on the EAG tab in the cost-effectiveness model. The correction has been applied to the EAG base case. The updated deterministic company base case results are shown in Table 76–Table 78.

Secondly, as requested, the Company has reviewed the EAG's changes to the data store, EAG VBA module, new EAG tab and the EAG's commented out lines in the VBA. The Company did not identify any errors in these changes; however, the data validations applied to cells B17:B23 and B34 on the EAG tab can cause issues if dropdown selections are used. An example of this can be seen in cell B23, where the dropdown options are sourced from cells H33:H34 (Control Panel). These options are "No" and "Yes (Please Specify Below)." The dependent cells expect either "TRUE" or "FALSE" values from these dropdowns and therefore if a user selects an option from the dropdown selection there are resultant errors in dependent cells L34:L38 (Data Store) and I57:I61 (Efficacy). To prevent these problems, the Company has removed the data validations applied to these cells.

Finally, the Company would like to confirm that the EAG's interpretation is correct regarding how to modify values entered on the Subgroup_Data tab. These inputs are not overwritten by VBA and therefore adjustments can be made directly to these inputs. However, it is worth noting that the EAG should change the user-definable inputs and not those in the 'Live' tables to prevent this functionality from breaking.

Table 76 Corrected base-case results for tirzepatide 5 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.997	-	-	-	-	-
Semaglutide (2.4 mg)	[redacted]	18.953	16.159	£131	0.062	0.162	£811	£811
Tirzepatide (5.0 mg)	[redacted]	19.200	16.686	£7,994	0.309	0.689	£11,600	£14,911

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

Table 77: Corrected base-case results for tirzepatide 10 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.997	-	-	-	-	-
Semaglutide (2.4 mg)	[redacted]	18.953	16.159	£131	0.062	0.162	£811	£811
Tirzepatide (10.0 mg)	[redacted]	19.161	16.658	£7,856	0.270	0.661	£11,891	£15,485

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

Table 78: Corrected base-case results for tirzepatide 15 mg (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	ICER (£/QALY)
				vs Baseline				Incremental
Diet and Exercise	[redacted]	18.891	15.997	-	-	-	-	-
Semaglutide (2.4 mg)	[redacted]	18.953	16.159	£131	0.062	0.162	£811	£811
Tirzepatide (15.0 mg)	[redacted]	19.225	16.771	£9,993	0.334	0.774	£12,913	£16,112

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

B13. Document B states that it is not possible to apply gradual 33% annual waning of reversal of pre-diabetes after discontinuation due to it being a categorical variable. The justification for the IPS is, essentially, that it permits categorical variables. Why is it not possible for there to be a 33% probability in the 1st year, a 50% probability in the 2nd year and a 100% probability in the 3rd year?

The Company agrees that the characterisation of gradual waning of pre-diabetes reversal suggested by the EAG can be implemented in the model and have included a pragmatic approach to implementing this characterisation in the model as a scenario, which can be enabled using the switch in cell I44 in the Settings sheet. Please note that this implementation is intended only to give indicative results due to the pragmatic implementation described as follows:

- In the first possible year of reversal (in the diet and exercise arm), or the first third of the efficacy waning period (in all other arms), the patient has a 33% chance of returning to prediabetes
- In the second possible year of reversal (in the diet and exercise arm), or the second third of the efficacy waning period (in all other arms), if reversal has not already occurred, the patient has a 50% chance of reversal
- Thereafter, if reversal has not already occurred, the patient has a 100% probability of returning to prediabetes

The first possible year of reversal to prediabetes in the diet and exercise arm is the user-specified time of return to diabetes (cell 43 in the Settings sheet). For other arms in the model the first possible year of reversal to prediabetes is at treatment discontinuation.

This scenario has a limited impact on results, generally decreasing the ICER versus semaglutide and increasing ICER versus diet and exercises. Deterministic results for the corrected base case and described scenario are given in Table 79 to Table 81.

Table 79. Results with gradual return to prediabetes for tirzepatide 5 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Corrected base case	£7,863	0.53	£14,911	£7,994	0.69	£11,600
Gradual return to prediabetes	£7,712	0.53	£14,569	£8,818	0.69	£12,796

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 80. Results with gradual return to prediabetes for tirzepatide 10 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Corrected base case	£7,724	0.50	£15,485	£7,856	0.66	£11,891
Gradual return to prediabetes	£7,606	0.50	£15,211	£8,711	0.66	£13,204

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Table 81. Results with gradual return to prediabetes tirzepatide 15 mg (deterministic)

Scenario	Versus semaglutide 2.4 mg			Versus diet and exercise		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Corrected base case	£9,862	0.61	£16,112	£9,993	0.77	£12,913
Gradual return to prediabetes	£9,673	0.62	£15,727	£10,779	0.77	£13,911

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

B14. The EAG has not been able to source the Framingham coefficients of the Risk Equations cells I381:J387 from D'Agostino et al 2008. Its appendix appears to suggest different values. The EAG would be grateful if a more explicit referencing could be provided; e.g. Table X, or page X, Para Y. The Risk Equations cells I388:J388 appear to contain the calculations for a representative patient, female and male. Are these used within the VBA for all patients, differentiated by sex, or does the VBA calculate patient specific values for each patient modelled?

The Framingham risk equation coefficients in cells I236:J242 (previously cells I381:J387, see response to C21) on the Risk Equations tab can be found in Supplementary Table 1 from the supplementary material for D'Agostino et al. 2008. The Company do not have appropriate copyright clearance to digitally share the PDF for this reference, but it is freely available online here: https://www.ahajournals.org/action/downloadSupplement?doi=10.1161%2FCIRCULATIONAHA.107.699579&file=ci068679.dstabs.doc.

The regression coefficients found in cells I243:J243 on the Risk Equations tab are used to inform the following general formula for risk estimation from D'Agostino *et al.* 2008 (shown in lines 2,332–2,337 of the Model_Simulation module in VBA):

$$\hat{p} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i\right)}$$

where $S_0(t)$ is baseline survival at follow-up time t, β_i is the estimated regression coefficient, X_i is the log-transformed value (if continuous) of the ith risk factor, (if continuous), X_i is the corresponding mean for centering the values, and p denotes the number of risk factors.

A patient-specific risk estimate ($\hat{p}$) is calculated for each patient, applying the relevant regression coefficient (β_i) to the patient's characteristic at the corresponding point in time (X_i). The regression coefficients (β_i) are sex-specific, as shown by the two sets of coefficients presented on the Risk Equations tab. The cells specifically calculated in I243:J243 represent the mean for all patients ($\sum_{i=1}^{p} \beta_i \bar{X}_i$), differentiated by sex, and are used in centering the calculated values.

B15. The knee replacement risk equations are not well documented. Please provide a full account of the input data and the methods used to arrive at the Risk Equations cells I530:I533, preferably alongside any internal report on this analysis, with a full account of the various models explored, goodness of fit and reasons for the choice made. Please also provide an account of the arithmetic application of the Risk Equations cells I530:I533 to arrive at an odds ratio for knee replacement within a worked example.

The knee replacement risk equation coefficients in cells I385:I390 (previously cells I530:I533 – see response to C21) on the Risk Equations tab were derived by conducting regression analyses using the odd ratios (ORs) reported in Wendelboe *et al.* 2003 (Table 3).[28]

A regression was conducted on the reported ORs as a function of BMI considered to be a continuous covariate. Continuous BMIs were derived from the reported BMI categories by taking the midpoint of the upper and lower limit of a BMI category, or the value of the limit if a category was denoted by only one limit (e.g. ≥40 was assigned a value of 40). A weighted analysis was conducted as weights could be derived from reported sample sizes and 95% CIs.

Linear and quadratic models, adjusting for and not adjusting for sex were considered. The quadratic models had a better fit (higher R^2 and lower AIC [Table 82] and smaller residuals [Figure 1]) which were statistically significant (indicated by the ANOVA p-value [Table 82]), so the quadratic models were selected. For the quadratic model, the adjustment for sex did not result in an improved model fit (similar R^2 and Akaike information criterion [AIC], non-significant ANOVA p-value). Therefore, the quadratic BMI model was selected as the chosen model. The regression coefficients for this model are given in Table 83 (with BMI centred around its mean) and align with the values reported in the model.

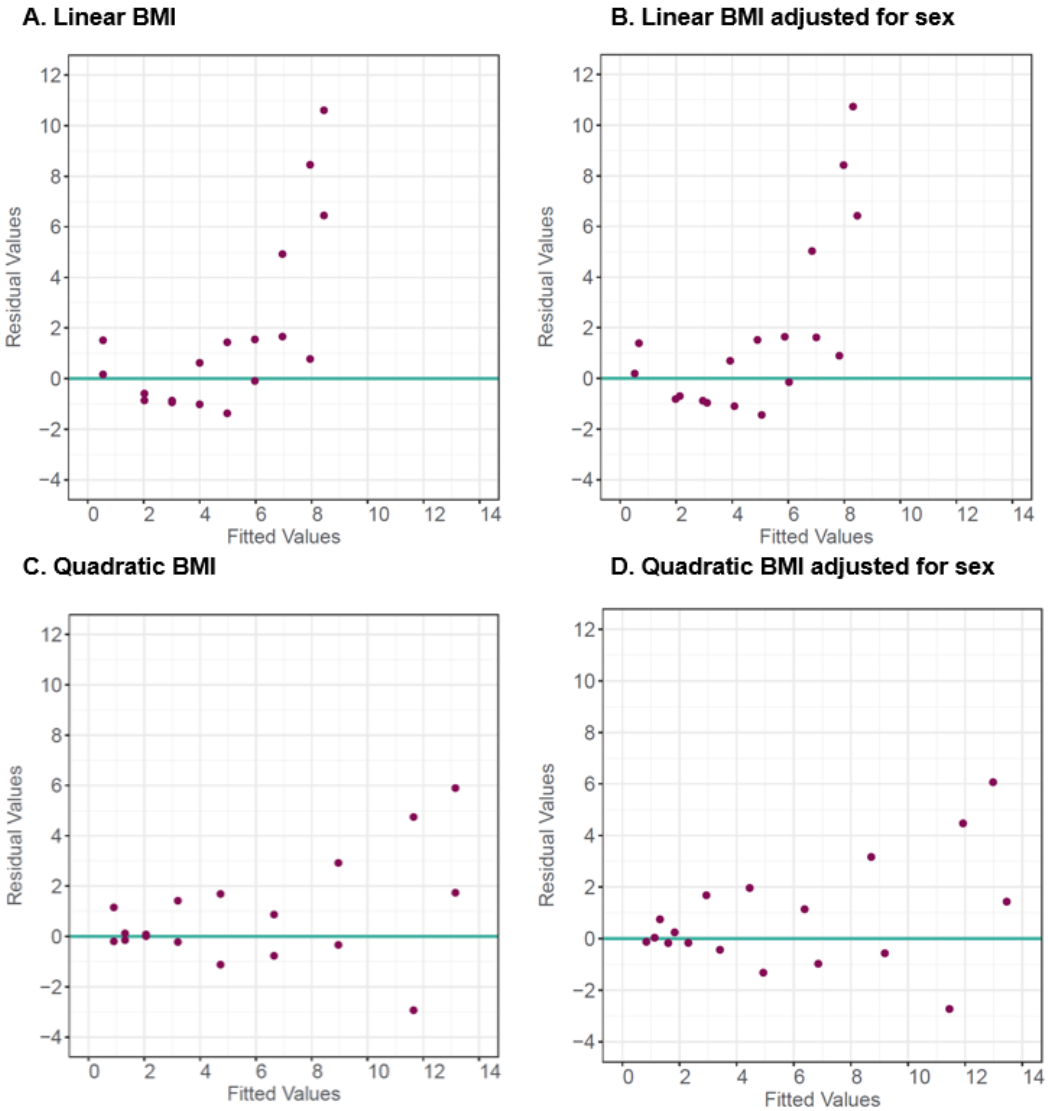
Table 82. Model fitting parameters for ORs of receiving a knee replacement

Model	Adjusted R^2	Regression p-value	AIC	ANOVA p-value (with vs without covariate)	ANOVA p-value (linear vs quadratic)
Linear BMI	0.7166	<0.0001	79.66	0.8023	0.0005*
Linear BMI adjusted for sex	0.6885	<0.0001	81.59	NA	0.0004*
Quadratic BMI	0.8652	<0.0001	66.51	0.2449	NA

Quadratic BMI adjusted for sex	0.8693	<0.0001	66.71	NA	NA

Abbreviations: AIC: Akaike information criterion; ANOVA: analysis of variance; BMI: body mass index; NA: not available; OR: odds ratio; SE: standard error; T2DM: type 2 diabetes mellitus.
Footnotes: *Statistically significant, p-value < 0.05.

Figure 1. Residual plots for analyses of ORs of receiving a knee replacement



Footnotes: enlarged versions of these figures are available in the reference pack.
Abbreviations: BMI: body mass index; NA: not available; OR: odds ratio; SE: standard error; T2DM: type 2 diabetes mellitus.

Table 83. Regression coefficients for the quadratic BMI model for the ORs of receiving a knee replacement

Model	Estimate	SE	p-value
Intercept	2.9174	0.3421	<0.0001*
Centred BMI	0.5004	0.0476	<0.0001*
(Centred BMI)^2	0.0311	0.0070	0.0005*

Abbreviations: BMI: body mass index; OR: odds ratio; SE: standard error.

Footnotes: *Statistically significant, p-value<0.05.

The resultant regression equation is as follows, which is applied in line 3,097 of the Model_Simulation module in VBA, where the mean BMI is derived from Wendelboe *et al.* 2003 based on the number of patients in each BMI category:

$$OR = 2.9174 + 0.5004(BMI - mean\ BMI) + 0.0311((BMI - mean\ BMI)^2)$$

Therefore, for a patient with a BMI of 26.5 kg/m^2, their OR for knee replacement can be calculated as: $OR = 2.9174 + 0.5004(26.5 - 28.12) + 0.0311((26.5 - 28.12)^2)$ to return a OR = 2.19 (compared to the weighted average categorical OR reported in Wendelboe *et al.* 2003 for the BMI category 25.0–27.49 kg/m^2 of OR = 2.10).

B16. The NAFLD risk equation values of the Risk Equations cells I562:I566 are "Adapted from Loomis et al. 2016". Please provide a full account of the input data and the methods used to arrive at the Risk Equations cells I562:I566, preferably alongside any internal report on this analysis, with a full account of the various models explored, goodness of fit and reasons for the choice made. Please also provide an account of the arithmetic application of the Risk Equations cells I562:I566 to arrive at a hazard ratio for NAFLD within a worked example.

The NAFLD risk equation coefficients in cells I417:I422 (previously cells I562:I566, see response to C21) on the Risk Equations tab were developed by fitting regression models to hazard ratios (HRs) reported in Loomis *et al.* 2016, specifically using data estimated from The Health Improvement Network (THIN) database.[29] Unlike knee replacement, the analyses did not account for the weight (sample size) in each BMI level, as the source article did not report the sample size by BMI level.

Three sets of HRs were provided in Loomis *et al.* 2016 (supplementary material Table 3A, 3B and 3D): HRs stratified by BMI category, HRs stratified by BMI category and sex and HRs stratified by BMI category and T2DM. Regression models were fitted to each of these three sets of input data from Loomis et al. 2016.[29] Specifically, the following models were fitted: linear and quadratic BMI with no further adjustment, linear and quadratic BMI adjusting for sex, and linear and quadratic BMI adjusting for T2DM. Table 84 summarises the model fit results, and the residual plots for all models are presented in Figure 2–Figure 4.

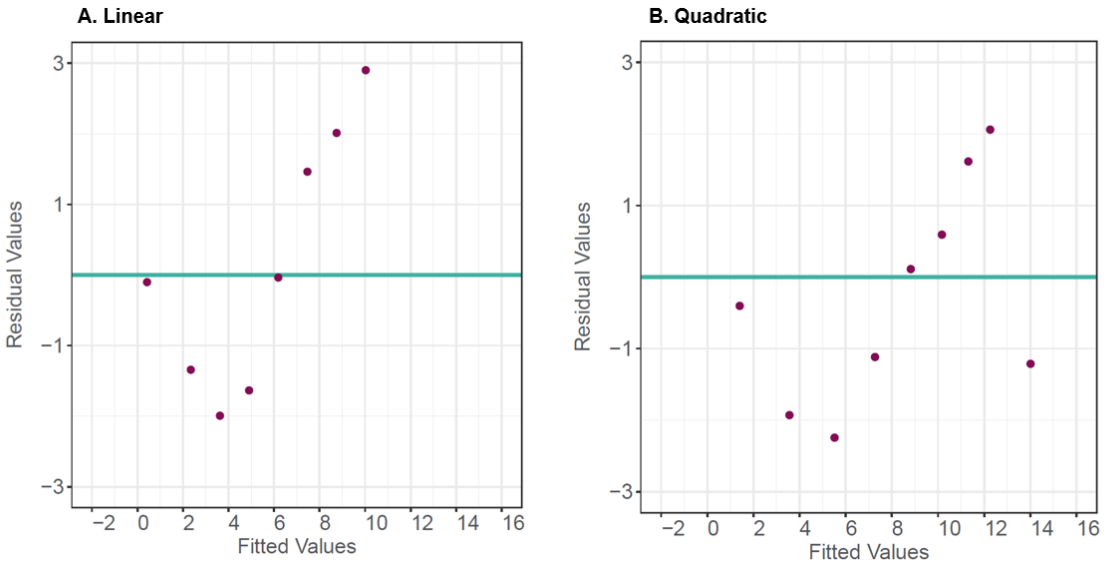
Table 84: Model fitting parameters for HRs of NAFLD, THIN database

Model	Adjusted R^2	Regression p-value	AIC	ANOVA p-value (with vs without covariate)	ANOVA p-value (linear vs quadratic)
HRs by BMI					
Linear BMI	0.7851	<0.0001*	50.55	NA	0.0335*
Quadratic BMI	0.8769	<0.0001*	45.65	NA	NA
HRs by BMI and sex					
Linear BMI	0.6334	<0.0001*	130.94	0.0397*	0.0142*

Linear BMI, adjusted for sex	0.6995	<0.0001*	127.82	NA	0.0053*
Quadratic BMI	0.7302	<0.0001*	125.66	0.0135*	NA
Quadratic BMI, adjusted for sex	0.8065	<0.0001*	119.80	NA	NA
HRs by BMI and T2DM					
Linear BMI	0.6038	<0.0001*	126.25	0.0004*	0.0676
Linear BMI, adjusted for T2DM	0.8009	<0.0001*	113.34	NA	0.0059*
Quadratic BMI	0.6573	<0.0001*	124.21	<0.0001*	NA
Quadratic BMI, adjusted for T2DM	0.8701	<0.0001*	105.59	NA	NA

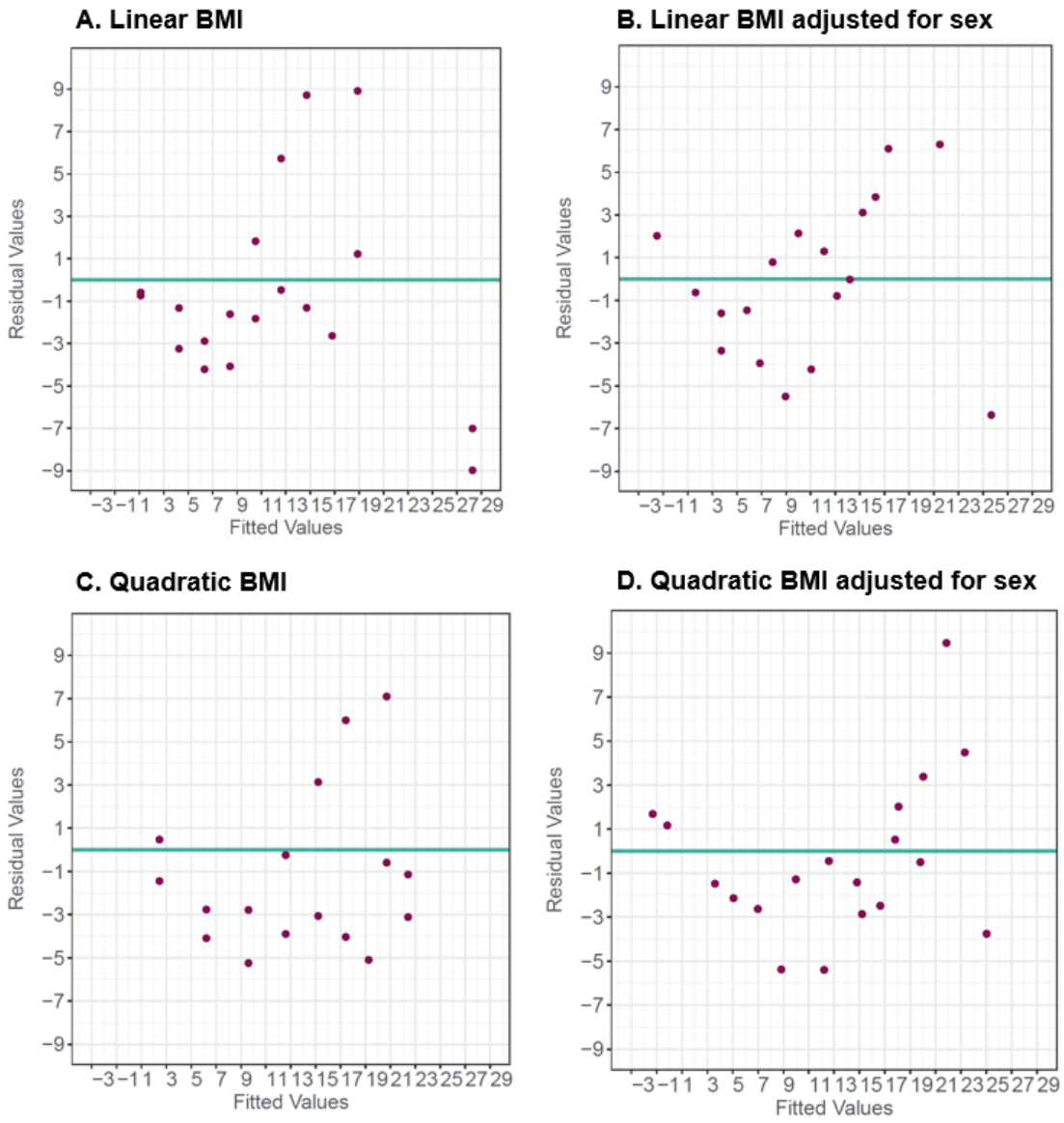
Abbreviations: AIC: Akaike information criterion; ANOVA: analysis of variance; BMI: body mass index; HR: hazard ratio; NA: not available; NAFLD: non-alcoholic fatty liver disease; THIN: The Health Improvement Network; T2DM: type 2 diabetes mellitus.
Footnotes: *Statistically significant, p-value < 0.05.

Figure 2. Residual plots for analyses of HRs of NAFLD for the unstratified HRs, THIN database



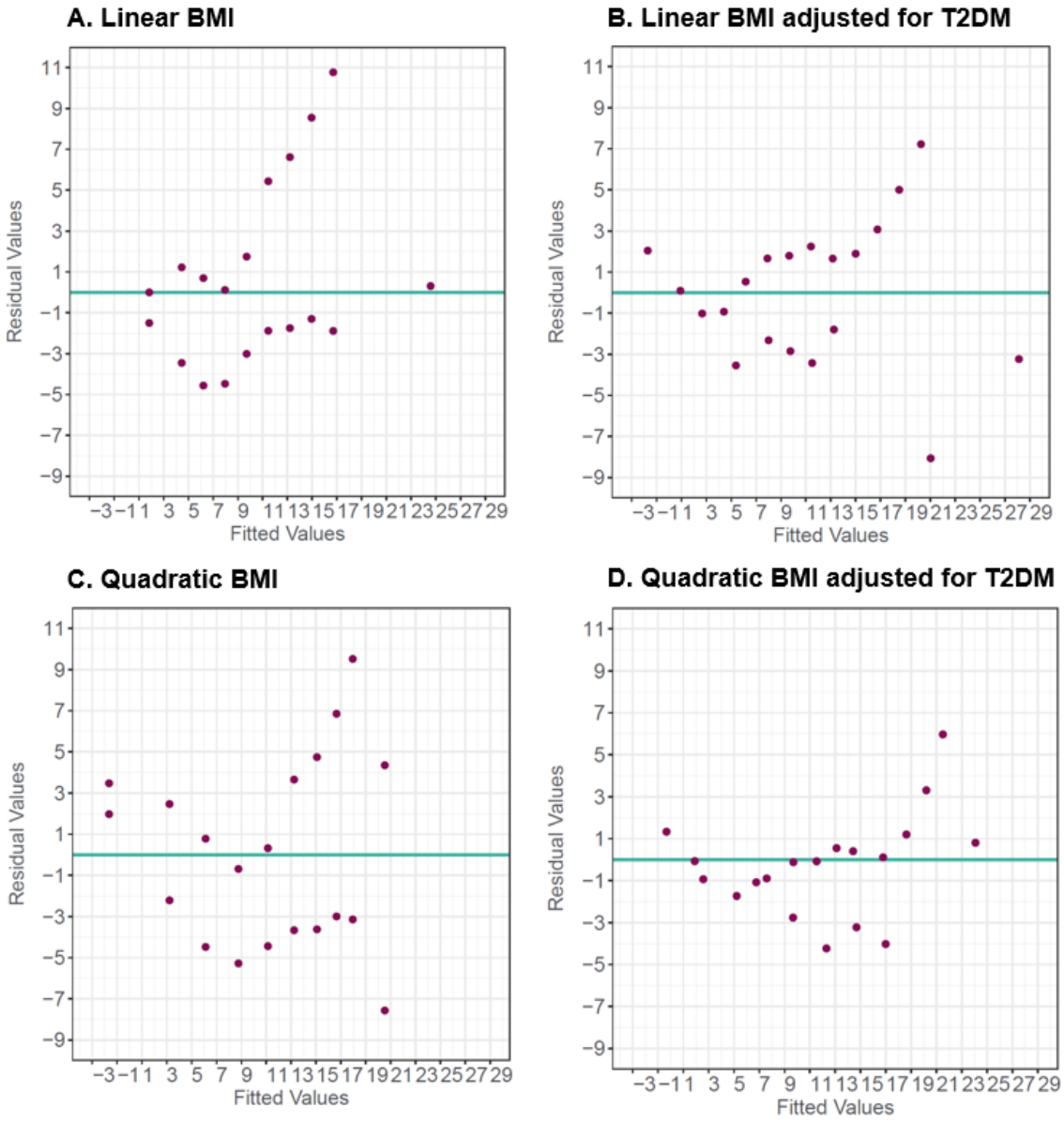
Footnotes: enlarged versions of the graphs are available in the reference pack.
Abbreviations: HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; THIN: The Health Improvement Network.

Figure 3. Residual plots for analyses of HRs of NAFLD adjusted for sex, THIN database



Footnotes: enlarged versions of the graphs are available in the reference pack.
Abbreviations: BMI: body mass index; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; THIN: The Health Improvement Network.

Figure 4. Residual plots for analyses of HRs of NAFLD adjusted for T2DM, THIN database



Footnotes: enlarged versions of the graphs are available in the reference pack.
Abbreviations: BMI: body mass index; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; THIN: The Health Improvement Network; T2DM: type 2 diabetes mellitus.

The quadratic model adjusted for T2DM was selected as it demonstrated a strong predictability for the relationship between BMI and HR (R^2=0.8701, p-value<0.0001), and the model fit was better than both the linear models and the quadratic BMI model (p-value<0.05 when compared to linear model adjusted for T2DM and quadratic BMI model). The regression coefficients for the quadratic model adjusted for T2DM are presented in Table 85.

Table 85: Regression coefficients for the quadratic model adjusted for T2DM for the HRs of NAFLD

Model	Estimate	SE	p-value
Intercept	5.7689	1.0236	<0.0001*

Centred BMI	0.9783	0.1144	<0.0001*
(Centred BMI)^2	-0.0213	0.0067	0.0059*
T2DM	7.0910	1.3202	<0.0001*

Abbreviations: BMI: body mass index; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; SE: standard error; T2DM: type 2 diabetes mellitus.
Footnote: *Statistically significant, p-value<0.05.

Based on the regression coefficients above, the regression equation for BMI and HRs of NAFLD adjusted for T2DM is as follows, which is applied in Line 3,062 of the Model Simulation module in VBA, where the mean BMI is as per the population in Loomis *et al.* 2016:[29]

$$HR = 5.7689 + 0.9783(BMI - mean\ BMI) - 0.0213((BMI - mean\ BMI)^2) + 7.0910 \times T2DM$$

Therefore, for a patient with a BMI of 31.5 kg/m^2 with T2DM, their HR for NAFLD can be calculated as: $HR = 5.7689 + 0.9783(31.5 - 26.81) - 0.0213((31.5 - 26.81)^2) + 7.0910 \times 1$ to return a HR =16.98 (compared to the weighted average categorical OR reported in Loomis *et al.* 2016 for the BMI category 30.0<32.50 kg/m^2 of HR=16.89).[29]

B17. Additional question raised during the clarification meeting on 2nd October: When setting the NAFLD hazard ratio for mortality to 1 (I48 on the Mortality tab), why does the incremental QALY gain increase?

The EAG are correct in their observation that changing the NALFD hazard ratio (HR) from 1.93 to 1 increases the incremental QALYs of tirzepatide versus comparators.

Reducing the mortality HR for patients with NAFLD decreases the probability of death due to NAFLD, resulting in fewer deaths in all treatment arms, and an increase in QALYs for all treatments. As the comparators have a greater number of NAFLD cases than tirzepatide, it could be expected that the incremental QALYs for tirzepatide versus comparators decreases. However, this is not observed as patients who live longer (due to having no increased risk of mortality from NAFLD) are then at risk of developing other comorbidities and die from other causes. Specifically, it is observed that when the NAFLD HR is set to 1, there is an increase in cardiovascular events and deaths. This occurs in all treatment arms, but the increase in cardiovascular events and deaths is observed to a greater degree in the comparator arms than the tirzepatide arms, as comparator arms are all at an overall higher risk of such events occurring. As cardiovascular events are associated with a disutility (one-off and ongoing disutilities) and an impact on mortality, the development of these events counter any benefit from reducing the NAFLD mortality risk and the net impact on incremental QALYs is positive.

Given the competing risks in the model, it should be noted that the relationship between incremental QALYs and the NAFLD mortality HR (or other HRs) might not necessarily be linear.

Section C: Textual clarification and additional points

C1. PRIORITY: CS Table 55 - please provide NCT numbers of ongoing trials.

The NCT numbers of the ongoing trials for tirzepatide are presented in Table 86.

Table 86. Ongoing studies for tirzepatide with associated NCT numbers

Study	NCT number
SURMOUNT-CN	NCT05024032
SURMOUNT-J	NCT04844918
SURMOUNT-OSA	NCT05412004
SURMOUNT-5	NCT05822830
SURMOUNT-MMO	NCT05556512

Abbreviations: NCT: national clinical trial.

C2. CS Appendix D.2.1 states there were 129 unique studies, which aligns with CS Figure 13 – please explain why CS p74 (and summary on CS p71) states 118 unique studies.

This misalignment is due to a typographical error on pages 71 and 74. Overall, there were 129 unique studies identified across the original SLR and update which were considered for the NMA. Of these 129 studies, 123 were excluded from the NMA, leaving 6 studies for inclusion in the NMA analyses; details of each study that was excluded from the NMA are provided in Table 12, Appendix D.

C3. Please provide the pdf and CSR from the phase II trial (CS reference 88 Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. The Lancet 2018;392:2180-2193).

The CSR and publication (Frias *et al*., 2018) for the Phase 2 I8F-MC-GPGB trial for tirzepatide are provided in the reference pack accompanying these responses (File Names: Frias 2018, I8F-MC-GPGB CSR).

C4. CS Table 27 - please provide O'Neil ref 106 pdf.

O'Neil, 2018 is provided in the reference pack alongside these responses.

C5. In CS Doc B, on page 146-149 and tables 58 and 59 the reference 'Source Subgroup: Lilly data on file 2023' is cited. Please clarify which filename(s) in the reference pack relate to these or supply any missing document(s).

The raw data files for each of the relevant baseline characteristics used in the model for each subgroup are provided in the reference pack; file names are summarised in Table 87.

Table 87. Raw data file names for the relevant baseline patient characteristics used in the model for subgroups

Parameter	BMI ≥30 kg/m^2 with ≥1 weight-related comorbidity	BMI ≥30 kg/m^2	BMI ≥35 kg/m^2	BMI ≥35 kg/m^2 with prediabetes and high CVD risk

Age (years)	gphk_8_4_subset3a_taffy	gphk_8_4_subset2_taffy	gphk_8_4_subset5_taffy	gphk_8_4_subset4_taffy
Sex (% female)	gphk_8_4_subset3a_taffy	gphk_8_4_subset2_taffy	gphk_8_4_subset5_taffy	gphk_8_4_subset4_taffy
Weight (kg)*	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
Height (m)	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
BMI (kg/m^2)	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
SBP (mmHg)	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
Total cholesterol (mg/dL)	gphk_8_6_subset3a	gphk_8_6_subset2	gphk_8_6_subset5	gphk_8_6_subset4
HDL (mg/dL)	gphk_8_6_subset3a	gphk_8_6_subset2	gphk_8_6_subset5	gphk_8_6_subset4
% of Patients with Hypertension	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
eGFR (ml/min/1.73 m^2)	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
Triglycerides (mg/dL)	gphk_8_6_subset3a	gphk_8_6_subset2	gphk_8_6_subset5	gphk_8_6_subset4
% of Female Patients with PCOS	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients with T1DM†	N/A	N/A	N/A	N/A
FPG (mmol/L)‡	gphk_8_51_subset3a_taffy	gphk_8_51_subset2_taffy	gphk_8_51_subset5_taffy	gphk_8_51_subset4_taffy
% of Patients with Treated Hypertension	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy
% of Patients with COPD	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients with Hypothyroidism	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients with Gestational Diabetes	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients with Systemic Lupus Erythematosus	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients with Acromegaly†	N/A	N/A	N/A	N/A

% of Male Patients with Erectile Dysfunction	gphk_8_11_subset3a_taffy	gphk_8_11_subset2_taffy	gphk_8_11_subset5_taffy	gphk_8_11_subset4_taffy
% of Patients using Corticosteroids	smcm_subset3a	smcm_subset2	smcm_subset5	smcm_subset4
% of Patients using Statins	smcm_subset3a	smcm_subset2	smcm_subset5	smcm_subset4
% of Patients with Prediabetes	gphk_8_5_subset3a_taffy	gphk_8_5_subset2_taffy	gphk_8_5_subset5_taffy	gphk_8_5_subset4_taffy

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HDL: high-density lipoprotein; PCOS: polycystic ovarian syndrome; T1DM: type 1 diabetes mellitus.
Footnotes: *Calculated from BMI and height † These comorbidities are not listed in the baseline comorbidities files (gphk_8_11) as patients with T1DM were excluded from the SURMOUNT-1, and no patients had acromegaly. ‡ Raw FPG data are available in mg/dL; these data were converted to mmol/L within the model.

C6. Appendices for the two CSRs (SURMOUNT-1 CSR and SURMOUNT-2 CSR) are not supplied. Please supply these missing documents.

The Appendices for the SURMOUNT-1 and SURMOUNT-2 CSRs comprise a substantial number of documents with considerable page counts (as detailed on Page 2,996 and 3,040 in the SURMOUNT-1 and SURMONT-2 CSRs, respectively), which the Company consider to be of limited relevance to the appraisal given the extensive evidence provided to date. It should also be noted that the Appendices for SURMOUNT-1 contain patient listings, which, if inappropriately shared, would compromise the ongoing trial blinding. For these reasons, the Company have not provided these Appendices at this time. Instead, to limit the risk of trial unblinding and for the purposes of simplicity and efficiency on both the Company and EAG's parts, the Company would ask that the EAG be specific in their data request (referring to the contents listings of the appendices that are available in the CSRs already provided) so that the Company can identify and summarise any required data.

C7. Clinical and cost-effectiveness SLRs (CS appendices D and G) - please provide a list of systematic review references (and PDFs if available) that were checked in this part of the search:

- "Reference lists of published SLRs: To supplement the information sources listed above, the reference lists of published SLRs that were closely aligned with the patients, interventions, comparators, time frame, and study design (PICOTS) for this SLR were also assessed." (CS appendix D)
- "Reference list searching: The bibliographies of relevant SLRs, NMAs, economic evaluations and HTAs identified through the electronic database searches and grey literature searches, were hand-searched to identify any additional studies of relevance." (CS Appendix G)

In the clinical SLR, the reference lists of two SLRs were hand searched:

- Vosoughi *et al*., 2021: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8633575/
- Shi *et al*., 2022: https://linkinghub.elsevier.com/retrieve/pii/S0140-6736(21)01640-8

From handsearching these SLRs, 16 potentially relevant studies were identified (listed below). However, these had been already obtained in the database searches and were therefore not captured separately.

- NCT03842202 (Friedrichsen, 2020)
- NCT02911818 (Wadden, 2019)
- STEP 1
- STEP 2
- STEP 4
- STEP 3
- Nexøe-Larsen, 2018
- NCT02453711 (O'Neil, 2018)
- NCT02647944 (Halawi, 2017)
- SCALE Maintenance
- NCT00480909 (Astrup, 2009)
- NCT02905864 (Gudbregsen, 2021)
- SCALE Obesity and Prediabetes
- SCALE Sleep Apnea
- SCALE Insulin
- SCALE Diabetes

For the cost-effectiveness studies SLR (detailed in Appendix G), a total of 39 records were hand-searched, including SLRs, NMAs, economic evaluations and HTAs. These records are listed in Table 88. Four abstracts could not be located (denoted with an asterisks) and therefore were not screened. All other PDFs are included in the reference pack accompanying these responses. From abstract and full-text screening the 36 records, a total of 8 studies were included in the SLR (Table 89)

Table 88. List of hand-searched records in the cost-effectiveness studies SLR

No.	Full reference
1	Adams et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol. 2007 Jul 1;166(1):36-45.
2	Ahn J, Schatzkin A, Lacey JV Jr, Albanes D, Ballard-Barbash R, Adams KF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann MF Adiposity, adult weight change, and post-menopausal breast cancer risk Arch Intern Med. 2007 Oct 22;167(19):2091-102.
3	Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991; 121 (1 Part 2): 293–298.

4	Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991; 83: 356–362.
5	Beaudet A, Palmer JL, Timlin L, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. J Med Econ. 2011; 14(3):357-66.
6	Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999;341:1097–105.
7	Cederholm J, Eeg-Olofsson, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S, Risk Prediction of Cardiovascular Disease in Type 2 Diabetes A risk equation from the Swedish National Diabetes Register, Diabetes Care. 2008 October; 31(10): 2038–2043
8	D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
9	D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. American heart journal. 2000;139(2 Pt 1):272-81.
10*	D'Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, Kannel. 'A General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study'. 2008;11:478-86
11	Davies MJ, Chubb BD, Smith IC and Valentine WJ. Cost-utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus (Structured abstract). Diabet Med. 2012; 29.
12*	Escudero GS, Idrovo J and Zapata L. Economic evaluation of metformin, metformin sibutramine or acarbose in the management of overweight and obese diabetes patients. Value Health. 2009; 12(3):A101.
13	Finkelstein EA, Kruger E and Karnawat S. Cost-effectiveness analysis of qsymia for weight loss (Provisional abstract). PharmacoEconomics. 2014; 33(7):699-706.
14*	Foxcroft D, Ludders J. Orlistat for the treatment of obesity. Wessex Institute Development & Evaluation Committee Report No. 101. Southampton: Wessex Institute for Health Research and Development; 1999.
15	Galani C, Al M, Schneider H, Rutten FF. Uncertainty in decision-making: value of additional information in the cost-effectiveness of lifestyle intervention in overweight and obese people. Value Health 2008;11:424–34. http://dx.doi.org/10.1111/j.1524-4733.2007.00284.x
16	Hayes A, Leal J, Gray A, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013; 56(9):1925-33.
17	Hippisley-Cox J and Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ. 2017; 359.
18	Hippisley-Cox J, Coupland C and Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017; 357:j2099.
19*	Holmes M. Literature review for evidence to populate the Novo obesity model. In Press2017.
20	Lewis L, Taylor M, Broom J and Johnston K. The cost-effectiveness of the LighterLife weight management programme as an intervention for obesity in England. Clin Obes. 2014; 4(3):180-8.

21	M. Y. Bertram, S. S. Lim, J. J. Barendregt, and T. Vos, “Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care,” Diabetologia, vol. 53, no. 5, pp. 875–881, 2010.
22	Yang TY, Cairns BJ, Allen N, Sweetland S, Reeves GK, Beral V; Million Women Study, Post-menopausal endometrial cancer risk and body size in early life and middle age: prospective cohort study, Br J Cancer. 2012 Jun 26;107(1):169-75.
23	National Institute for Health and Care Excellence. Obesity: Full Guideline, Section 6 – Health Economics: Evidence Statements and Reviews. Clinical guideline 43. London: NICE; 2006. URL: www.nice.org.uk/nicemedia/live/11000/38300/38300.pdf
24	National Institute for Health and Care Excellence. Review of Clinical Guideline (CG43) — obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children; 2011. Available:http://www.nice.org.uk/nicemedia/live/11000/57615/57615.pdf
25	National Institute for Health and Care Excellence. TA22:Orlistat for the treatment of obesity in adults. London: NICE; 2001. Available at: https://www.nice.org.uk/guTA22dance/ta22
26	Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-578. PubMed
27	Schlesinger S, Lieb W, Koch M, et al. Body weight gain and risk of colorectal cancer: a systematic review and meta-analysis of observational studies. Obes Rev. 2015;16(7):607-619. PubMed
28	Van Baal PH, Hoeymans N, Hoogenveen RT, de Wit GA, Westert GP. Disability weights for comorbidity and their influence on health-adjusted life expectancy. Popul Health Metr 2006;4:1–7.
29	Warren E, Brennan A and Akehurst R. Cost-effectiveness of sibutramine in the treatment of obesity. Med Dec Making. 2004; 24(1):9-19.
30	Wendelboe AM, Hegmann KT, Biggs JJ, et al. Relationships between body mass indices and surgical replacements of knee and hip joints. Am J Prev Med. 2003; 25(4):290-5.
31	Wilson et al. Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study, Archives of Internal Medicine 2007
32	Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002; 162(8):893-900.
33	Centers for Disease Control and Prevention. Defining adult overweight & obesity. 2021. Accessed July 19, 2021. https://www.cdc.gov/obesity/adult/ defining.html
34	Wyatt HR. Update on treatment strategies for obesity. J Clin Endocrinol Metab. 2013;98(4):1299-306. doi:10.1210/ jc.2012-3115
35	Ryan DH, Kahan S. Guideline recommendations for obesity management. Med Clin North Am. 2018;102(1):49-63. doi:10.1016/j.mcna.2017.08.006
36	American College of Cardiology/ American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel. Expert panel report: Guidelines (2013) for the management of overweight and obesity in adults. Obesity (Silver Spring). 2014;22 Suppl 2:S41-410. doi:10.1002/ oby.20660
37	Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017;19(9):1242-51. doi:10.1111/ dom.12932

38	Gibbons C, Blundell J, Tetens Hoff S, Dahl K, Bauer R, Baekdal T. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. Diabetes Obes Metab. 2021;23(2):581-88. doi:10.1111/dom.14255
39	Wilding JP, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989. doi:10.1056/ NEJMoa2032183

Abbreviations: SLR: systematic literature review.

Table 89. Included studies from reference list handsearching in the cost-effectiveness SLR.

No.	Full reference
1	Cederholm J, Eeg-Olofsson, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S, Risk Prediction of Cardiovascular Disease in Type 2 Diabetes A risk equation from the Swedish National Diabetes Register, Diabetes Care. 2008 October; 31(10): 2038–2043
2	D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
3	D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. American heart journal. 2000;139(2 Pt 1):272-81.
4	Hayes A, Leal J, Gray A, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013; 56(9):1925-33.
5	Hippisley-Cox J and Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ. 2017; 359.
6	Hippisley-Cox J, Coupland C and Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017; 357:j2099.
7	Wendelboe AM, Hegmann KT, Biggs JJ, et al. Relationships between body mass indices and surgical replacements of knee and hip joints. Am J Prev Med. 2003; 25(4):290-5.
8	Wilson et al. Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study, Archives of Internal Medicine 2007

Abbreviations: SLR: systematic literature review

C8. Cost-effectiveness SLR (Appendix G) - please provide full references and PDFs for the 27 included studies.

The full references of the 27 studies included in the cost-effectiveness and risk equations SLR are presented in Table 90 below. The PDFs for these studies are available in the reference pack.

Table 90. Studies included in the cost-effectiveness and risk equations SLR

#	Author/HTA agency and year	Full reference
1	Ara 2012	Ara R, Blake L, Gray L, et al. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A

		systematic review. Health Technology Assessment (Winchester, England) 2012;16:iii-xiv, 1-195.
2	CADTH 2022	CADTH. Semaglutide (Wegovy). Available at: https://www.cadth.ca/semaglutide-1. 2022.
3	CADTH 2021	CADTH. liraglutide (Saxenda). Available at: https://www.cadth.ca/liraglutide-1. 2021.
4	Caderholm 2008	Cederholm J, Eeg-Olofsson K, Eliasson Br, et al. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes care 2008;31:2038-2043.
5	D'Agostino 2008	D'Agostino Sr RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-753.
6	D'Agostino 2000	D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. American heart journal 2000;139:272-281.
7	Hayes 2013	Hayes AJ, Leal J, Gray A, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925-1933.
8	Hippisley-Cox 2017a	Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. bmj 2017;357.
9	Hippisley-Cox 2017b	Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. bmj 2017;359.
10	Hoerger 2020	Hoerger TJ, Kaufmann M, Neuwahl S, et al. 1520-P: Developing New Risk Equations to Predict Diabetes-Related Complications and Mortality in US Adults with Type 2 Diabetes. Diabetes 2020;69.
11	Iannazzo 2008	Iannazzo S, Zaniolo O, Pradelli L. Economic evaluation of treatment with orlistat in Italian obese patients. Current Medical Research & Opinion 2008;24:63-74.
12	Kabiri 2020	Kabiri M, Sexton Ward A, Ramasamy A, et al. The Societal Value of Broader Access to Antiobesity Medications. Obesity 2020;28(2):429-436.
13	Kim 2022	Kim N, Wang J, Burudpakdee C, et al. Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States. Journal of Managed Care and Specialty Pharmacy 2022;28(7):740-752.
14	Lamotte 2002	Lamotte M, Annemans L, Lefever A, et al. A health economic model to assess the long-term effects and cost-effectiveness of orlistat in obese type 2 diabetic patients. Diabetes Care 2002;25:303-308.
15	Lee 2020	Lee M, Lauren BN, Zhan T, et al. The cost-effectiveness of pharmacotherapy and lifestyle intervention in the treatment of obesity. Obesity Science and Practice 2020;6(2):162-170.
16	Maetzel 2003	Maetzel A, Ruof J, Covington M, et al. Economic evaluation of orlistat in overweight and obese patients with type 2 diabetes mellitus. PharmacoEconomics 2003;21(7):501-512.

17	NCPE 2021	NCPE. Cost-effectiveness of liraglutide 3mg (Saxenda®) as an adjunct to a reduced calorie diet and increased physical activity for weight management in adult patients with a body mass index of ≥35kg/m2 with pre-diabetes and high risk of cardiovascular disease. Available at: https://www.ncpe.ie/wp-content/uploads/2021/02/Summary-Liraglutide-weight-management-Saxenda-09-02-2021.pdf. 2021.
18	NICE 2020 (TA664)*	National Institute for Health and Care Excellence (NICE). Liraglutide for managing overweight and obesity [TA664]. Available at: https://www.nice.org.uk/guidance/ta664.
19	NICE 2021 (T875)†	National Institute for Health and Care Excellence (NICE). Semaglutide for managing overweight and obesity [TA875]. Available at: https://www.nice.org.uk/guidance/TA875/.
20	Olivieri 2022	Olivieri AV, Larsen S, Luckevich M, et al. EE464 The Cost-Effectiveness of Subcutaneous Semaglutide 2.4MG Injection in the Management of Obesity in Canada Using the Core Obesity Model. Value in Health 2022;25(7 Supplement):S426.
21	PBAC 2022	PBAC. SEMAGLUTIDE, Injection 0.25 mg, 0.5 mg and 1.0 mg in 0.5 mL prefilled single dose pen Injection 1.7 mg and 2.4 mg in 0.75 mL pre-filled single dose pen, Wegovy® , Novo Nordisk Pharmaceuticals Pty. Limited. Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/semaglutide-psd-03-2022.pdf. 2022.
22	Quinones 2021	Quinones S, Goyal A, Ahmed ZU. Geographically weighted machine learning model for untangling spatial heterogeneity of type 2 diabetes mellitus (T2D) prevalence in the USA. Scientific reports 2021;11(1):6955.
23	Roux 2006	Roux L, Kuntz KM, Donaldson C, et al. Economic evaluation of weight loss interventions in overweight and obese women. Obesity 2006;14:1093-1106.
24	Ruof 2005	Ruof J, Golay A, Berne C, et al. Orlistat in responding obese type 2 diabetic patients: Meta-analysis findings and cost-effectiveness as rationales for reimbursement in Sweden and Switzerland. International Journal of Obesity 2005;29(5):517-523.
25	SMC 2022 (SMC2455)	Scottish Medicines Consortium (SMC). Liraglutide (Saxenda) [SMC2455]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/liraglutide-saxenda-resub-smc2455/.
26	Wendelboe 2003	Wendelboe AM, Hegmann KT, Biggs JJ, et al. Relationships between body mass indices and surgical replacements of knee and hip joints. American journal of preventive medicine 2003;25:290-295.
27	Wilson 2007	Wilson PW, Meigs JB, Sullivan L, et al. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Archives of internal medicine 2007;167:1068-1074.

Footnotes: *corrected from TA740 in Appendix G.† Updated from GID-TA10765 in Appendix G.

C9. Cost-effectiveness SLR (Appendix G) - please provide a table of full references and reasons for exclusion for the 59 records excluded at full text.

The full references of excluded studies and reasons for exclusion from the cost-effectiveness

SLR are provided in Table 91.

Table 91. Studies excluded at the full text review stage in the cost-effectiveness SLR

#	Reference	Reason for Exclusion
1	Ackroyd R, Mouiel J, Chevallier JM, et al. Cost-effectiveness and budget impact of obesity surgery in patients with type-2 diabetes in three European countries. Obesity Surgery 2006;16:1488-1503.	No relevant economic outcomes reported
2	Alouki K, Delisle H, Bermudez-Tamayo C, et al. Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies. Journal of Diabetes Research 2016;2016 (no pagination).	Irrelevant study design
3	Anderson LM, Quinn TA, Glanz K, et al. The Effectiveness of Worksite Nutrition and Physical Activity Interventions for Controlling Employee Overweight and Obesity. A Systematic Review. American Journal of Preventive Medicine 2009;37(4):340-357.	Irrelevant study design
4	Annemans L, Lamotte M, Clarys P, et al. Health economic evaluation of controlled and maintained physical exercise in the prevention of cardiovascular and other prosperity diseases. European Journal of Cardiovascular Prevention and Rehabilitation 2007;14:815-824.	No relevant economic outcomes reported
5	Anonymous. Corrigendum to: A health economic model to assess the cost-effectiveness of OPTIFAST for the treatment of obesity in the United States (Journal of Medical Economics, (2018), 21, 9, (835-844), 10.1080/13696998.2018.1468334). Journal of Medical Economics 2018;21(9):845.	Irrelevant study design
6	Ara R, Brennan A. The cost-effectiveness of sibutramine in non-diabetic obese patients: Evidence from four Western countries. Obesity Reviews 2007;8(4):363-371.	No relevant economic outcomes reported
7	Asp NG, Bjorntorp P, Britton M, et al. Obesity - problems and interventions. Sweden: The Swedish Council on Health Technology Assessment (SBU), 2002.	Irrelevant study design
8	Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. England, United Kingdom: NIHR Health Technology Assessment programme, 2004.	No relevant economic outcomes reported
9	Avenell A, Robertson C, Skea Z, et al. Corrigendum: Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2020;22:247-250.	No relevant economic outcomes reported
10	Boyers D, Avenell A, Stewart F, et al. A systematic review of the cost-effectiveness of non-surgical obesity interventions in men. Obesity Research & Clinical Practice 2015;9:310-27.	Irrelevant study design
11	Bromberger B, Porrett P, Choudhury R, et al. Weight loss interventions for morbidly obese patients with compensated cirrhosis: a Markov decision analysis model. Journal of Gastrointestinal Surgery 2014;18:321-7.	No relevant economic outcomes reported

#	Reference	Reason for Exclusion
12	Buckell J, Mei XW, Clarke P, et al. Weight loss interventions on health-related quality of life in those with moderate to severe obesity: Findings from an individual patient data meta-analysis of randomized trials. Obesity Reviews 2021;22(11) (no pagination).	Irrelevant study design
13	Buehler AM. Letter to the editor: Naltrexone sustained-release/bupropion sustained-release for the management of obesity: Review of the data to date. Drug Design, Development and Therapy 2015;9:419-423.	Irrelevant study design
14	Carson V, Faulkner G, Sabiston CM, et al. Patterns of movement behaviors and their association with overweight and obesity in youth. International journal of public health 2015;60(5):551-559.	Irrelevant study design
15	Chen F, Su W, Ramasamy A, et al. Ten-year Medicare budget impact of increased coverage for anti-obesity intervention. Journal of Medical Economics 2019;22(10):1096-1104.	No relevant economic outcomes reported
16	Development, Evaluation C. Orlistat for the treatment of obesity. England: Wessex Institute for Health Research and Development (WIHRD), 1999.	Irrelevant study design
17	Finkelstein EA, Kruger E. Meta- and cost-effectiveness analysis of commercial weight loss strategies. Obesity 2014;22:1942-51.	Irrelevant study design
18	Finkelstein EA, Verghese NR. Incremental cost-effectiveness of evidence-based non-surgical weight loss strategies. Clinical Obesity 2019;9:e12294.	Irrelevant study design
19	Forster M, Veerman JL, Barendregt JJ, et al. Cost-effectiveness of diet and exercise interventions to reduce overweight and obesity. International Journal of Obesity 2011;35(8):1071-1078.	No relevant economic outcomes reported
20	Foxcroft DR, Milne R. Orlistat for the treatment of obesity: rapid review and cost-effectiveness model. Obesity Reviews 2000;1:121-6.	No relevant economic outcomes reported
21	Foxcroft DR. Orlistat for the treatment of obesity: cost utility model. Obesity Reviews 2005;6:323-8.	No relevant economic outcomes reported
22	Gil-Rojas Y, Garzon A, Lasalvia P, et al. Cost-Effectiveness of Bariatric Surgery Compared With Nonsurgical Treatment in People With Obesity and Comorbidity in Colombia. Value in Health Regional Issues 2019;20:79-85.	No relevant economic outcomes reported
23	Gomez-Lumbreras A, Tan MS, Villa Zapata L, et al. EE2 A Cost-Effectiveness Analysis Comparing Obesity Drug Treatments from a U.S. Payer Perspective. Value in Health 2022;25(7 Supplement):S335.	No relevant economic outcomes reported
24	Hadziabdic MO, Mucalo I, Hrabac P, et al. Factors predictive of drop-out and weight loss success in weight management of obese patients.	Irrelevant study design

#	Reference	Reason for Exclusion
	Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 2015;28(Supplement 2):24-32.	
25	Hayes, Inc. Glucagon-like peptide-1 receptor agonists for the treatment of obesity in women with polycystic ovary syndrome. United States: HAYES, Inc., 2017.	Irrelevant study design
26	Hayes, Inc. Liraglutide (Saxenda) for weight loss in non-diabetic obese adults. United States: HAYES, Inc., 2015.	Irrelevant study design
27	Hayes, Inc. Obesity management, pharmacologic treatment with orlistat or sibutramine. United States: HAYES, Inc., 2003.	Irrelevant study design
28	Hertzman P. The cost effectiveness of orlistat in a 1-year weight-management programme for treating overweight and obese patients in Sweden : a treatment responder approach. Pharmacoeconomics 2005;23:1007-20.	No relevant economic outcomes reported
29	Hjern F, Wolk A, Hkansson N. Obesity, physical inactivity, and colonic diverticular disease requiring hospitalization in women: A prospective cohort study. American Journal of Gastroenterology 2012;107(2):296-302.	Irrelevant study design
30	Hong JL, Meier CR, Sandler RS, et al. Risk of colorectal cancer after initiation of orlistat: Matched cohort study. BMJ (Online) 2013;347(7923) (no pagination).	No relevant economic outcomes reported
31	Hu Y, Zheng SL, Ye XL, et al. Cost-effectiveness analysis of 4 GLP-1RAs in the treatment of obesity in a US setting. Annals of Translational Medicine 2022;10:152.	No relevant economic outcomes reported
32	Huang S, Xu Y, Yue L, et al. Evaluating the risk of hypertension using an artificial neural network method in rural residents over the age of 35 years in a Chinese area. Hypertension Research 2010;33(7):722-726.	Irrelevant study design
33	Kalashnikova MF, Uchamprina VA, Romantsova TI, et al. Clinical and economic analysis of the modern strategies for treating metabolic syndrome. Diabetes Mellitus 2014;17(2):116-125.	No relevant economic outcomes reported
34	Lacey LA, Wolf A, O'Shea D, et al. Cost-effectiveness of orlistat for the treatment of overweight and obese patients in Ireland. International Journal of Obesity 2005;29:975-82.	No relevant economic outcomes reported
35	Levy RL, Linde JA, Feld KA, et al. The association of gastrointestinal symptoms with weight, diet, and exercise in weight-loss program participants. Clinical Gastroenterology and Hepatology 2005;3(10):992-996.	Irrelevant study design
36	Lopes S, Meincke HH, Lamotte M, et al. A novel decision model to predict the impact of weight management interventions: The Core Obesity Model. Obesity Science and Practice 2021;7(3):269-280.	No relevant economic outcomes reported

#	Reference	Reason for Exclusion
37	MacEwan J, Kan H, Chiu K, et al. Antiobesity Medication Use Among Overweight and Obese Adults in the United States: 2015-2018. Endocrine Practice 2021;27(11):1139-1148.	Irrelevant study design
38	Malkin SJP, Russel-Szymczyk M, Psota M, et al. The Management of Type 2 Diabetes with Once-Weekly Semaglutide Versus Dulaglutide: A Long-Term Cost-Effectiveness Analysis in Slovakia. Advances in Therapy 2019;36:2034-2051.	No relevant economic outcomes reported
39	Mathur C, Stigler M, Lust K, et al. A latent class analysis of weight-related health behaviors among 2- and 4-year college students and associated risk of obesity. Health education & behavior : the official publication of the Society for Public Health Education 2014;41(6):663-672.	Irrelevant study design
40	McRobbie H, Hajek P, Peerbux S, et al. Randomised controlled trial and economic evaluation of a task-based weight management group programme. BMC Public Health 2019;19:365.	No relevant economic outcomes reported
41	McRobbie H, Hajek P, Peerbux S, et al. Tackling obesity in areas of high social deprivation: clinical effectiveness and cost-effectiveness of a task-based weight management group programme - a randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England) 2016;20:1-150.	No relevant economic outcomes reported
42	National Committee for Technology I. Orlistate para a redução de peso em indivíduos com sobrepeso ou obesidade. Brazil: National Committee for Technology Incorporation (CONITEC), 2020.	Irrelevant study design
43	National Institute for H, Clinical E. Liraglutide for the treatment of type 2 diabetes mellitus. England: National Institute for Health and Clinical Excellence (NICE), 2010.	Irrelevant study design
44	Neovius M, Narbro K. Cost-effectiveness of pharmacological anti-obesity treatments: a systematic review. International Journal of Obesity 2008;32:1752-63.	Irrelevant study design
45	Nihr HSC. Liraglutide for obesity or overweight in patients with associated co-morbidities. England, United Kingdom: NIHR Horizon Scanning Centre (NIHR HSC), 2013.	Irrelevant study design
46	Nuijten M, Dainelli L, Rasouli B, et al. A Meal Replacement Program for the Treatment of Obesity: A Cost-Effectiveness Analysis from the Swiss Payer's Perspective. Diabetes, Metabolic Syndrome and Obesity Targets and Therapy 2021;14:3147-3160.	No relevant economic outcomes reported
47	Nuijten M, Marczewska A, Araujo Torres K, et al. A health economic model to assess the cost-effectiveness of OPTIFAST for the treatment of obesity in the United States. Journal of Medical Economics 2018;21:835-844.	No relevant economic outcomes reported
48	Ollendorf DA, Cameron CG, Pearson SD. Effectiveness and value of treatment options for obesity-a report for the California technology assessment forum. JAMA Internal Medicine 2016;176(2):247-248.	No relevant economic outcomes reported

#	Reference	Reason for Exclusion
49	O'Meara S, Riemsma R, Shirran L, et al. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity. Health Technology Assessment (Winchester, England) 2001;5:1-81.	Irrelevant study design
50	Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes of metformin in patients with impaired glucose tolerance: modelling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom. Clinical Therapeutics 2004;26:304-321.	No relevant economic outcomes reported
51	Papamargaritis D, Al-Najim W, Lim J, et al. Effectiveness and cost of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in obesity services (STRIVE study): study protocol of an open-label, real-world, randomised, controlled trial. BMJ Open 2020;10:e034137.	Irrelevant study design
52	Robertson C, Archibald D, Avenell A, et al. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. Health Technology Assessment 2014;18(35):1-424.	Irrelevant study design
53	Schwander B, Nuijten M, Evers S, et al. Replication of Published Health Economic Obesity Models: Assessment of Facilitators, Hurdles and Reproduction Success. PharmacoEconomics 2021;39(4):433-446.	No relevant economic outcomes reported
54	Sewali B, Harcourt N, Everson-Rose SA, et al. Prevalence of cardiovascular risk factors across six African Immigrant Groups in Minnesota. BMC public health 2015;15:411.	Irrelevant study design
55	Tellwright H, Lock-Pullan P, Cherry I, et al. An insight into a dietetic-led Tier 3 weight management service providing Liraglutide. Obesity Surgery 2022;32(Supplement 1):S7-S8.	Irrelevant study design
56	Tran DT, Jorm LR, Johnson M, et al. Prevalence and risk factors of type 2 diabetes in older Vietnam-born Australians. Journal of community health 2014;39(1):99-107.	Irrelevant study design
57	Valdez-Huerta R, Moreno D, Paladio Hernandez JA. Cost-Effectiveness Analysis of Liraglutide for the Treatment of Obesity in Mexico. Value in Health 2022;25(7 Supplement):S350.	No relevant economic outcomes reported
58	van Baal PH, van den Berg M, Hoogenveen RT, et al. Cost-effectiveness of a low-calorie diet and orlistat for obese persons: modeling long-term health gains through prevention of obesity-related chronic diseases. Value in Health 2008;11:1033-1040.	No relevant economic outcomes reported
59	Veerman JL, Barendregt JJ, Forster M, et al. Cost-effectiveness of pharmacotherapy to reduce obesity. Plos One 2011;6.	No relevant economic outcomes reported

C10. Document B.3.1 states “Systematic searches for cost-effectiveness analyses, relevant risk equations, studies describing health-state utility values and costs and healthcare resource use were carried out simultaneously as a combined search to identify all relevant studies on adult patients with obesity, as detailed in Appendix G.” – whereas in fact different searches are reported for cost-effectiveness, HRQoL and costs/resources use in Appendices G, H and I. Please clarify whether any results of the SLRs reported in appendices H and I are used in the CS.

Results from the SLRs reported in Appendices H and I were not used in the CS. The aim of the Company was to align the cost-effectiveness model with previous NICE committee decisions and preferences where possible. Therefore, most inputs were sourced from NICE 2021 (TA875) and NICE 2020 (TA664). The Company evaluated the inputs from the SLR, in case more appropriate inputs were found. However, no other more suitable sources were identified, as utility values were not presented in a suitable form, i.e. the utilities extracted were not reported as decrements.

C11. Re. Document B.3.2, table 47 ‘source of utilities’ and B.3.4.5 ‘Health-related quality-of-life data used in the cost-effectiveness analysis’, how were the literature sources used here identified and selected?

The Company used references from NICE 2021 [TA875][3] and NICE 2020 [TA664][23] that were identified in the SLR as sources for utility values, in order to ensure the cost-effectiveness model was aligned with previous NICE committee decisions and preferences. Other sources identified in the SLR were also reviewed (as noted above in response to Question C10), but no more suitable sources were identified. Further detail on the sources selected can be found in Document B, Section B.3.4.5.

C12. HRQoL SLR (Appendix H) - please provide full references and PDFs for the 20 included studies.

The full references of the included studies and are provided in Table 92. The PDFs for these studies are available in the reference pack.

Table 92. Studies included in the HRQoL SLR

No.	Author/HTA agency and year	Full reference
1	Avenell 2018	Avenell A, Robertson C, Skea Z, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2018;22:1-246.
2	Betts 2020	Betts MB, Rane P, Bergrath E, et al. Utility value estimates in cardiovascular disease and the effect of changing elicitation methods: a systematic literature review. Health & Quality of Life Outcomes 2020;18:251.
3	Blieden Betts 2018	Blieden Betts M, Gandra SR, Cheng LI, et al. Differences in utility elicitation methods in cardiovascular disease: a systematic review. Journal of Medical Economics 2018;21(1):74-84.

4	CADTH 2017b	CADTH. Edoxaban (Lixiana). Available at: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0500_Lixiana_NVAF_PE_Report.pdf. 2017.
5	CADTH 2021	CADTH. Ranolazine (Corzyna). Available at: https://www.cadth.ca/sites/default/files/attachments/2021-08/sr0655PE-corzyna.pdf. 2021.
6	CADTH 2018	CADTH. Rivaroxaban (Xarelto). Available at: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0569_Xarelto_PE_Report.pdf. 2018.
7	CADTH 2018	CADTH. Dual Antiplatelet Therapy Following Percutaneous Coronary intervention: Clinical and Economic Impact of Standard Versus Extended Duration. Canadian Agency for Drugs and Technologies in Health. CADTH Optimal Use Reports 2018.
8	Carrello 2021	Carrello J, Hayes A, Killedar A, et al. Utility Decrements Associated with Adult Overweight and Obesity in Australia: A Systematic Review and Meta-Analysis. PharmacoEconomics 2021;39(5):503-519.
9	Health Information and Quality Authority 2022	Health Information and Quality Authority. Health technology assessment of metabolic surgery for the treatment of comorbid type 2 diabetes and obesity. Ireland: Health Information and Quality Authority (HIQA), 2022.
10	Health Quality Ontario 2017	Health Quality Ontario. Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment. Ontario Health Technology Assessment Series 2017;17:1-106.
11	Joundi 2022	Joundi RA, Adekanye J, Leung AA, et al. Health State Utility Values in People With Stroke: A Systematic Review and Meta-Analysis. Journal of the American Heart Association 2022;11:e024296.
12	Mok 2021	Mok CH, Kwok HHY, Ng CS, et al. Health State Utility Values for Type 2 Diabetes and Related Complications in East and Southeast Asia: A Systematic Review and Meta-Analysis. Value in Health 2021;24:1059-1067.
13	NICE 2022	NICE. Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea. Available at: https://www.nice.org.uk/guidance/ta776/resources/pitolisant-hydrochloride-for-treating-excessive-daytime-sleepiness-caused-by-obstructive-sleep-apnoea-pdf-82611499729093. 2022.
14	NICE 2022b	NICE. Solriamfetol for treating excessive daytime sleepiness caused by obstructive sleep apnoea. Available at: https://www.nice.org.uk/guidance/ta777/resources/solriamfetol-for-treating-excessive-daytime-sleepiness-caused-by-obstructive-sleep-apnoea-pdf-82611501408709. 2022.
15	Rebchuk 2020	Rebchuk AD, O'Neill ZR, Szefer EK, et al. Health Utility Weighting of the Modified Rankin Scale: A Systematic Review and Meta-analysis. JAMA Network Open 2020;3:e203767.
16	Rendez 2022	Redenz G, Ibaceta MC, Aceituno D, et al. Health State Utility Values of Type 2 Diabetes Mellitus and Related Complications: A Systematic Review and Meta-Analysis. Value in Health Regional Issues 2022;34:14-22.
17	SMC 2019	SMC. rivaroxaban (Xarelto). Available at: https://www.scottishmedicines.org.uk/media/4130/rivaroxaban-xarelto-final-jan-2019-for-website.pdf. 2019.

18	SMC 2022	SMC. solriamfetol (Sunosi). Available at: https://www.scottishmedicines.org.uk/media/6732/solriamfetol-sunosi-final-feb-2022-for-website.pdf. 2022.
19	SMC 2017	SMC. ticagrelor (Brilique). Available at: https://www.scottishmedicines.org.uk/media/2390/ticagrelor_brilique_final_march_2017_for_website.pdf. 2017.
20	Xia 2020	Xia Q, Campbell JA, Ahmad H, et al. Health state utilities for economic evaluation of bariatric surgery: A comprehensive systematic review and meta-analysis. Obesity Reviews 2020;21:e13028.

C13. HRQoL SLR (Appendix H) - please provide a table of full references and reasons for exclusion for the 17 records excluded at full text.

The full references of excluded studies and reasons for exclusion for the HRQoL SLR are provided in Table 93.

Table 93. Publications excluded at the full text review stage in the HRQoL SLR

No.	Reference	Reason for exclusion
1	Afshari S, Ameri H, Baharinya S, et al. Assessment of the properties of the EQ-5D-5L in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Expert Review of Pharmacoeconomics & Outcomes Research 2022;22:351-364.	Irrelevant patient population
2	Bala MM, Celinska-Lowenhoff M, Szot W, et al. Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome. Cochrane Database of Systematic Reviews 2017;10:CD012169.	No relevant HSUV outcomes reported
3	Cameron LJ, Wales K, Casey A, et al. Self-reported quality of life following stroke: a systematic review of instruments with a focus on their psychometric properties. Quality of Life Research 2022;31:329-342.	No relevant HSUV outcomes reported
4	Chaudhry H, Ponnusamy K, Somerville L, et al. Revision Rates and Functional Outcomes Among Severely, Morbidly, and Super-Obese Patients Following Primary Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. JBJS Reviews 2019;7:e9.	No relevant HSUV outcomes reported
5	Creber RM, Dimagli A, Spadaccio C, et al. Effect of coronary artery bypass grafting on quality of life: a meta-analysis of randomized trials. European Heart Journal Quality of Care & Clinical Outcomes 2022;8:259-268.	No relevant HSUV outcomes reported
6	Essat M, Aber A, Phillips P, et al. Patient-Reported Outcome Measures in Carotid Artery Revascularization: Systematic Review and Psychometric Analysis. Annals of Vascular Surgery 2018;50:275-283.	Irrelevant patient population
7	Health Technology W. Freestyle Libre flash glucose monitoring for the management of diabetes. Wales, United Kingdom: Health Technology Wales (HTW), 2021.	Irrelevant patient population
8	Health Technology W. Transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis who are at intermediate surgical risk. Wales, United Kingdom: Health Technology Wales (HTW), 2020.	No relevant HSUV outcomes reported

No.	Reference	Reason for exclusion
9	Macisaac RL, Ali M, Taylor-Rowan M, et al. Use of a 3-Item Short-Form Version of the Barthel Index for Use in Stroke: Systematic Review and External Validation. Stroke 2017;48(3):618-623.	No relevant HSUV outcomes reported
10	Magliano C, Monteiro AL, de Oliveira Rebelo AR, et al. Patients' preferences for coronary revascularization: a systematic review. Patient preference & adherence 2019;13:29-35.	No relevant HSUV outcomes reported
11	Mansilla-Chacon M, Gomez-Urquiza JL, Martos-Cabrera MB, et al. Effects of Supervised Cardiac Rehabilitation Programmes on Quality of Life among Myocardial Infarction Patients: A Systematic Review and Meta-Analysis. Journal of Cardiovascular Development & Disease 2021;8:27.	No relevant HSUV outcomes reported
12	McGregor G, Powell R, Kimani P, et al. Does contemporary exercise-based cardiac rehabilitation improve quality of life for people with coronary artery disease? A systematic review and meta-analysis. BMJ Open 2020;10:e036089.	Irrelevant patient population
13	Reynard C, Morris N, Moss P, et al. Optimising antiplatelet utilisation in the acute care setting: a novel threshold for medical intervention in suspected acute coronary syndromes. Emergency Medicine Journal 2019;36:163-170.	Irrelevant study design
14	Schatz C, Klein N, Marx A, et al. Preoperative predictors of health-related quality of life changes (EQ-5D and EQ VAS) after total hip and knee replacement: a systematic review. BMC Musculoskeletal Disorders 2022;23:58.	No relevant HSUV outcomes reported
15	Thieu VT, Robinson S, Kennedy-Martin T, et al. Patient preferences for glucagon-like peptide 1 receptor-agonist treatment attributes. Patient preference & adherence 2019;13:561-576.	Irrelevant patient population
16	Valentine W, Norrbacka K, Boye KS. Evaluating the Impact of Therapy on Quality of Life in Type 2 Diabetes: A Literature Review of Utilities Associated with Treatment-Related Attributes. Patient Related Outcome Measures 2022;13:97-111.	Irrelevant patient population
17	Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. BMC Musculoskeletal Disorders 2019;20:493	Irrelevant patient population

Abbreviations: HRQoL: health-related quality of life; HSUV: health state utility value; SLR: systematic literature review.

C14. CRU SLR (Appendix I) - please provide full references and PDFs for the 29 included studies.

The full references for studies included in the CRU SLR are provided in Table 94. The PDFs for these studies are available in the reference pack.

Table 94. Studies included in the CRU SLR

#	Author/HTA agency and year	Full reference
1	Al-Rubeaan 2020	Al-Rubeaan K, Tong C, Taylor H, et al. Enhanced recovery programmes versus conventional care in bariatric surgery: A systematic literature review and meta-analysis. PLoS ONE [Electronic Resource] 2020;15:e0243096.
2	Ansari 2020	Ansari-Moghaddam A, Setoodehzadeh F, Khammarnia M, et al. Economic cost of diabetes in the Eastern Mediterranean region countries: A meta-analysis. Diabetes & Metabolic Syndrome 2020;14:1101-1108.
3	Artime 2021	Artime E, Romera I, Diaz-Cerezo S, et al. Epidemiology and Economic Burden of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus in Spain: A Systematic Review. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2021;12:1631-1659.
4	Avenell 2018	Avenell A, Robertson C, Skea Z, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2018;22:1-246.
5	Bidonde 2017	Bidonde J, Fagerlund BC, Frønsdal KB, et al. FreeStyle Libre Flash Glucose Self-Monitoring System: A Single-Technology Assessment. Norway: Norwegian Institute of Public Health (NIPH), 2017.
6	CADTH 2017a	CADTH. Drugs for type 2 diabetes: second-line therapy review update. Canada: Canadian Agency for Drugs and Technologies in Health (CADTH), 2017.
7	CADTH 2021	CADTH. Ranolazine (Corzyna). Available at: https://www.cadth.ca/sites/default/files/attachments/2021-08/sr0655PE-corzyna.pdf. 2021.
8	CADTH 2018a	CADTH. Rivaroxaban (Xarelto). Available at: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0569_Xarelto_PE_Report.pdf. 2018.
9	CADTH 2018b	CADTH. Dual Antiplatelet Therapy Following Percutaneous Coronary intervention: Clinical and Economic Impact of Standard Versus Extended Duration. Canadian Agency for Drugs and Technologies in Health. CADTH Optimal Use Reports 2018.
10	Einarson 2018	Einarson TR, Acs A, Ludwig C, et al. Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review. Value in Health 2018;21:881-890.
11	Ganasegeran 2020	Ganasegeran K, Hor CP, Jamil MFA, et al. A Systematic Review of the Economic Burden of Type 2 Diabetes in Malaysia. International Journal of Environmental Research & Public Health [Electronic Resource] 2020;17:07.
12	Health Information and Quality Authority 2022	Health Information and Quality Authority. Health technology assessment of metabolic surgery for the treatment of comorbid type 2 diabetes and obesity. Ireland: Health Information and Quality Authority (HIQA), 2022.
13	Health Quality Ontario 2017	Health Quality O. Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment. Ontario Health Technology Assessment Series 2017;17:1-106.
14	Langhorne 2017	Langhorne P, Baylan S, Early Supported Discharge T. Early supported discharge services for people with acute stroke. Cochrane Database of Systematic Reviews 2017;7:CD000443.

15	Lim 2021	Lim BL, Lee WF, Ng WM, et al. Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic review and meta-analysis of randomised trials. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2021;06.
16	Lo 2021	Lo J, Chan L, Flynn S. A Systematic Review of the Incidence, Prevalence, Costs, and Activity and Work Limitations of Amputation, Osteoarthritis, Rheumatoid Arthritis, Back Pain, Multiple Sclerosis, Spinal Cord Injury, Stroke, and Traumatic Brain Injury in the United States: A 2019 Update. Archives of Physical Medicine and Rehabilitation 2021;102(1):115-131.
17	Malczak 2017	Malczak P, Pisarska M, Piotr M, et al. Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis. Obesity Surgery 2017;27(1):226-235.
18	Ontario Health Technology Assessment 2020	Ontario H. Automated CT Perfusion Imaging to Aid in the Selection of Patients With Acute Ischemic Stroke for Mechanical Thrombectomy: A Health Technology Assessment. Ontario Health Technology Assessment Series 2020;20:1-87.
19	Ormstad 2019	Ormstad SS, Lund UH, Chudasama KK, et al. Prehospital CT for early diagnosis and treatment of suspected acute stroke or severe head injury. Norway: Norwegian Institute of Public Health (NIPH), 2019.
20	Rochmah 2021	Rochmah TN, Rahmawati IT, Dahlui M, et al. Economic burden of stroke disease: A systematic review. International Journal of Environmental Research and Public Health 2021;18(14) (no pagination).
21	Ryder 2019	Ryder S, Fox K, Rane P, et al. A Systematic Review of Direct Cardiovascular Event Costs: An International Perspective. Pharmacoeconomics 2019;37:895-919.
22	SMC 2019	SMC. rivaroxaban (Xarelto). Available at: https://www.scottishmedicines.org.uk/media/4130/rivaroxaban-xarelto-final-jan-2019-for-website.pdf. 2019.
23	SMC 2017	SMC. ticagrelor (Brilique). Available at: https://www.scottishmedicines.org.uk/media/2390/ticagrelor_brilique_final_march_2017_for_website.pdf. 2017.
24	Stegbauer 2020	Stegbauer C, Falivena C, Moreno A, et al. Costs and its drivers for diabetes mellitus type 2 patients in France and Germany: a systematic review of economic studies. BMC health services research 2020;20(1):1043.
25	Strilciuc 2021	Strilciuc S, Grad DA, Radu C, et al. The economic burden of stroke: a systematic review of cost of illness studies. Journal of Medicine & Life 2021;14:606-619.
26	Tsang 2022	Tsang MP, Man GCW, Xin H, et al. The effectiveness of telerehabilitation in patients after total knee replacement: A systematic review and meta-analysis of randomized controlled trials. Journal of telemedicine and telecare 2022:1357633X221097469.
27	van Schoonhoven 2019	van Schoonhoven AV, Gout-Zwart JJ, de Vries MJS, et al. Costs of clinical events in type 2 diabetes mellitus patients in the Netherlands: A systematic review. PLoS ONE [Electronic Resource] 2019;14:e0221856.
28	Walker 2018	Walker IF, Garbe F, Wright J, et al. The Economic Costs of Cardiovascular Disease, Diabetes Mellitus, and Associated Complications in South Asia: A Systematic Review. Value in Health Regional Issues 2018;15:12-26.
29	Wilson 2017	Wilson A, Bath PMW, Berge E, et al. Understanding the relationship between costs and the modified Rankin Scale: A systematic review, multidisciplinary consensus and recommendations for future studies. European Stroke Journal 2017;2(1):3-12.

C15. CRU SLR (Appendix I) - please provide a table of full references and reasons for exclusion for the 90 records excluded at full text.

The full references and reasons for exclusion for the 90 records excluded at the full text stage for the CRU SLR are presented in Table 95 below.

Table 95. Publications excluded at the full text review stage in the CRU SLR

#	Reference	Reason for Exclusion
1	Abdelnoor M, Andersen JG, Arnesen H, et al. Early discharge compared with ordinary discharge after percutaneous coronary intervention - a systematic review and meta-analysis of safety and cost. Vascular Health & Risk Management 2017;13:101-109.	No relevant HCRU outcomes reported
2	Afroz A, Alramadan MJ, Hossain MN, et al. Cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries: a systematic review. BMC Health Services Research 2018;18:972.	Irrelevant patient population
3	Ahmed A, Ahmed Y, Duah-Asante K, et al. A cost-utility analysis comparing endovascular coiling to neurosurgical clipping in the treatment of aneurysmal subarachnoid haemorrhage. Neurosurgical Review 2022;45:3259-3269.	Irrelevant study design
4	Alemayehu B, Speiser J, Bloudek L, et al. Costs associated with long-acting insulin analogues in patients with diabetes. American Journal of Managed Care 2018;24:SP265-SP272.	Irrelevant patient population
5	Alzaid A, Ladron de Guevara P, Beillat M, et al. Burden of disease and costs associated with type 2 diabetes in emerging and established markets: systematic review analyses. Expert Review of Pharmacoeconomics and Outcomes Research 2020:1-14.	No relevant HCRU outcomes reported
6	Anonymous. Flash glucose monitoring system for people with type 1 or type 2 diabetes: A health technology assessment. Ontario Health Technology Assessment Series 2019;19(8):1-108.	Irrelevant patient population
7	Balla A, Batista Rodriguez G, Corradetti S, et al. Outcomes after bariatric surgery according to large databases: a systematic review. Langenbecks Archives of Surgery 2017;402:885-899.	No relevant HCRU outcomes reported
8	Barclay RE, Stevenson TJ, Poluha W, et al. Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke. Cochrane Database of Systematic Reviews 2020;5:CD005950.	No relevant HCRU outcomes reported
9	Beckmann S, Drent G, Ruppar T, et al. Body Weight Parameters are Related to Morbidity and Mortality After Liver Transplantation: A Systematic Review and Meta-analysis. Transplantation 2019;103:2287-2303.	Irrelevant patient population
10	Breen K, Finnegan L, Vuckovic K, et al. Multimorbidity in Patients With Acute Coronary Syndrome Is Associated With Greater Mortality, Higher Readmission Rates, and Increased Length of Stay: A Systematic Review. Journal of Cardiovascular Nursing 2020;35:E99-Irrelevant study design10.	No relevant HCRU outcomes reported
11	Brown K, El Husseini N, Grimley R, et al. Alternative Payment Models and Associations With Stroke Outcomes, Spending, and Service Utilization: A Systematic Review. Stroke 2021:STROKEAHA121033983.	No relevant HCRU outcomes reported
12	Cahill LS, Carey LM, Lannin NA, et al. Implementation interventions to promote the uptake of evidence-based practices in stroke rehabilitation. Cochrane Database of Systematic Reviews 2020;10:CD012575.	No relevant HCRU outcomes reported
13	Chow JY, McClure G, Belley-Cote EP, et al. Costs of surgical ablation of atrial fibrillation in Ontario, Canada from 2006 to 2017. Journal of Cardiac Surgery 2020;35:3451-3454.	Irrelevant study design

#	Reference	Reason for Exclusion
14	Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018;391:1693-1705.	No relevant HCRU outcomes reported
15	Crosland P, Ananthapavan J, Davison J, et al. The economic cost of preventable disease in Australia: a systematic review of estimates and methods. Australian & New Zealand Journal of Public Health 2019;43:484-495.	No relevant HCRU outcomes reported
16	Daghash H, Lim Abdullah K, Ismail MD. The effect of acute coronary syndrome care pathways on in-hospital patients: A systematic review. Journal of Evaluation in Clinical Practice 2020;26(4):1280-1291.	No relevant HCRU outcomes reported
17	Dargad RR, Prajapati MR, Dargad RR, et al. Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor. Indian Heart Journal 2018;70 Suppl 1:S102-S110.	Irrelevant study design
18	de Vries EE, Baldew VGM, den Ruijter HM, et al. Meta-analysis of the costs of carotid artery stenting and carotid endarterectomy. British Journal of Surgery 2017;104:1284-1292.	No relevant HCRU outcomes reported
19	Denissen S, Staring W, Kunkel D, et al. Interventions for preventing falls in people after stroke. Cochrane Database of Systematic Reviews 2019;10:CD008728.	No relevant HCRU outcomes reported
20	Desse TA, Vakil K, Mc Namara K, et al. Impact of clinical pharmacy interventions on health and economic outcomes in type 2 diabetes: A systematic review and meta-analysis. Diabetic Medicine 2021;38:Irrelevant study design4526.	Irrelevant patient population
21	Dhippayom T, Dilokthornsakul P, Laophokhin V, et al. Clinical burden associated with postsurgical complications in major cardiac surgeries in Asia-Oceania countries: A systematic review and meta-analysis. Journal of Cardiac Surgery 2020;35:2618-2626.	Irrelevant patient population
22	Ding C, Bao Y, Bai B, et al. An update on the economic burden of type 2 diabetes mellitus in China. Expert Review of Pharmacoeconomics & Outcomes Research 2022;22:617-625.	Irrelevant patient population
23	Doble B, Wordsworth S, Rogers CA, et al. What Are the Real Procedural Costs of Bariatric Surgery? A Systematic Literature Review of Published Cost Analyses. Obesity Surgery 2017;27:2179-2192.	No relevant HCRU outcomes reported
24	Dobrow L, Estrada I, Burkholder-Cooley N, et al. Potential Effectiveness of Registered Dietitian Nutritionists in Healthy Behavior Interventions for Managing Type 2 Diabetes in Older Adults: A Systematic Review. Frontiers in Nutrition 2021;8:737410.	No relevant HCRU outcomes reported
25	Dokollari A, Torregrossa G, Sicouri S, et al. Pearls, pitfalls, and surgical indications of the Intuity TM heart valve: A rapid deployment bioprosthesis. A systematic review of the literature. Journal of Cardiac Surgery 2022;20:20.	No relevant HCRU outcomes reported
26	Duplain-Cyr G, Rousseau MP, Dufort I, et al. État des connaissances - La pharmacothérapie dans le traitement de l'obésité. Canada: Institut national d'excellence en sante et en services sociaux (INESSS), 2022.	No relevant HCRU outcomes reported
27	Duvel JA, Damm O, Greiner W. Costs of stroke in Germany: A systematic review. [German]. Gesundheitsokonomie und Qualitatsmanagement 2021;26(1):40-50.	Irrelevant study design
28	Elbadawi A, Sedhom R, Dang AT, et al. Fractional flow reserve versus angiography alone in guiding myocardial revascularisation: a systematic review and meta-analysis of randomised trials. Heart 2022;108:1699-1706.	No relevant HCRU outcomes reported
29	Elbardesy H, McLeod A, Gul R, et al. Midterm results of modern patellofemoral arthroplasty versus total knee arthroplasty for isolated patellofemoral arthritis: systematic review and meta-analysis of comparative studies. Archives of Orthopaedic & Trauma Surgery 2022;142:851-859.	No relevant HCRU outcomes reported

#	Reference	Reason for Exclusion
30	Ferrone SR, Boltyenkov AT, Lodato Z, et al. Clinical Outcomes and Costs of Recurrent Ischemic Stroke: A Systematic Review. Journal of Stroke & Cerebrovascular Diseases 2022;31:106438.	No relevant HCRU outcomes reported
31	Fridman M, Lucas ME, Paprocki Y, et al. Impact of Weight Change in Adults with Type 2 Diabetes Mellitus: A Literature Review and Critical Analysis. Clinicoeconomics & Outcomes Research 2020;12:555-566.	Irrelevant patient population
32	Fried LF, Folkerts K, Smela B, et al. Targeted literature review of the burden of illness in patients with chronic kidney disease and type 2 diabetes. American Journal of Managed Care 2021;27:S168-S177.	Irrelevant patient population
33	Gaba K, Morris D, Halliday A, et al. Improving Quality of Carotid Interventions: Identifying Hospital-Level Structural Factors that can Improve Outcomes. Annals of Vascular Surgery 2021;72:589-600.	No relevant HCRU outcomes reported
34	Gheorghe A, Griffiths U, Murphy A, et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. BMC Public Health 2018;18:975.	No relevant HCRU outcomes reported
35	Giske L, Elvsaas I, Tingulstad A, et al. Intermitterende pneumatisk kompresjon for forebygging av dyp venetrombose ved akutt hjerneslag, en fullstendig metodevurdering. Norway: Norwegian Institute of Public Health (NIPH), 2020.	No relevant HCRU outcomes reported
36	Giske L, Stoinska-Schneider A, Hjelmesæth J, et al. Fedmekirurgi ved diabetes type 2 og kroppsmasseindeks under 35. Norway: Norwegian Institute of Public Health (NIPH), 2018.	No relevant HCRU outcomes reported
37	Gloria LA, Mariela SV, Merlo JAM, et al. Asystematic literature review of treatment costs for patients with Acute Myocardial Infarction. Revista Latinoamericana de Hipertension 2019;14(2):168-172.	Irrelevant study design
38	Goetz G, Walter M, Wohlhoefner K, et al. Robotics and functional electrical stimulation for stroke rehabilitation: systematic review. Austria: Austrian Institute for Health Technology Assessment (AIHTA), 2021.	No relevant HCRU outcomes reported
39	Hagerman A, Schorer R, Putzu A, et al. Cardioprotective Effects of Glucose-Insulin-Potassium Infusion in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis. Seminars in Thoracic & Cardiovascular Surgery 2022;08:08.	Irrelevant patient population
40	Hamersky CM, Fridman M, Gamble CL, et al. Injectable Antihyperglycemics: A Systematic Review and Critical Analysis of the Literature on Adherence, Persistence, and Health Outcomes. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2019;10:865-890.	Irrelevant patient population
41	Health I, Quality A. Health technology assessment of a national emergency endovascular service for mechanical thrombectomy in the management of acute ischaemic stroke. Ireland: Health Information and Quality Authority (HIQA), 2017.	No relevant HCRU outcomes reported
42	Health Technology W. Freestyle Libre flash glucose monitoring for the management of diabetes. Wales, United Kingdom: Health Technology Wales (HTW), 2021.	Irrelevant patient population
43	Health Technology W. Synovasure® Alpha Defensin Lateral Flow Test Kit for the assessment of periprosthetic joint infection. Wales, United Kingdom: Health Technology Wales (HTW), 2019.	No relevant HCRU outcomes reported
44	Jobin N, Arbour S, Nieminen J. Avis: système de mesure du glucose en continu (Dexcom G6, Dexcom). Canada: Institut national d'excellence en sante et en services sociaux (INESSS), 2020.	Irrelevant patient population
45	Kennedy-Martin T, Boye KS, Peng X. Cost of medication adherence and persistence in type 2 diabetes mellitus: a literature review. Patient preference & adherence 2017;11:1103-1117.	Irrelevant patient population

#	Reference	Reason for Exclusion
46	Kent S, Fusco F, Gray A, et al. Body mass index and healthcare costs: a systematic literature review of individual participant data studies. Obesity Reviews 2017;18:869-879.	No relevant HCRU outcomes reported
47	Khayyat SM, Walters PA, Whittlesea C, et al. Interventions developed to reduce secondary care utilisation in patients with type 2 diabetes mellitus: a narrative review. International Journal of Pharmacy Practice 2022;30:116-128.	Irrelevant patient population
48	Kingsbury SR, Smith LK, Czoski Murray CJ, et al. National Institute for Health and Care Research. Health and Social Care Delivery Research 2022;6:6.	No relevant HCRU outcomes reported
49	Knoedler MA, Jeffery MM, Philpot LM, et al. Risk Factors Associated With Health Care Utilization and Costs of Patients Undergoing Lower Extremity Joint Replacement. Mayo Clinic Proceedings. Innovations, Quality & Outcomes 2018;2:248-256.	No relevant HCRU outcomes reported
50	Lee AYL, Wong AKC, Hung TTM, et al. Nurse-led Telehealth Intervention for Rehabilitation (Telerehabilitation) Among Community-Dwelling Patients With Chronic Diseases: Systematic Review and Meta-analysis. Journal of Medical Internet Research 2022;24:e40364.	No relevant HCRU outcomes reported
51	Legg LA, Rudberg AS, Hua X, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database of Systematic Reviews 2021;11:CD009286.	No relevant HCRU outcomes reported
52	Li X, Tse VC, Au-Doung LW, et al. The impact of ischaemic stroke on atrial fibrillation-related healthcare cost: a systematic review. Europace 2017;19:937-947.	No relevant HCRU outcomes reported
53	Lin JS, Evans CV, Johnson E, et al. Agency for Healthcare Research and Quality 2018:07.	No relevant HCRU outcomes reported
54	Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database Of Systematic Reviews And Implementation Reports 2019;17:520-547.	No relevant HCRU outcomes reported
55	Luo ZY, Zhang T, Meng WK, et al. Cost comparing home-based rehabilitation with hospital-based rehabilitation following total joint replacement: Systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 2017;10(12):15825-15833.	No relevant HCRU outcomes reported
56	Marin S, Serra-Prat M, Ortega O, et al. Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review. BMJ Open 2020;10:e031629.	Irrelevant patient population
57	Moucheraud C, Lenz C, Latkovic M, et al. The costs of diabetes treatment in low- and middle-income countries: a systematic review. BMJ Global Health 2019;4:e001258.	Irrelevant patient population
58	Muller D, Stock S. Diabetes and cost of illness. [German]. Diabetologe 2019;15(6):504-513.	Irrelevant patient population
59	National Committee for Technology I. Empagliflozina e dapagliflozina para o tratamento de diabetes mellitus tipo 2. Brazil: National Committee for Technology Incorporation (CONITEC), 2020.	Irrelevant study design
60	Nepal G, Kharel S, Kumar Yadav J, et al. Low-dose alteplase for the management of acute ischemic stroke in South Asians: A systematic review on cost, efficacy and safety. Journal of Clinical Neuroscience 2022;103:92-99.	No relevant HCRU outcomes reported
61	Nombela Manzaneque N, Perez-Arechaederra D, Caperos Montalban JM. Side effects and practices to improve management of type 2 diabetes mellitus from the viewpoint of patient experience and health care management. A narrative review. Endocrinologia Diabetes Y Nutricion 2019;66:596-610.	Irrelevant study design

#	Reference	Reason for Exclusion
62	Nunez M, Diaz S, Dilla T, et al. Epidemiology, Quality of Life, and Costs Associated with Hypoglycemia in Patients with Diabetes in Spain: A Systematic Literature Review. Diabetes Therapy 2019;10(2):375-392.	Irrelevant patient population
63	Ohtsubo T, Shibata R, Kai H, et al. Angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in hypertensive patients with myocardial infarction or heart failure: a systematic review and meta-analysis. Hypertension Research - Clinical & Experimental 2019;42:641-649.	No relevant HCRU outcomes reported
64	Olm M, Stark RG, Beck N, et al. Impact of interventions to reduce overnutrition on healthcare costs related to obesity and type 2 diabetes: a systematic review. Nutrition Reviews 2020;78:412-435.	No relevant HCRU outcomes reported
65	Onggo JR, Onggo JD, De Steiger R, et al. Robotic-assisted total knee arthroplasty is comparable to conventional total knee arthroplasty: a meta-analysis and systematic review. Archives of Orthopaedic and Trauma Surgery 2020;140(10):1533-1549.	No relevant HCRU outcomes reported
66	Ontario H. Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Valve Stenosis at Low Surgical Risk. Canada: Ontario Health, 2020.	No relevant HCRU outcomes reported
67	Ontario H. Transcatheter Aortic Valve Implantation in Patients With Severe, Symptomatic Aortic Valve Stenosis at Intermediate Surgical Risk: A Health Technology Assessment. Canada: Ontario Health, 2020.	No relevant HCRU outcomes reported
68	Perera R, Stevens R, Aronson JK, et al. NIHR Journals Library. Programme Grants for Applied Research 2021;8:8.	No relevant HCRU outcomes reported
69	Perivoliotis K, Sioka E, Katsogridaki G, et al. Laparoscopic Gastric Plication versus Laparoscopic Sleeve Gastrectomy: An Up-to-Date Systematic Review and Meta-Analysis. Journal of Obesity 2018;2018 (no pagination).	No relevant HCRU outcomes reported
70	Petrucciani N, Boru CE, Lauteri G, et al. A Narrative Review on Bariatric ERAS. Chirurgia (Bucuresti) 2022;117:505-516.	No relevant HCRU outcomes reported
71	Pietrasik A, Gasecka A, Szarpak L, et al. Catheter-Based Therapies Decrease Mortality in Patients With Intermediate and High-Risk Pulmonary Embolism: Evidence From Meta-Analysis of 65,589 Patients. Frontiers in Cardiovascular Medicine 2022;9:861307.	Irrelevant patient population
72	Pousinho S, Morgado M, Placido AI, et al. Clinical pharmacists' interventions in the management of type 2 diabetes mellitus: a systematic review. Pharmacy Practice 2020;18:2000.	Irrelevant patient population
73	Pouwels XGLV, Wolff R, Ramaekers BLT, et al. Ticagrelor for Secondary Prevention of Atherothrombotic Events After Myocardial Infarction: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics 2018;36(5):533-543.	No relevant HCRU outcomes reported
74	Powell J, Piszczatoski C, Taylor JR. Oral Semaglutide: The First-available Noninjectable Glucagon-like Peptide 1 Receptor Agonist. Clinical Therapeutics 2020;42(10):2100-2116.	Irrelevant study design
75	Prasad SS, Duncanson K, Keely S, et al. A Role for Primary Care Pharmacists in the Management of Inflammatory Bowel Disease? Lessons from Chronic Disease: A Systematic Review. Pharmacy : A Journal Of Pharmacy Education And Practice 2020;8:02.	Irrelevant patient population
76	Price CI, White P, Balami J, et al. National Institute for Health and Care Research. Programme Grants for Applied Research 2022;5:5.	Irrelevant study design
77	Radwan H, Ballout RA, Hasan H, et al. The Epidemiology and Economic Burden of Obesity and Related Cardiometabolic Disorders in the United Arab Emirates: A Systematic Review and Qualitative Synthesis. Journal of Obesity 2018;2018:2185942.	No relevant HCRU outcomes reported

#	Reference	Reason for Exclusion
78	Rajsic S, Gothe H, Borba HH, et al. Economic burden of stroke: a systematic review on post-stroke care. European Journal of Health Economics 2019;20:107-134.	No relevant HCRU outcomes reported
79	Rawal L, Sahle BW, Smith BJ, et al. Lifestyle interventions for type 2 diabetes management among migrants and ethnic minorities living in industrialized countries: a systematic review and meta-analyses. BMJ Open Diabetes Research & Care 2021;9:04.	Irrelevant patient population
80	Reynolds AC, King N. Hybrid coronary revascularization versus conventional coronary artery bypass grafting: Systematic review and meta-analysis. Medicine 2018;97:Irrelevant study design1941.	No relevant HCRU outcomes reported
81	Rice JB, White AG, Scarpati LM, et al. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. Clinical Therapeutics 2017;39:2216-2229.	No relevant HCRU outcomes reported
82	Rinaldi G, Hijazi A, Haghparast-Bidgoli H. Cost and cost-effectiveness of mHealth interventions for the prevention and control of type 2 diabetes mellitus: A systematic review. Diabetes Research & Clinical Practice 2020;162:108084.	Irrelevant patient population
83	Robinson S, Boye KS, Mody R, et al. Real-World Effectiveness of Dulaglutide in Patients with Type 2 Diabetes Mellitus: A Literature Review. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2020;11:1437-1466.	Irrelevant patient population
84	Saumur TM, Gregor S, Xiong Y, et al. Quantifying the amount of physical rehabilitation received by individuals living with neurological conditions in the community: a scoping review. BMC Health Services Research 2022;22:349.	No relevant HCRU outcomes reported
85	Scherdjow A, Kiefer S, Luske J, et al. The Global Threat of Non-Communicable Diseases-Cost and Drivers for Diabetes Type 2 in Germany. Gesundheitsokonomie und Qualitatsmanagement. 2022.	Irrelevant study design
86	Sevick LK, Ghali S, Hill MD, et al. Systematic Review of the Cost and Cost-Effectiveness of Rapid Endovascular Therapy for Acute Ischemic Stroke. Stroke 2017;48:2519-2526.	No relevant HCRU outcomes reported
87	Suarez DF, Gangemi A. How Bad Is "Bad"? A Cost Consideration and Review of Laparoscopic Gastric Plication Versus Laparoscopic Sleeve Gastrectomy. Obesity Surgery 2021;31:307-316.	No relevant HCRU outcomes reported
88	Tremmel M, Gerdtham UG, Nilsson PM, et al. Economic Burden of Obesity: A Systematic Literature Review. International Journal of Environmental Research & Public Health [Electronic Resource] 2017;14:19.	No relevant HCRU outcomes reported
89	Vandenberghe D, Albrecht J. The financial burden of non-communicable diseases in the European Union: a systematic review. European Journal of Public Health 2020;30:833-839.	No relevant HCRU outcomes reported
90	Yang CY, Chen YR, Ou HT, et al. Cost-effectiveness of GLP-1 receptor agonists versus insulin for the treatment of type 2 diabetes: a real-world study and systematic review. Cardiovascular Diabetology 2021;20:21.	No relevant HCRU outcomes reported

C16. SLR – please provide pdfs of all studies excluded from the NMA at the full text stage (all publications for 123 studies).

The PDFs for all studies excluded from the NMA are provided in the reference pack accompanying these responses.

C17. The FAD for semaglutide states a 2-year maximum treatment duration. The FAD for liraglutide does not appear to do so. Please clarify this with reference to the economic modelling assumptions and Document B Table 56.

Table 56 of Document B states that in TA664, patients receiving liraglutide were modelled to receive treatment for 2 years. This reflects the Committee conclusions in the FAD for liraglutide, in which it was suggested that while a 2-year maximum treatment duration may not be ideal given that obesity is a chronic condition, it was reasonable for a 2-year stopping rule to be included in the model for liraglutide in the context of NHS Tier 3 SWMS,[23] which can only be accessed for up to 2 years.[3]

C18. The base case results of Document B Tables 109 and 110 suggest a slightly lower LYG and QALY for tirzepatide 10mg than for tirzepatide 5mg. Please provide an intuitive account of this with reference to the clinical effect estimates inputted to the model. Is this solely due to AEs and AE discontinuation rates?

The LYG and QALY results are lower for tirzepatide 10 mg compared to tirzepatide 5 mg in the base case, despite the key efficacy inputs (CfB in weight, SBP, HDL and total cholesterol) being more favourable for tirzepatide 10 mg compared to tirzepatide 5 mg. This is driven by a number of factors which include AE discontinuation and AE rates; prediabetes reversal also has a small impact. The impact of these parameters on the LYG and QALY results are further outlined in Table 96. Moreover, it should be noted that when these variables are equated between the two doses, higher LYG and QALYs are observed for tirzepatide 10 mg than tirzepatide 5 mg, as shown in Table 97.

Table 96: Factors contributing to increased QALYs and LYG for tirzepatide 10 mg vs tirzepatide 5 mg

Factor	Input value for tirzepatide 5 mg	Input value for tirzepatide 10 mg	Explanation
Annual discontinuation due to AE	3.11%	5.13%	The ongoing probability of discontinuing treatment is lower for tirzepatide 5 mg than tirzepatide 10 mg; thus, patients are likely to discontinue treatment sooner on tirzepatide 10 mg than on tirzepatide 5 mg over the modelled time horizon. Since patients' weight is modelled to increase to align with the expected weight increase if they had received diet and exercise alone, modelled patients may therefore have a greater weight in the tirzepatide 10 mg arm compared to the 5 mg arm at the same timepoint (driven by earlier discontinuation in the tirzepatide 10 mg arm), leading to overall worse outcomes in the tirzepatide 10 mg arm compared with the tirzepatide 5 mg arm. The potential for patients in the

			tirzepatide 10 mg arm to have a greater weight than patients in the 5 mg arm at a specific timepoint also impacts the likelihood of other events, such as bariatric surgery, which further contribute to the QALY and LYG differences observed.
Annual proportion of patients experiencing severe or serious GI AEs	1.23%	2.26%	The probability of experiencing AEs is higher in the tirzepatide 10 mg arm than the tirzepatide 5 mg arm. Therefore, a greater overall disutility due to AEs is applied to the average patient in the tirzepatide 10 mg arm compared to the tirzepatide 5 mg arm.
Proportion of patients experiencing reversal of prediabetes upon initiating treatment	94.44%	93.95%	The proportion of patients experiencing prediabetes reversal is lower for tirzepatide 10 mg than tirzepatide 5 mg; this leads to an increased proportion of patients in the prediabetic health state and hence an increased chance of developing T2DM earlier in the 10 mg arm (which subsequently leads to lower utility values and LYGs). This also impacts the likelihood of other events, such as bariatric surgery.

Abbreviations: AE: adverse event; GI: gastrointestinal; LY: life year; QALY: quality-adjusted life year; T2DM: type 2 diabetes mellitus.

Table 97: Scenarios investigating LYs and QALYs for tirzepatide 5 mg vs tirzepatide 10 mg

Scenario	Tirzepatide 5 mg		Tirzepatide 10 mg	
	LYG	QALYs	LYG	QALYs
Corrected company base case	19.200	16.686	19.162	16.658
Results when tirzepatide 5 mg values for AEs, discontinuation due to AEs and prediabetes reversal are replaced with tirzepatide 10 mg values	19.126	16.561	19.162	16.658

Abbreviations: AE: adverse event; GI: gastrointestinal; LYG: life year gain; QALY: quality-adjusted life year.

C19. Document B Section B.3.3.2.1 - 1st paragraph, when read literally, states that the proportions with prediabetes at baseline differ between tirzepatide and semaglutide. Please clarify if this is the case or if the proportions with pre-diabetes are equal at baseline but the subsequent treatment effects upon pre-diabetes reversal differ between tirzepatide and semaglutide. If the baseline proportions differ between treatments, please augment Table 68 with the values for semaglutide and liraglutide.

The Company would like to clarify that as per the interpretation of the EAG, the proportion of simulated patients with pre-diabetes at baseline are equal between the tirzepatide and semaglutide arms (assuming they are patients within the same subgroup), but that subsequent

treatment effects upon pre-diabetes reversal differ between tirzepatide and semaglutide, as shown by the different proportions experiencing prediabetes reversal in the tirzepatide and semaglutide arms in Table 69 in the CS.

C20. The EAG is having some difficulty sourcing the QDiabetes Model B and Model C coefficients of Hippisley-Cox et al 2017a. It would be much appreciated if an electronic link could be provided to these.

The coefficients were extracted from the source code of the algorithm used in Model B and Model C. The source code is available online here: https://qdiabetes.org/2018/src.php. For reference, the coefficients for each model and gender are found under the sections labelled "Sum from continuous values". The coefficients for Model C can also be found in Appendix M of NICE 2020 (TA664).

C21. Some of the risk functions are duplicated within the Risk Equations worksheet. Is there any intention behind this and what if any effect does it have upon the modelling?

Firstly, the Company would like to thank the EAG for identifying the repeated tables in the Risk Equations tab; these were unnecessary duplicates, but had no impact on results. The following amendments have been made to rectify this, resulting in no changes to the model results:

- Rows 225–369 have been deleted
    - These were all duplicate rows, not used in any named ranges or modelling in any other way
- The data store has been updated to reflect these changes

Further updates to the Risk Equations tab include:

- Updating text in cell I14 to QDiabetes (Model C), instead of Model B
- Removing 'Base Case' from cell H29, and adding it to cell H80

Please note that the QDiabetes (Model B) section beginning in row 31 and its respective named range (rng_RE_T2DM_QDiabetes_B) are not used in the model, and are presented for reference only. As per the response to B7, Model C is the recommend risk equation as, unlike Model B, it includes HbA1c, which is important for the prediction of T2DM, in particular in order to differentiate the risk of developing T2DM between individuals with and without prediabetes. This method aligns with the approach taken in TA875 and TA664.[3, 23]

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Single Technology Appraisal
Tirzepatide for managing overweight and obesity [ID6179]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**Sarah Le Brocq**
2. Name of organisation	All About Obesity (AAO)
3. Job title or position	Director
4a. Brief description of the organisation (including who funds it). How many members does it have?	All About Obesity is a third sector organisation, we aim to be the leading trusted source of information and educational resources, for people living with obesity, HCP's and policy makers. Our primary objective is to drive research in obesity as well as campaign for better treatments and support for people living with obesity. We have been funded to date by Novo Nordisk, Lilly and the NHS. We are not a membership organisation yet. We have a steering group of lived experience members of approx. 10 people.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes, we have received corporate sponsorship from Lilly of £25,000 to support the running of the organisation, build of website and creation of resources.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	**I have my own experience of living with obesity and we also have a steering group of approx. 10 people that have lived experience of obesity that have shared their thoughts.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with obesity feels very shameful, I have spent the majority of my adult life blaming myself for living the condition and have been made to feel that way by society, HCP's, policy makers and the media. You are fighting against the stigma and discrimination of obesity on a daily basis. You don't know where to go to get advice or support, you feel like you are hitting brick walls repeatedly. Caring for someone living with obesity is frustrating because there are not enough services, resources or support for people.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Patients are very frustrated at the limited access to weight management treatments, historically there has only really been diet and exercise advice, orlistat or bariatric surgery, which is very restrictive.** **More recently with the addition of Liraglutide and Semaglutide, this has given patients hope, however being able to access these treatments is difficult and very much a postcode lottery at the moment, which is frustrating.** **The more therapeutic indications that are available for people living with obesity the better, because one size will not fit all.**
8. Is there an unmet need for patients with this condition?	Yes, patients need to be able to manage the chronic long term condition of obesity, with a long term medication. Currently there is a 2 year cap to GLP-1 treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**The weight loss that is being seen in the clinical trials of 20-25% is very similar to that seen with bariatric surgery, so this gives patients the opportunity to lose a significant amount of weight and hopefully maintain it, without the need of surgery.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It Is an injectable, which puts some people off and the side effects of nausea/GI

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People that are not suitable for surgery would benefit for these treatments.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The delivery of the technology will be important, currently GLP-1's can only be delivered through specialist weight management services, and only 50% of the country has access to weight management services, so that is restricting a large portion of the population and creating postcode lottery effect.

Other issues

13. Are there any other issues that you would like the committee to consider?	I would like to see more exploration/scope of prescribing within primary care. No caps on treatment length

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Much needed technology that is providing hope to people living with obesity that they will be able to live healthier lives and maintain a healthier weight. • Weight loss results matching bariatric surgery outcomes. • More choice when it comes to pharmaceutical interventions. • I bring a wealth of lived experience knowledge to the TA •

Thank you for your time.

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Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	The Association for the Study of Obesity (ASO)
3. Job title or position	ASO Trustee; [redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify): representative of ASO representing clinicians and non-clinicians with expertise in Obesity.
5a. Brief description of the organisation (including who funds it).	Founded in 1967, the ASO has become the UK's foremost charitable organisation dedicated to the understanding, prevention and treatment of obesity. The ASO aims to develop an understanding of obesity through the pursuit of excellence in research and education, the facilitation of contact between individuals and organisations, and the promotion of action to prevent and treat obesity.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]

If so, please state the name of manufacturer, amount, and purpose of funding.

Novo Nordisk

The funding below was received from Novo Nordisk. None is ongoing. None is related to Tirzepatide

Invoice date	Gross	
27/7/2022	£11896.80	Sponsorship of June ASO webinar (30/06/2022)
31/8/2022	£11896.80	Sponsorship of September ASO webinar (29/09/2022)
31/8/2022	£15000	UK Congress on Obesity (UKCO) 2022 Principal sponsor
08 Dec 2022	£11896.80	Sponsorship of December ASO webinar (29/09/2022)

The publication from the ASO annual conference 2021 was published in 2023: Luli M, Yeo G, Farrell E, Ogden J, Parretti H, Frew E, Bevan S, Brown A, Logue J, Menon V, Isack N, Lean M, McEwan C, Gately P, Williams S, Astbury N, Bryant M, Clare K, Dimitriadis GK, Finlayson G, Heslehurst N, Johnson B, Le Brocq S, Roberts A, McGinley P, Mueller J, O'Kane M, Batterham RL, Miras AD. The implications of defining obesity as a disease: a report from the Association for the Study of Obesity 2021 annual conference. EClinicalMedicine. 2023 Apr 6;58:101962. doi: 10.1016/j.eclinm.2023.101962. PMID: 37090435; PMCID: PMC10119881. Novo Nordisk was one of the sponsors of the annual meeting in 2021.

The ASO is reporting the funding received during the previous 12 months as requested from NICE, and that this will differ to the sponsorship that the ASO has received as reported on Disclosure UK which reports funding for the calendar year, January to December.

	The ASO does not accept corporate sponsorship for undefined activities and all sponsorship is for specific activities as described in our sponsorship policy which is publicly available on our website (https://aso.org.uk/sponsorship-and-collaborative-partnerships).
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent the complications of obesity
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	>10% weight loss
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is major need to support people with obesity in weight loss.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treated through the tiered system, with lifestyle modification, limited pharmacotherapy options and bariatric surgery
9a. Are any clinical guidelines used in the	NICE Clinical Guidelines 189 Obesity

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined, but the provision of obesity services nationally is suboptimal and variable.
9c. What impact would the technology have on the current pathway of care?	The medication would facilitate the pathway and deliver significant improvement in quality of life while at the same time reducing the complications of obesity.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it would be a substantial improvement on the current best pharmacotherapy (liraglutide). It is noted that the semaglutide 2.4mg once weekly has been approved by NICE, but currently has not been launched in the UK. Indirect comparisons between tirzepatide 10 and 15mg and semaglutide 2.4mg suggest that tirzepatide at both these doses may be more effective in terms of weight loss.
10a. How does healthcare resource use differ between the technology and current care?	Similar
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with tirzepatide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years. This has disadvantaged patients who are being looked after in a community tier 3 service, whom the medication should also be available to. Moreover, semaglutide 2.4mg once weekly has been approved for a duration of 2 years, which is also problematic, as ceasing medication leads to weight regain as demonstrated at STEP-1 extension study. The committee should also consider other health economic models for tirzepatide that may make it more cost-effective. This includes its use in the primary care setting (Tier 2) and led by General practitioners, instead of

	purely in specialist weight management service (Tier 3). A similar successful model has been applied to the care of people with diabetes who are now predominantly looked after in the community but have access to a Community Consultant Diabetologist when necessary. Similar to semaglutide 2.4mg once weekly TA guideline (875), we feel that a multidisciplinary team including dietitian should support lifestyle changes and nutritional advise at initiation and weight loss phase with tirzepatide (either in primary care or in specialist weight management services).
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It may require training of the multidisciplinary team on monitoring for potential adverse events with the medication.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it is the most effective medication for obesity available currently.
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Vast majority of people living with obesity and especially those with class II obesity and above (BMI>35) with obesity-related complications will benefit from tirzepatide (5 to 15mg dose). Tirzepatide 15mg together with a moderate intensity lifestyle programme (SURMOUNT-1 and SURMOUNT-2 studies) leads to 14.7% weight loss in people with type 2 diabetes (T2D) and 20.9% weight loss in people without diabetes. It may also be particularly beneficial for people with Metabolic Associated Steatotic Liver Disease, as recent evidence suggests that it can reduce the liver fat content in people with T2D levels which may be associated with improvement in steatosis/fibrosis.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Multiple titration steps that may require some more close monitoring during the first months after initiation of the treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The usual stopping rule of 5% weight loss after full titration of the medication dose should apply (if patients don't lose 5% of their weight after 24 weeks on treatment, then the drug should be stopped. This will stop the use of the medication in patients who do not respond. The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with tirzepatide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years.

	Whilst we appreciate the health economic analyses, it is uncommon to treat a chronic disease like Obesity for 2 years and then stop. Discontinuation of the medication almost inevitably leads to disease relapse. We therefore recommend that if tirzepatide is effective, it should be continued long term. No additional testing needed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Some people with type 2 diabetes and obesity treated with tirzepatide will achieve diabetes remission. The health economic models are not always able to capture this benefit. Moreover, it is likely that there will be improvement in Metabolic Associated Steatotic Liver Disease, as recent evidence suggests that it can reduce the liver fat content in levels which may be associated with improvement in steatosis/fibrosis.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Most people will achieve >15% weight loss which appears to be required to reverse many of the complications of obesity.
16a. Is the technology a 'step-change' in the management of the condition?	Tirzepatide 10 and 15mg once weekly are the most effective treatments for Obesity at the current moment, causing approximately 5% more weight loss than semaglutide 2.4mg once weekly (Wegovy) and almost tripled the weight loss observed by Saxenda. It is therefore a step-change in the

	management of the condition as this weight loss is expected to improve quality of life, ameliorate obesity-related complications and avoid the need for bariatric surgery for some patients. It is also likely to facilitate other treatments these patients need for obesity-related complications e.g., in vitro fertilisation, joint replacement surgery.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, patients at high risk of the complications of obesity are not provided treatments which can reverse the existing complications.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are similar to the existing treatments for obesity (such as Saxenda and Wegovy), thus no change in management required.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, weight loss and improvement in obesity-related complications such as type 2 diabetes, hypertension and dyslipidaemia (>85% achieved HbA1c< 7%).

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate measures were used for cardiovascular event prevention (blood pressure, lipid improvement). These are the standard measures used.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	Not specifically for obesity.
21. How do data on real-world experience compare with the trial data?	Very limited currently real-world data (only from US in people with type 2 diabetes). It is noted that tirzepatide has currently been approved for treatment of type 2 diabetes, but not for treatment of obesity. It is expected that will receive approval for management of obesity until the end of 2023.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with Semaglutide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years. This has disadvantaged patients who are being looked after in a community tier 3 service, whom the medication should also be available to. Moreover, people with mental health disorders (especially those receiving atypical antipsychotic medication) may have increased risks of developing obesity. However, their ability to access Tirzepatide may be hindered by their mental health condition. Similarly, people with disabilities are disproportionately affected by obesity and their ability to access treatment for obesity may be adversely impacted by their disability. Tirzepatide may provide suitable weight loss in people with disabilities who may not be able to provide consent and/or may not be eligible for bariatric surgery. These considerations should be taken into account.
22b. Consider whether these issues are different from issues with current care and why.	Similar to current care

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Most effective obesity therapy available currently - mean weight loss with tirzepatide 5mg is 15% at 72 weeks and mean weight loss with tirzepatide 10 and 15mg is around 20% at 72 weeks. • Effect on glucose which is independent of the effect on weight (so people with T2D may benefit even with less weight loss) • Obesity is a chronic disease, so as with any chronic disease requires long-term management with the treatment that works (stopping the medication at 2 years will not be appropriate for responders to treatment) • Needs to be prescribed both in primary care and secondary care with support from a MDT team.

Thank you for your time.

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Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Obesity Metabolic Surgery Society
3. Job title or position	Consultant Surgeon, Council Member BOMSS
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	BOMSS is a society of surgeons and other health professionals (physicians, nurses, dieticians, psychologists and GPs) who specialise in the treatment of severe obesity and its metabolic complications.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce weight and improve obesity related comorbidities and increase life expectancy
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Total body weight loss of more than 15%
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Huge. Given the main study was done in patients with BMI>27 that is almost the whole adult population now.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Other medications – saxenda. Bariatric surgery
9a. Are any clinical guidelines used in the	Current NICE Guidance CG189. NICE TA 664. NICE TA875

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined pathway Regional variation base on NICE guidance
9c. What impact would the technology have on the current pathway of care?	Current evidence base suggests that Tirzepatide is far superior to other medications currently used (saxenda/weogvy) and could be used in place of these for superior results.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There is regional variation across the country in current use of saxenda/wegovy due to costs and not all ICB's funding. I would anticipate similar variability for similar reasons with Tirzepatide
10a. How does healthcare resource use differ between the technology and current care?	similar
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribed by a specialist within a multidisciplinary team managing patients with complex obesity. Given the whole population nearly has a bmi >27 then it may be that this will have to be targeted more due to NHS restraints. I would not use routinely in patients with BMI 45 as they would be best served by surgery and whilst you could use tirzepatide as a bridge to surgery in someone with extremely high BMI I don't believe there is cost benefit to routinely using tirzepatide for those who are likely to need surgery.
10c. What investment is needed to introduce the technology? (For example,	Minimal as the MDT's exist already

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as improvements in weight and comorbidity. The question is for how long and whether patients will need to stay on for every/long term or once reached lower weight stop, see if weight regains and if so restart.
11a. Do you expect the technology to increase length of life more than current care?	Yes if results can be maintained
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Similar as similar medications currently prescribed. Tirzepatide is only once a week compared to daily of others so less sharp disposal etc

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To Start need BMI 30 or above or 27 with one obesity related comorbidity
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
16a. Is the technology a 'step-change' in the	Yes. Significant increase in weight loss compared to previous medications

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes so many struggled with obesity disease
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Current UK practice uses earlier GLP1/GIP so these new trials does reflect but with a newer medication
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Weight loss, hba1c reduction, weight loss maintainence Yes though we still need the longer term data about what happens to those who stop using the medication
18c. If surrogate outcome measures were used, do they adequately predict	n/a

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	Not specifically around medications but bariatric surgery evidence still mounts confirming it is the most effective and enduring treatment for complex obesity
21. How do data on real-world experience compare with the trial data?	Match in my experience

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Only with availability around the UK – will all ICB adopt?
22b. Consider whether these issues are different from issues with current care and why.	no

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Target those with raised BMI • Given only by specialist within specialist MDT dealing with complex obesity • In theory too many are eligible and the NHS cannot afford to treat all • How long should patients be on it • Will all ICB's adopt

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tirzepatide for managing overweight and obesity [ID6179]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is the country's leading diabetes charity representing the 4.9 million people living with diabetes in the UK. We help people manage their diabetes effectively by providing information, advice and support. We campaign with people with diabetes and healthcare professionals to improve the quality of diabetes care across the UK's health services. We fund pioneering research into care, cure and prevention for all types of diabetes. In addition to this we are supporting the 2 million people with non-diabetic hyperglycaemia currently at high risk of developing type 2 diabetes, of which obesity is a major risk factor. We are increasing awareness and supporting these individuals to make lifestyle changes that will lower their risk, including lowering their bodyweight. The majority of Diabetes UK's income is from legacies and donations. We also earn income from activities which support our charitable mission, such as our Diabetes UK Professional Conference. A small percentage of our income is from support for specific programmes of work from or sponsorship of events by the pharmaceutical industry.

	We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families – and more than 100,000 lay and healthcare professional members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Eli Lilly - £229,259 supporting our CPD programme <u>Comparator Funding</u> Novo Nordisk £174,345 supporting our Clinical Champions programme and as a conference exhibitor Sanofi £70,500 as a conference sponsor All are ongoing partnerships
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Focus groups completed by Diabetes UK Obesity Health Alliance (OHA) report on weight management services Evidence reviews

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with obesity or overweight increases a person's risk of developing type 2 diabetes and around 90% of people with (newly diagnosed) type 2 diabetes are living with obesity or overweight. Two thirds of the UK population are currently classified as having obesity or overweight and many experience significant stigma as a result. Many of these people would benefit from being able to access support to help them to lose weight and maintain weight loss.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Effective treatment of overweight and obesity reduces adverse health effects including improvements in blood pressure, HDL & LDL cholesterol levels and insulin resistance. Currently GLP-1 RAs Wegovy (semaglutide) and Saxenda (liraglutide), and Orlistats Alli and Xenical are licensed for weight loss within the UK. GLP-1 RAs have been shown to be the most effective method of reducing body weight using drugs, with semaglutide and liraglutide reducing body weight by a mean of 14.9% and 6% respectively. Although both have been approved by NICE to be used within the NHS, Wegovy is yet to be launched due to supply issues and Saxenda has been affected by national GLP-1 shortages. As a result, patients have limited access to GLP-1s for managing overweight and obesity. GLP-1s licensed for managing Type 2 diabetes have also been used off-label to treat overweight and obesity, however, this off-label prescribing has contributed to shortages and DHSC guidance is that prescriptions are only issued for licensed use. Access to GLP-1s is achieved through referral to a specialist weight management service. Evidence raised in the 2018 Obesity APPG found that tier 3 services were commissioned in only 57% of (then) CCGs. Subsequently, a major barrier to accessing GLP-1s is the ability to access the services required to be prescribed these drugs. This is exacerbated by a lack of consistent funding for weight management services with a short-term view often being taken. This leads services to rely on multiple funding sources that are difficult for both clinicians and patients to navigate. Specialist weight management services (including tier 3 services) offer multi-component programmes which can be delivered to an individual or in group sessions, including exercise classes, psychological support and motivational interviewing. There is currently a lack of evaluation and clear evidence on what is the most effective non-pharmacological/surgical interventions within tier 3 weight management services. Systematic reviews have highlighted that tier 3 services in the UK are found to reduce weight considerably to improve other health outcomes but this affect wanes 6 months after the intervention. People with type 2 diabetes have told Diabetes UK that keeping weight off in the long term is a key challenge to them and that services that offer long term support appeal for this reason. Most people within focus groups carried out by Diabetes UK reported that they consistently struggle to access the tier 3 services, but those who have state that the attention to their psychological needs had been instrumental in supporting their weight loss. The DiRECT trial into low calorie diets to achieve remission in type 2 diabetes via weight loss has highlighted that long term weight loss is possible with the right level of support. Participants in the original trial highlighted that person centred, flexible, and ongoing support with healthcare professionals was vital to their weight loss and to their ability to mainitain this.

	Bariatric surgery is the most effective treatment for severe obesity, leading to remission or resolution of obesity related co-morbidities and improved life expectancy. For example, there is evidence that bariatric surgery can lead to remission of type 2 diabetes in 30–62% of individuals following surgery. In adults, gastric bypass produces the greatest long-term weight change of any intervention or weight-management programme, delivering significant cost-benefit over 30 years. In England, bariatric surgery is recommended by NICE for people with a body mass index (BMI) over 40 kg/m2, with lower thresholds for those with medical conditions that are likely to be improved with weight loss and for those from ethnic minority backgrounds who are at greater risk of weight related medical conditions. NICE also recommends that expediated assessment for surgery is offered to people with a BMI over 35 who have been diagnosed with type 2 diabetes with the past 10 years (as long as they are willing or have already received assessment in a specialist weight management service). However, the NHS currently offers surgery to just 6,000 of the 2 million eligible adults each year, one of the lowest rates of any high-income country. Less than 1 per cent of those who could benefit receive this treatment option and there is significant regional variation in patients' ability to access bariatric surgery within the UK. One of the key reasons for the lack of surgeries is that there is not enough tier 3 or 4 services on offer in the UK. Diabetes UK have also found there is significant stigmatising attitudes towards surgery from both HCPs and people with diabetes which prevents people from accessing this effective weight loss option. Broader insight work into barriers to weight management services by Diabetes UK carried out recently highlights key issues impacting their success. The insight work included perspectives of providers of tier 3 and 4 services and the perspectives of people living with type 2 diabetes. Diabetes UK found that: • Support and signposting about weight management was not regularly offered • Stigmatising exchanges with healthcare professional have a large impact on access and completion of weight management services • Peer support was an important component in achieving weight loss aims, and services that facilitate this are likely to achieve better results • Person-centred support, particularly for those with comorbidities such as type 2 diabetes, is key to successful weight management.

8. Is there an unmet need for patients with this condition?	Currently there are limited available/accessible GLP-1 receptor agonists licensed for managing overweight and obesity. The current shortage of GLP-1s has, rightly, led to guidance to restrict off-label use for managing overweight and obesity in order to prioritise those with type 2 diabetes. There is a need for further drugs for managing overweight and obesity, such as Tirzepatide, to be approved and made accessible to provide more options for patients, particularly in the face of the current supply issues.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People with type 2 diabetes are concerned to lower their blood glucose without using medication that promotes weight gain. Some are unable to lose weight through diet and exercise. Tirzepatide has been shown to be incredibly effective at lowering body weight and HbA1C when compared to other available weight loss medications, reducing body weight by 26.6%, compared to a mean weight loss of 14.9% when using Wegovy.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know there are significant health inequalities that lead to and exacerbate overweight and obesity, and disproportionately affect lower socio-economic communities. A contributing factor to the current GLP-1 RA shortage is the use of private healthcare services to access these drugs. It has been reported that approximately 50% of GLP-1s are accessed through private healthcare services. For those from lower socioeconomic backgrounds who are unable to afford private healthcare, access to GLP-1s is dependent on limited availability within the NHS. The decision to approve Tirzepatide for obesity and overweight would result in greater and more effective treatment options for patients with overweight and obesity from all backgrounds. It is important that provision of specialist weight management services is improved to increase the number of patients that have access to GLP-1s. In addition, this will reduce the need for patients to turn to private healthcare services, which will increase supply of GLP-1s to the NHS and promote equitable access. Continued efforts must be made to accelerate access to tier 3 services to prevent a socioeconomic divide.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Approval will provide greater options for treatment of overweight and obesity • The ability for this to be prescribed on the NHS will reduce unequal access currently seen with off-label use • • •

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External Assessment Group's report draft

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mubarak Patel critiqued statistical analysis in the company submission. Emma Loveman critiqued clinical effectiveness evidence. Rachel Court critiqued the company's searches and conducted additional EAG searches. Jill Colquitt reviewed clinical effectiveness evidence and report. Richard Hill shadowed this appraisal and provided support to clinical effectiveness evidence.Ewen Cummins critiqued the cost-effectiveness evidence and undertook EAG's modelling. Lena Al-Khudairy supported the critique of the clinical effectiveness evidence, coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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Executive summary

The CS provided evidence comparing tirzepatide one weekly maintenance doses of 5 mg, 10 mg and 15 mg in addition to diet and exercise with placebo in addition to diet and exercise. One study was identified in the company SLR, SURMOUNT-1, which is an international double-blind placebo-controlled phase III RCT. SURMOUNT-1 is ongoing but the primary efficacy analysis at 72 weeks has been undertaken.

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition in section 1, technology and evidence and information on non-key issues are in the main EAG report in sections 2, and 3.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID 6179	Summary of issue	Report sections
Issue 1	Trial evidence and the focus of the CS	1.3, 2.2.7, 2.3.6
Issue 2	The dose administration of tirzepatide in the trial evidence was not reflective of how tirzepatide will be used in clinical practice	2.2.3
Issue 3	NMA heterogeneity (NMA base case)	2.5.1
Issue 4	NMA heterogeneity (lipid markers definitions)	2.3.4
Issue 5	The company assumes that semaglutide and liraglutide have 2-year stopping rules but that tirzepatide use is ongoing.	5.1, 5.2.6
Issue 6	The company assumes that active treatment occurs in primary care. Current guidelines for semaglutide and liraglutide are that it occurs in secondary care.	5.4.1
Issue 7	The company assumes that after treatment cessation weight will be regained over a 3 year period. There is evidence from the semaglutide and liraglutide trials that weight regain is quicker than this.	5.2.7
Issue 8	The company assumes that the end of trial weight loss will be maintained while on treatment. There is evidence from the liraglutide trial that the treatment effect may wane in the medium term.	5.2.7
Issue 9	Related to the above issue, the company assumes that those on placebo will have an ongoing annual increase in weight. The net effect of treatment increases to more than that observed in the trials, this net effect increasing over time.	3.1.12
Issue 10	The proportion with prediabetes reversal and the proportion with at least 5% weight loss for placebo differed between the trials. The estimates for these are taken from the active treatment arms of the trials without controlling for the placebo effect.	2.5.2

ID 6179	Summary of issue	Report sections
Issue 11	There are quite large cost offsets from preventing or delaying the onset of diabetes. The company annual cost for diabetes without complications of £1,771 is based upon averaging some hospital costs. The EAG prefers an estimate of £674 derived from the UKPDS study.	5.4.2
Issue 12	Due to data availability the company assumes that BMI related mortality multipliers do not vary with age. Other evidence suggests that they vary strongly with age. Data availability means that this may not be quantifiable, but it somewhat increases modelling uncertainty.	5.2.2
Issue 13	The annualization of multi-year event risks seems likely to estimate events occurring too soon, and too many events occurring.	5.2.17

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Note that all cost effectiveness estimates are based upon the prices assumed by the company. Semaglutide and liraglutide have commercially confidential prices. The results from applying these prices are presented in a confidential appendix.

The company target group is the subset of the SURMOUNT-1 trial for which semaglutide was approved under TA875: those with a BMI ≥ 30 kgm^{-2} and at least one obesity related comorbidity. The company modelling assumes that active treatments are administered in primary care, that semaglutide and where relevant liraglutide have a 2-year stopping rule and that tirzepatide is continued indefinitely or until adverse events cause treatment discontinuation.

In line with the NICE methods guide the EAG presents a fully incremental analysis, also presenting the pairwise cost effectiveness estimates for a comparison with semaglutide and a comparison with placebo.

Table 2. Company base case cost effectiveness estimates: Deterministic

			Cost per QALY		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	£24,598	15.986	..	..	..
SEMA	£24,730	16.153	£785	..	£785
TIRZ 10mg	£32,454	16.653	Ext. Dom	£15,454	£11,777
TIRZ 5mg	£32,593	16.680	£14,910	£14,910	£11,510
TIRZ 15mg	£34,591	16.767	£23,076	£16,062	£12,792

The modelling assumptions that have the largest quantifiable effect are:

- Whether a 2-year stopping rule should be applied and if so for which treatments.
- Whether it is reasonable to model that the treatment effect increases over time by assuming weight increases for those off treatment but not for those on treatment.
- Whether discontinuations due to adverse events are ongoing or largely occur during the first year with few thereafter.
- Whether treatments are administered in primary care or a tier 3 Specialised Weight Management Service (SWMS), and if the latter what the annual costs of SWMS are.
- What additional annual cost should be applied for those developing diabetes but without any of the complications of diabetes.

Other modelling assumptions whose effect has not been quantified but which may have a large impact upon results are:

- BMI mortality multipliers being affected by age.
- A possible waning of the treatment effect not having been explored.
- Assuming that at baseline patients have none of the complications of obesity that are modelled.

- Applying the same clinical effect estimates to those who respond with a weight loss of at least 5% and so continue with treatment as to those who do not respond and so cease treatment.

The annualised risk equations possibly bringing forward the modelled events and probably estimating too many events.

1.3 *The decision problem: summary of the EAG's key issues*

Issue 1: There are generalisability issues with the trial evidence and the focus of the CS

Report section	1.3, 2.2.3
Description of issue and why the EAG has identified it as important	The NICE scope includes people with BMI ≥27 to <30 and at least one weight-related comorbidity. The whole trial population of SURMOUNT-1 included people with BMI ≥27 to <30, but limited to those with at least one of hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. People with BMI ≥27 to <30 other weight-related comorbidities such as chronic kidney disease were excluded, and people with prediabetes were only eligible if they also had one of the four specified comorbidities. The population with BMI ≥27 to <30 and comorbidities was also excluded from the company's base case and was not analysed as a separate subgroup. In addition, SURMOUNT-1 eligibility did not allow for reduced BMI thresholds for people from some ethnic backgrounds and therefore there is no evidence available for these subgroups.
What alternative approach has the EAG suggested?	No comparison is possible due to a lack of available data for the relevant subgroups.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence of the effectiveness of tirzepatide in the people with BMI ≥27 to <30 with different weight-related comorbidities and in different ethnic backgrounds with lower BMI thresholds would improve the generalisability of the evidence base. The EAG is aware of ongoing studies of tirzepatide that address some of these issues.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2: The dose administration of tirzepatide in the trial evidence was not reflective of how tirzepatide will be used in clinical practice

Report section	2.2.3
Description of issue and why the EAG has identified it as important	In clinical practice, the maintenance dose of tirzepatide is decided by an individual's response on weight measures and adverse events, although guidance on the amount of weight loss that should occur for a decision to maintain at 5mg or to increase to 10 mg and then to 15 mg is not provided in the draft SmPC. In SURMOUNT-1 participants in each of the three dose arms could only receive the maximum maintenance dose they were allocated to. The economic models each arm of the SURMOUNT-1 trial separately. It is also unclear if the escalation and de-escalations of doses in SURMOUNT-1 during titration had an impact on the relative effectiveness of the doses or the adverse events because no data were provided. This may to lead to biased estimates of effectiveness and cost effectiveness, but the direction of this potential bias is unclear.
What alternative approach has the EAG suggested?	No analysis was possible due to a lack of available data for the average doses used in SURMOUNT-1 or when de-escalations occurred.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence comparing doses as they would be titrated and used in clinical practice would provide supportive information to assess the validity of the treatment effect seen.

Issue 3: NMA heterogeneity (NMA base case)

Report section	2.5.1
Description of issue and why the EAG has identified it as important	Statistical heterogeneity where the I-squared of the base case NMA and the NMA of the whole trial population were, for some outcomes (mainly change from baseline in HDL and total cholesterol) 69% or more.
What alternative approach has the EAG suggested?	Investigate sources of heterogeneity, conduct sensitivity analyses to assess the impact of different modelling assumptions and statistical methods, explore clinical and methodological factors influencing heterogeneity, consider conducting meta-regression to examine relationships between patient-level characteristics and treatment effects, and effectively communicate the associated uncertainty in the results.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Exploration of the feasibility of a meta-regression, or a breakdown of the factors that heavily influence heterogeneity.

Issue 4: NMA heterogeneity (lipid markers definitions)

Report section	2.3.4
Description of issue and why the EAG has identified it as important	Differences in the definitions of the change from baseline in HDL and total cholesterol outcomes between studies.
What alternative approach has the EAG suggested?	This was due to the absence of necessary data, as converting absolute change to percentage change required data that is not available in the related studies.
What is the expected effect on the cost-effectiveness estimates?	Unknown but it would potentially benefit the intervention.
What additional evidence or analyses might help to resolve this key issue?	Group studies based on similar outcome definitions and perform separate analyses on these. Further sensitivity analyses excluding the studies with divergent outcome definitions

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 5: 2-year stopping rules

Report section	5.1, 5.2.6
Why important	The company base case assumes tirzepatide treatment is ongoing but semaglutide and liraglutide treatment is withdrawn at 2 years.
EAG alternative approach	Assuming that all treatments have a 2-year stopping rule or that no treatments have a 2-year stopping rule.
Effect on ICER	If all treatments have a 2-year stopping rule the company base case ICER for tirzepatide 15mg compared to placebo improves from £12,792 to £5,343 per QALY, and compared to semaglutide worsens from £16,062 to £18,534 per QALY. If no treatments have a 2-year stopping rule the ICER for tirzepatide 15mg compared to placebo is unchanged, and compared to semaglutide worsens from £16,062 to £23,622 per QALY.
Additional evidence or analyses.	None.

Issue 6: Will treatments be in primary care or secondary care?

Report section	5.4.1
Why important	The company base case assumes that while on active treatments patient treatment and monitoring is given in primary care. Current NICE guidance for semaglutide and liraglutide is that this should be in secondary care. This affects the ongoing treatment and monitoring costs. It may also affect whether any confidential prices for tirzepatide, semaglutide and liraglutide will apply.
EAG alternative approach	Assuming that all active treatments occur in secondary care, and assuming the semaglutide and liraglutide occur in secondary care but that tirzepatide occurs in primary care. The EAG assumes that secondary care is more intensive in the first year, but thereafter requires 2 consultant OP visits and 4 dietician OP visits annually*.
Effect on ICER	If all active treatments occur in secondary care the company base case ICER for tirzepatide 15mg compared to placebo worsens from £12,792 to £23,315 per QALY, and compared to semaglutide worsens from £16,062 to £25,745 per QALY.
Additional evidence or analyses.	Expert opinion about the first year and subsequent years costs of Specialist Weight Management Services.

* The EAG assumption is that the company primary care costs are applied to all patients throughout. If these are only applied to active treatments the EAG SWMS ongoing annual cost relates to quarterly consultant OP visits rather than six monthly consultant OP visits, in addition to the quarterly dietician OP visits.

Issue 7: How quickly is effect lost after treatment cessation

Report section	5.2.7
Why important	The company assumes that when treatment is withdrawn it takes three years for the patient to fully regain their weight loss. There is evidence from the semaglutide trial and more limited data from the liraglutide trial that when treatment is withdrawn weight is regained more quickly. This worsens the cost effectiveness of the active treatments relative to placebo.
EAG alternative approach	A scenario analysis reducing the duration of loss of effect to 2 years.
Effect on ICER	If all active treatments occur in secondary care the company base case ICER for tirzepatide 15mg compared to placebo worsens from £12,792 to £13,417 per QALY. If it is assumed that tirzepatide also has a 2-year stopping rule while retaining all other company modelling assumptions the ICER for tirzepatide 15mg compared to placebo worsens from £5,343 to £8,863 per QALY.
Additional evidence or analyses.	Data on time to loss of effect for withdrawal of tirzepatide.

Issue 8: Will the weight loss be maintained

Report section	5.2.7
Why important	There is some evidence from the liraglutide trial that in the medium term patient weight loss reverses, and also that the net effect compared to placebo falls.
EAG alternative approach	Modifying the model to permit a waning of the treatment effect to be explored.
Effect on ICER	Due to the model structure the EAG cannot quantify the effect of this. It would worsen the cost effectiveness of tirzepatide relative to placebo. If the same treatment waning is applied to all active treatments it is likely to worsen the cost effectiveness of tirzepatide relative to the other active treatments.
Additional evidence or analyses.	Modifying the model to permit a waning of the treatment effect to be explored.

Issue 9: Will the weight loss relative to placebo increase over time

Report section	3.1.12
Why important	The model assumes a constant weight for those remaining on active treatment but an annual increase in weight for those on placebo. This means that the weight loss compared to placebo increases over time.
EAG alternative approach	Not applying the increase in weight for those on placebo.
Effect on ICER	Not applying the increase in weight for placebo causes the company base case ICER for tirzepatide 15mg compared to placebo to worsen from £12,792 to £15,102 per QALY, and compared to semaglutide to worsen from £16,062 to £18,365 per QALY.
Additional evidence or analyses.	None.

Issue 10: Should prediabetes reversal and responder percentages be estimated within the NMA

Report section	2.5.2.2
Why important	The placebo prediabetes reversal rates differ notably between the tirzepatide, semaglutide and liraglutide trials. The placebo responder rates differ slightly between the tirzepatide, semaglutide and liraglutide trials. The company does not adjust for the placebo effect.
EAG alternative approach	Estimating these values taking into account the trials' different placebo effects: i.e. within an NMA.
Effect on ICER	If these values are estimated within an NMA the company base case ICER for tirzepatide 15mg compared to placebo worsens from £12,792 to £13,122 per QALY, and compared to semaglutide worsens from £16,062 to £17,073 per QALY. These effects may seem muted but they apply to the company base case 2-year stopping rules for semaglutide and liraglutide, which reduces the importance of their prediabetes reversal rates and responder rates. Note that the EAG revised base cases do not incorporate the EAG NMA results, only presenting these within scenario analyses.
Additional evidence or analyses.	None.

Issue 11: Annual cost of diabetes

Report section	5.4.2
Why important	Avoiding diabetes and its costs is one of the main cost offsets within the model. The company estimates an annual cost of diabetes without complications of £1,771.
EAG alternative approach	An annual cost of £674 based upon the UKPDS.
Effect on ICER	If the annual cost for diabetes without complications is £674 the company base case ICER for tirzepatide 15mg compared to placebo worsens from £12,792 to £16,970 per QALY, and compared to semaglutide worsens from £16,062 to £19,790 per QALY.
Additional evidence or analyses.	None

Issue 12: BMI mortality multipliers being age dependent

Report section	5.2.2
Why important	The company model assumes that the multiplicative effect of BMI upon mortality does not change with age. There is evidence that the mortality multipliers fall quite dramatically with age. This is also the age group with the highest mortality to which the multipliers are applied.
EAG alternative approach	Estimating age specific BMI mortality multipliers. This may or may not be possible given the data within the literature.
Effect on ICER	The EAG has not been able to quantify the effect of this. The EAG thinks that this considerably increases modelling uncertainty.
Additional evidence or analyses.	Age specific BMI mortality multipliers.

Issue 13: Annualisation of multi-year event risks may bias the analysis

Report section	5.2.17
Why important	The company annualises e.g. the ten year risk of an event assuming a constant event rate. This may not be accurate and events may be brought forward in time. More seriously the annual risk of an event is updated each year. Due to the patient progressing the annualised event risk in subsequent years will be higher than that of the original year. Compounding these annualised risks over a ten year period will result in a higher ten year risk than was estimated at the start of the ten year period, possibly considerably so. Too many events will be modelled.
EAG alternative approach	None, other than to note that the model may have unavoidable inbuilt bias.
Effect on ICER	If this could be addressed it would be expected to worsen the cost effectiveness of tirzepatide.
Additional evidence or analyses.	The literature may permit some conclusions about whether the annual risk is constant. Given the model structure the EAG cannot think how the overestimation of events due to the compounding of updated annual risks can be addressed.

1.6 *Other key issues: summary of the EAG's view*

None.

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG makes the following changes to the company base case.

- EAG01: All treatments have a 2-year stopping rule or no treatments have a 2-year stopping rule.

- EAG02: Only applies the BMI mortality multipliers
- EAG03: No annual worsening of BMI for those off treatment
- EAG04: Mainly applying the adverse event discontinuation rates in the first year, with a common 1% annual rate thereafter
- EAG05: An annual NAFLD rate of 0.06/1,000 patient years
- EAG06: A 5 year OSA risk of 2.85%
- EAG07: Revising the quality of life function intercepts to align with SURMOUNT-1 quality of life data and align the two quality of life functions at 35 kgm^{-2}
- EAG08: Only applying the QoL coefficients of the main BMI quality of life function
- EAG09: Adding first year SWMS costs of £1,645 and annual costs of £698 for those remaining on treatment thereafter
- EAG10: An annual cost for T2DM of £674
- EAG11: The minor issues revisions outlined in section 5.5.7 above[†].

The EAG presents two full sets of analyses:

- EAG BC01: A 2-year stopping rule for all active treatments: EAG01 to EAG11
- EAG BC02: No 2-year stopping rule: EAG02 to EAG11

The effect of the individual changes upon the company base case are presented below.

Table 3: EAG changes: pairwise cost effectiveness estimates vs placebo

		ICER vs PLAC		
	Section	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
Company base case	4.2	£11,510	£11,777	£12,792
EAG01a: All 2-year stopping	5.2.6	£3,372	£5,372	£5,343
EAG01b: No 2-year stopping	5.2.6	£11,510	£11,777	£12,792
EAG02: Only BMI SMRs	5.2.3	£11,181	£11,050	£12,598

[†] The EAG has tried to amend the company VBA as per the revised model sent at clarification but this has no apparent effect upon results. The company notes that the error had minimal effects upon overall results.

EAG03: No BMI worsening	5.2.7	£14,683	£14,150	£15,102
EAG04: AE Disc. Year 1	5.2.14	£12,114	£12,898	£13,825
EAG05: NAFLD 0.06/1,000	5.2.15	£11,750	£11,760	£13,089
EAG06: OSA 5 year 2.85%	**Error! Reference source not found.**5.2.16	£11,727	£11,989	£13,035
EAG07: QoL intercepts	5.3.2	£10,791	£10,950	£11,958
EAG08: Only BMI QoL function	5.3.3	£12,336	£12,002	£13,131
EAG09: EAG SWMS costs	5.4.1	£24,076	£23,498	£23,315
EAG10: T2DM cost £674	5.4.2	£15,550	£16,323	£16,970
EAG11: Minor issues	5.5	£11,633	£11,886	£13,015
EAG BC01: EAG01a to EAG11	..	£30,489	£27,106	£26,373
EAG BC02: EAG01b to EAG11	..	£35,386	£30,739	£31,955

Table 4: EAG changes: pairwise cost effectiveness estimates vs semaglutide

		ICER vs SEMA		
	Section	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
Company base case	4.2	£14,910	£15,454	£16,062
EAG01a: All 2-year stopping	5.2.6	£14,716	£41,524	£18,534
EAG01b: No 2-year stopping	5.2.6	£23,858	£26,855	£23,622
EAG02: Only BMI SMRs	5.2.3	£13,774	£13,627	£15,220
EAG03: No BMI worsening	5.2.7	£18,709	£17,918	£18,365
EAG04: AE Disc. Year 1	5.2.14	£14,776	£15,154	£16,009
EAG05: NAFLD 0.06/1,000	5.2.15	£15,430	£15,509	£16,573
EAG06: OSA 5 year 2.85%	5.2.16	£15,228	£15,770	£16,403
EAG07: QoL intercepts	5.3.2	£14,000	£14,351	£15,022
EAG08: Only Søltoft QoL	5.3.3	£16,265	£15,767	£16,535
EAG09: EAG SWMS costs	5.4.1	£27,146	£26,544	£25,745
EAG10: T2DM cost £674	5.4.2	£18,383	£19,570	£19,790
EAG11: Minor issues	5.5	£14,922	£15,408	£16,191
EAG BC01: EAG01a to EAG11	..	Dom'ted	£33,513	£28,738
EAG BC02: EAG01b to EAG11	..	£294k	£32,677	£36,370

The resulting EAG base cases within a fully incremental analysis is presented below, the pairwise comparisons with semaglutide and placebo also being presented.

Table 5: EAG BC01: 2-year stopping rule for all treatments: Deterministic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	£15,179	15.867	..	..	..
SEMA	£18,627	16.003	£25,524	..	£25,524
TIRZ 5mg	£19,223	16.000	Dominated	Dominated	£30,489
TIRZ 10mg	£19,745	16.036	Ext. Dom	£33,513	£27,106
TIRZ 15mg	£20,020	16.051	£28,738	£28,738	£26,373

Table 6: EAG BC02: No 2-year stopping rule for any treatment: Deterministic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	£15,179	15.867	..	..	..
SEMA	£36,130	16.566	£29,996	..	£29,996
TIRZ 5mg	£40,410	16.580	Ext. Dom	£294k	£35,386
TIRZ 10mg	£44,879	16.834	£32,677	£32,677	£30,739
TIRZ 15mg	£47,404	16.876	£59,784	£36,370	£31,955

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

1.2 *Background*

The disease and treatment introduction to the company submission (CS) appropriately describes obesity as a chronic, progressive disease where genetic, biological, psychological, social, and environmental factors interplay towards an imbalance between food energy intake and expenditure in affected individuals.
The resulting abnormal or excessive body fat accumulation (BMI ≥30 kg/m^2) presents a risk to health,[1-4] which may manifest in comorbidities of: numerous cardiovascular, respiratory, musculoskeletal and metabolic conditions; certain types of cancers;[5] and psychological impacts such as personality disorder, obesity stigmatisation, anxiety, and depression.
The CS frames the resulting quality of life effects on individuals with overweight, or obesity and their comorbidities by citing the large-scale, population-based retrospective study in the UK (N=64,631) that reported 4.9 and 11.3 percentage points fewer on the EQ-5D quality of life summary scale for overweight and obese individuals compared to people categorised a normal weight BMI ≥ 18 kg/m^2 to < 25 kg/m^2 .[6]
It is estimated that overweight and obesity-related comorbidities are responsible for more than 30,000 deaths nationally each year, on average depriving an individual of an additional 9 years of life, preventing many from reaching retirement age. In the future, obesity could overtake tobacco smoking as the biggest cause of preventable death.[7]
The CS reports estimates of £6.1 billion spent by the NHS on obesity-related ill-health, and wider societal costs of £27 billion in 2014–15.[7]
Although the NICE final scope of this Technology Appraisal (TA);[8] and the expected licensed indication for tirzepatide in the United Kingdom supplied with the CS include individuals of BMI ≥27 <30 kg/m^2 , categorised as overweight with at least one weight-related comorbidity, in addition to BMI ≥30 kg/m^2 (obese) – the company focusses on a narrower population of BMI ≥30 kg/m^2 with at least one weight-related

comorbidity (discussed more in Section 1.3).
This is because the company believes evidence suggests tirzepatide is a more effective treatment than current pharmacological options used in clinical practice for this obese group (who particularly benefit from significant weight loss).[2, 5, 9-13]
In 2022, NICE updated its clinical guideline on Obesity: identification, assessment and management [CG189] to address evidence of increased health risks of overweight and obesity-related conditions for people of Black, Asian or Minority Ethnic family backgrounds at lower BMIs than European ethnic backgrounds.[2] For Black, Asian or Minority Ethnic groups, overweight is now defined as having a BMI of 23 kg/m^2 to 27.4 kg/m^2 and obesity having a BMI of 27.5 kg/m^2 or above. In response to this and also – as it states – with the aims of, "transparency and comprehensiveness"; in its introductory sections to the CS, the company commits to supplying evidence on these and other affected groups in addition to its target population for the submission of obese individuals BMI ≥30 kg/m^2 and at least one weight-related comorbidity.[2]

Critique of CS background information on current treatment

The CS centres on the guideline Obesity: identification, assessment and management [CG189] to outline how people with obesity and overweight are managed in the health and care services of England once they present to the system and where they believe tirzepatide, based on evidence supplied, should fit into this.[2]

Once treatment is initiated, a mainstay from start to the end of the treatment course for overweight and obesity is a package of multi-component care interventions that aim to increase physical activity, decrease food calorific intake, ensure diet quality and eating behaviours. Waist-to-height ratio evaluation has recently been introduced alongside BMI calculation as an easy way for people to monitor their central adiposity: increased prevention and supported self-management being key emphases of the NHS Long Term Plan.[2, 14]

The first tier 1 and tier 2 levels of clinical management that deliver these 'lifestyle' interventions are via local authority public health, community and primary care services. Disease-modifying pharmacotherapy for obesity and overweight disease

starts only after a sustained evaluation of the mentioned lifestyle components of care and is at the time of writing restricted largely to the prescription of orlistat in these lower tiers. (Orlistat is additionally available over-the-counter at community dispensing pharmacies without a prescription.) NICE CG189 recommends orlistat for managing obesity in adults with a BMI of 30 kg/m^2 or more, and in people with a BMI of 28 kg/m^2 or more with associated risk factors.[2]

The EAG clinical expert concurs with the CS view of evidence that people who are overweight and obese, and who are eligible for pharmacological (alternatives to orlistat) and/ or surgical treatment (see surgical treatment details below) currently have low and inequitable access to these interventions due to the low and uneven distribution of higher tier 3 and tier 4 services across England and Wales geographies. Approximately one third of the population of England and Wales do not have access to tier 3 services.[15] The same barrier limits access to effective treatments for certain obese and overweight sub-groups such as those who might be obese with learning difficulties; or who are attempting to lose weight ahead of life quality-enhancing knee or hip surgery.

The CS goes on to refer to the government's proposed two-year trial [16] that aims to give greater and more consistent access to pharmacotherapy *wider* than these mostly secondary care-set services and proposes that tirzepatide should be used in addition in tiers 1 and 2.

With little current, available detail of how this two-year trial and any other service changes would govern and manage pharmacotherapy alternatives to orlistat however, the EAG believes there is insufficient evidence within the CS to support tirzepatide use outside of the mostly tier 3 and tier 4 Specialist Weight Management Services (SWMS) at the time of writing of this report. The EAG clinical advisor confirmed that tirzepatide will be offered in tier 3 services.

CG-189 clinical guideline criteria for referral to the mostly tier 3 and tier 4 SWMS are one or more of:

- the underlying causes of overweight or obesity need to be assessed

• the person has complex disease states or needs that cannot be managed adequately in tier 2 (for example, the additional support needs of people with learning disabilities)
• conventional treatment has been unsuccessful
• drug treatment is being considered for a person with a BMI of >50 kg/m^2
• specialist interventions (such as a very-low-calorie diet) may be needed
• surgery is being considered

Following assessment, the following treatments may be made available alongside a continuation of the mainstay lifestyle components:

- NICE TA875 recommends semaglutide as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased activity in adults with one weight-related comorbidity and a BMI of at least 35 kg/m^2 or a BMI of 30 kg/m^2 to 34 kg/m^2 and meet the criteria for referral to SWMS.[1]

- NICE TA664 recommends liraglutide as an option for managing overweight and obesity alongside a reduced-calorie diet and increased activity in adults with a BMI of at least 35 kg/m^2 (or at least 32.5 kg/m^2 for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population), non-diabetic hyperglycaemia, and a high risk of cardiovascular disease.[17]

- If dietary and lifestyle advice, behaviour modification, and drug treatments are unsuccessful, NICE Clinical Guideline (CG)189 recommends bariatric surgery for people with: a BMI of ≥40 kg/m^2; a BMI of between 35 kg/m^2 and 40 kg/m^2 and other significant disease, or a BMI between 30 kg/m^2 and <35 kg/m^2 and with recent-onset of type 2 diabetes (surgery can be considered for people of Asian family background who have recent-onset type 2 diabetes at a lower BMI than other populations).[2]

1.3 *Critique of company's definition of decision problem*

Table 7: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults who have a BMI of: • ≥30 kg/m^2 (obesity) or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) and at least one weight-related comorbidity	Adults who have a BMI of ≥30 kg/m^2 (obesity) and at least one weight-related comorbidity. For transparency and comprehensiveness, clinical data and economic analyses will also be provided in additional relevant subpopulations, and for the entire indication.	The population addressed in this submission will be adults who have a BMI of ≥30 kg/m^2 (obesity) and at least one weight-related comorbidity; this represents a narrower population than the population defined in the NICE final scope.	The main evidence submission is from the SURMOUNT-1 (obesity or overweight with ≥1 weight-related comorbidity in people who did not have T2DM). SURMOUNT-1 is wider than the population considered in the company decision problem (adults who have a BMI of ≥30 kg/m^2)and at least one weight-related comorbidity. The company's decision problem excludes those with BMI ≥30 and no weight-related comorbidity (part of a subgroup analysis) and BMI ≥27 to <30 with weight-related comorbidity. Results for the company's decision subgroup were

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				requested during clarification to inform economic analysis. The EAG clinical advisor confirmed that the exclusion of T2DM is logical as it: • Relates to the indications and licensing; • T2DM and obesity are two separate indications; • There will be clinical instances where the intervention will be used for both obesity and T2DM.
Intervention	Tirzepatide	Tirzepatide	N/A – In line with the NICE final scope.	Dose escalations and de-escalations: The EAG clinical advisor confirmed that the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				doses used in clinical practice are based on patient tolerability. Reductions in doses would occur because of GI adverse events.
Comparator(s)	• Standard management without tirzepatide (including a reduced calorie diet and increased physical activity) • Semaglutide (for the population for whom semaglutide is recommended in TA875) • Liraglutide (for the population for whom liraglutide is recommended in TA664) • Orlistat (prescription dose)	• Standard management without tirzepatide (including a reduced calorie diet and increased physical activity) • Semaglutide as an adjunct to diet and exercise (for the population of patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity, given that no data are available specifically for the population for whom semaglutide is	Consistent with the conclusions of the Committee across three previous appraisals in obesity and overweight management [TA875, TA664],[1, 17] orlistat is not widely used in clinical practice due to its reported poor efficacy and undesirable side effects, which lead to poor adherence and treatment outcomes.[1, 17] This is highlighted by data published by NHS England, which demonstrate a consistent decline in the	Per NICE scope with the exception of orlistat.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		recommended in TA875[1] • Liraglutide as an adjunct to diet and exercise (for the population for whom liraglutide is recommended in TA664)[17]	prescription of orlistat over the last decade.[18] Based on these data demonstrating the limited role of orlistat within current UK clinical practice, and the clear Committee determination made in prior appraisals in this indication, orlistat should not be considered a relevant comparator for tirzepatide for the treatment of overweight and obesity.	
Outcomes	The outcome measures to be considered include: • BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • cardiovascular events	The outcome measures to be considered include: • BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status	Due to the long-term follow-up required to collect direct evidence for the incidence of T2DM, CV events and mortality, data on these outcomes is not currently available. The probability of each event occurring is therefore determined using	Per NICE scope with the exception of incidence of T2DM, mortality and CV events. Surrogate outcomes of SBP, HDL cholesterol and total cholesterol were used in the NMA and economic

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• mortality • adverse effects of treatment • health-related quality of life	• adverse effects of treatment • health-related quality of life	surrogate endpoints employed in risk equations, including BMI, systolic blood pressure (SBP), total cholesterol and high-density lipoprotein (HDL). A detailed explanation of how the incidence of these outcomes is determined in the model is provided.	model to capture treatment benefit. Surrogate outcomes used different treatment definitions with exception of SBP (reported as absolute change across all studies).
Economic analysis				
Subgroups	None.	• Adults who have a BMI of ≥35 kg/m^2, non-diabetic hyperglycaemia and a high risk of cardiovascular disease (i.e. the population of patients for whom treatment with liraglutide is recommended in TA664).[17]	People who are eligible for liraglutide are a subset of the population of relevance for this submission. The subgroup of adults with a BMI of ≥35 kg/m^2, non-diabetic hyperglycaemia and a high risk of cardiovascular disease is to be considered in order to accurately	The company economic modelling uses the subgroup specific NMA estimates for change in body weight, SBP, HDL and total cholesterol. NMAs for the proportion of those with at least 5% weight loss, the proportion of those with prediabetes

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		• Adults with a BMI of ≥30 kg/m^2 (irrespective of any weight-related comorbidities, i.e., including those with and those without comorbidities) • Adults with a BMI of ≥35 kg/m^2 (irrespective of any weight-related comorbidities).	compare tirzepatide with liraglutide. For transparency and comprehensiveness, clinical data and economic analyses are also provided in additional relevant subpopulations, and for the entire indication.	having this reversed to normal glycaemia, adverse events or discontinuations due to adverse events are not undertaken.
Special considerations including issues related to equity or equality			The following equality issues should be considered relevant for this appraisal: • Socioeconomic inequalities • BMI variations between different ethnicities • Access inequalities for treatment of other disabilities	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			If tirzepatide is approved, any recommendations should include similar wording to previous appraisals [TA875, TA664],[1, 17] to adjust BMI thresholds for certain populations.	

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The methods used in the company submission (CS) for their systematic literature review (SLR) to identify and synthesise evidence in support of the clinical effectiveness of tirzepatide for managing overweight and obesity was reviewed by the EAG. The steps to search for, assess eligibility, extract data, assess the risk of bias and synthesise evidence in the SLR were assessed for quality using a modification of the ROBIS tool.[19] Overall the EAG found the SLR to be of unclear concern although and the EAG considers it is likely to have identified all studies relevant to the decision problem. Table 8 provides a summary of the EAG critique and cross-references to the relevant section in the CS. The full EAG assessment using the modified ROBIS can be found in Appendix 1.

Table 8. Summary of the EAG's critique of the company SLR

Method step	**Section(s) of CS of relevance**	**EAG overall assessment**
Eligibility criteria	CS Appendix D, Table 7	Unclear concern
Searches and selection of studies	CS Appendix D, Section D.1.1-D1.2 and D.1.4.1-D.1.4.2	Unclear concern
Data extraction and risk of bias assessment	CS Appendix D, Section D.1.4.3 and D.2.2	Low concern
Evidence synthesis	CS section B.2.3 and B.2.9; Appendix D, Section D.5- D.6	Unclear concern

The CS SLR identified two RCTs investigating tirzepatide, one of these, a phase II trial (Frias et al. 2018 [20]) was excluded as it was included patients with type 2 diabetes mellitus (T2DM) and participants were eligible if their BMI was between 23–50 kg/m^2. An additional RCT investigating tirzepatide was published after the search dates of the SLR, SURMOUNT-2 trial.[21] The SURMOUNT-2 trial investigated the use

of tirzepatide for weight loss in people with T2DM. The CS provide summary data from this trial in an Appendix but the study was not considered to be eligible for inclusion. As discussed earlier, the EAG consider the exclusion of the SUROMUNT-2 trial as appropriate. Finally, the CS included top-line summary results for two other ongoing trials, SURMOUNT-3 and SURMOUNT-4 in CS Appendix M. SURMOUNT-3 has subsequently been published.[22] In SURMOUNT-3 participants enrolled on a 12 week intensive lifestyle programme and had to lose ≥5% body weight before being eligible to be randomised to tirzepatide or placebo. The dosing was also different to SURMOUNT-1. As a two-arm trial the tirzepatide arm had a maximum tolerated dose of 10 mg or 15 mg. The EAG view is that the SURMOUNT-3 trial is not fully in line with the NICE scope because of the very specific, and motivated, subgroup (the mean weight reduction prior to starting tirzepatide was 6.9%) and the SURMOUNT-3 trial clinical effectiveness results have not been included here. The top line results are available in CS Appendix M.5.1.1. The EAG has summarised the key adverse events in 2.2.9.3 for consideration alongside those reported from SUMROUNT-1 and SURMOUNT-2.

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The source of evidence for the assessment of clinical effectiveness of tirzepatide comes from a single RCT, the SURMOUNT-1 trial. The SURMOUNT-1 trial is an ongoing study (NCT04184622) although the 72 week treatment comparison until primary end-point assessment has completed (a two year extension study for those with pre-diabetes is ongoing).[23] SURMOUNT-1 is an international multi-centre, double-blind, randomised Phase 3 trial and is one of four studies investigating the use of tirzepatide for overweight and obesity (SURMOUNT-2, -3 and -4 studies have slightly different focuses and are ongoing, see CS Table 5). Tirzepatide is also indicated for Type 2 diabetes (T2DM) and the relevant studies, the SURPASS trials, were included in the NICE TA924 which has been published recently.[24] Of note, SURMOUNT-1 excludes people with T2DM.

SURMOUNT-1 is a four arm trial comparing tirzepatide 5 mg, tirzepatide 10 mg, tirzepatide 15 mg and placebo, each administered once weekly. Treatment or placebo are combined with diet and exercise. A summary overview of SURMOUNT-1 methodology is provided in Table 9 with relevant cross-references to the relevant

sections in the CS where more detail can be found. Where the EAG has identified areas for further consideration these are discussed in the subsequent sections.

Table 9. Summary overview of the SURMOUNT-1 trial methodology

Method step	Summary of approach used	Section(s) of CS of relevance or other source
Method of randomisation	Randomisation was stratified by country, sex, and the presence or absence of prediabetes with assignment determined by a computer-generated random sequence using an Interactive Web Response System.	CS Section B.2.3.2, Table 7, Jastreboff et al. 2022[23]
Eligibility criteria	At least one self-reported unsuccessful dietary effort to lose body weight and BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one of the following weight-related comorbidities: • Hypertension • Dyslipidaemia • OSA • Cardiovascular disease	CS Section B.2.3.2, Table 7
Trial drugs by period of study	Once-weekly tirzepatide 5 mg, 10 mg or 15 mg or placebo as an adjunct to a 500-calorie deficit diet and increased physical activity for 72 weeks	CS Section B.2.3.1, Figure 3
Primary endpoints of relevance to the decision problem	Mean percent change in body weight for tirzepatide 10 mg and 15 mg	CS Section B.2.3.2, Table 7

	Percent achieving ≥5% body weight reduction for tirzepatide 10 mg and 15 mg	
Statistical analysis	Data from the intention-to-treat population were used to assess efficacy from two different perspectives: • The treatment regimen estimand • The efficacy estimand Discussed below in 2.2.3	CS Section B.2.4

2.2.1 SURMOUNT-1

The CS presents data from the SURMOUNT-1 trial in CS Sections B.2.3 to B.2.7. However, the population in SURMOUNT-1 is wider than the population considered in the company DP, as outlined in 1.3. The DP population excludes those with BMI ≥30 and no weight-related comorbidity (although they are part of a subgroup analysis) and BMI ≥27 to <30 with weight-related comorbidity.

As the key results from the DP population are pivotal to the economic analysis the EAG requested in clarification A1 results from the DP population and these are reported in the subsequent section below. The EAG presents here a summary overview of the key findings of the SURMOUNT-1 whole trial population, focusing on issues of methodology which are relevant to interpreting the results of the network meta-analysis (NMA) and / or economic evaluation.

2.2.2 Dose escalations and de-escalations

The draft SmPC specifies a starting dose of tirzepatide of 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. This is to minimise any potential for adverse events. The recommended maintenance doses are 5, 10 and 15 mg, which is the maximum dose once weekly. The maintenance dose is decided by an individual's response on weight measures and adverse events and is in line with the SmPC for tirzepatide in

T2DM[25]. Guidance on the amount of weight loss that should occur for a decision to maintain at 5mg or to increase to 10 mg and then to 15 mg is not provided in the draft SmPC.

Unlike the draft SmPC posology, the SURMOUNT-1 trial provides evidence for three maintenance doses of tirzepatide (5, 10 and 15 mg once weekly after titration), compared with placebo. A pre-specified dose-escalation scheme was used for each of the tirzepatide arms as described in CS B.2.3.1.1 and Figure 4. Dosing starts at 2.5 mg once weekly and is increased by 2.5 mg every 4 weeks, taking four weeks to reach 5 mg, 12 weeks to reach 10 mg and 20 weeks to reach 15 mg. As per the study randomisation participants in the three dose arms of SURMOUNT-1 can only receive the maintenance dose they are allocated to. This restriction to maintenance dose is therefore not in line with the anticipated use in clinical practice which allows for titration according to response.

In the SURMOUNT-1 trial protocol there is also a dose de-escalation strategy for intolerable GI symptoms. If after following diet adjustments, anti-emetic use or temporary interruption these intolerable GI symptoms persisted blinded de-escalation to a lower tolerated maintenance dose could occur, e.g participants in the 5 mg could decrease to placebo; 10 mg could decrease to 5 mg and 15 mg could decrease to 10 mg (SURMOUNT-1 protocol). Only 1 dose reduction per participant was allowed during the entire course of the study (protocol 6.6.1). If GI symptoms were still intolerable after these measures the participant was discontinued from study drug. The implications of these restrictions to clinical practice is unclear, e.g whether more de-escalations would occur in clinical practice. There is no specific de-escalation strategy outlined in the draft SmPC. This is discussed in more detail in Section 2.2.9.2 [adverse events] and Section 2.3.4 [NMA].

The doses and dose-escalation scheme were based on evidence from phase 1 and 2 studies in populations with T2DM, the early population tirzepatide was authorised for, and was used in SURMOUNT-1 to improve tolerability and enable higher doses to maximize the effects on body weight (SURMOUNT-1 protocol).

The EAG clinical adviser confirmed that in clinical practice the doses used are based on tolerability, in general the dose of tirzepatide would increase as long as it is tolerable. Reductions in doses to the next level would occur if GI AEs are intolerable

and would stay at the reduced level if tolerated, because the higher dose would be deemed intolerable. Advice to the EAG was also that monitoring of weight and tolerability and subsequent dose escalations or de-escalations as appropriate would generally occur in secondary care outpatients but that a GP may be involved.

2.2.3 Analysis sets

Table 12 of CS B.2.3.4 described the various analysis sets. The EAG asked the company (clarification A6) for clarification on which analysis set was used when presenting the main results. The company clarified that results were presented using the efficacy analysis set (EAS), and that the mITT pertains to the selection of participants, whereas the efficacy analysis set (EAS) pertains to the selection of data from relevant participants, aligned with the estimand definitions used. The EAS relates to the efficacy estimand and uses 'data obtained during the treatment period from the mITT population, excluding data after discontinuation of study drug (last dose + 7 days)

2.2.4 SURMOUNT-1 trial population

CS Tables 8, 9, and 10 present baseline demographic characteristics, baseline clinical characteristics, and baseline comorbidities respectively for all randomised participants (n = 2,539) in the whole trial population. CS Table 10 additionally includes two metrics reflecting each of the baselines for the number of participants using at least one lipid-lowering treatment and the number using at least one antihypertensive treatment. Further details on the specific types of antihypertensive and lipid-lowering therapies used by participants at baseline can be found in the clinical study report (CSR) provided alongside the submission (filename: 'Eli Lilly, 2022 (SURMOUNT-1 CSR)'). The EAG present the key baseline characteristics from the whole trial population in Table 10 and has checked these against the CSR.

The EAG concurs with the CS that the balance of baseline characteristics was similar across treatment groups. Most participants were female (67.1% to 67.8%, lowest to highest percentage arms) as per the SURMOUNT-1 protocol, which capped enrolment for females at 70% and under the age of 65 (94.7%, 91.7%, 95.1%, and 94.4% across placebo, 5mg, 10mg, and 15mg treatment arms, respectively). Clinical advice to the EAG suggests the profile of baseline characteristics – in the majority part – are similar to the characteristics of people with

overweight and obesity in the UK. However there are some differences, see Section 2.2.3 [Generalisability].

Table 10. Key baseline characteristics from the whole trial population of SURMOUNT-1

	Placebo	**Tirzepatide 5mg**	**Tirzepatide 10mg**	**Tirzepatide 15mg**
Attribute	(n = 643)	(n = 630)	(n = 636)	(n = 630)
Mean ± SD unless stated otherwise				
Age, yr.	44.4 ± 12.5	45.6 ± 12.7	44.7 ± 12.4	44.9 ± 12.3
Female, n (%)	436 (67.8)	426 (67.6)	427 (67.1)	425 (67.5)
Age Category 1, n (%)				
<65	609 (94.7)	578 (91.7)	605 (95.1)	595 (94.4)
≥65	34 (5.3)	52 (8.3)	31 (4.9)	35 (5.6)
Race, n (%)				
Asian	71 (11.0)	68 (10.8)	71 (11.2)	66 (10.5)
Black or African American	55 (8.6)	48 (7.6)	47 (7.4)	51 (8.1)
White	450 (70.0)	447 (71.0)	452 (71.1)	443 (70.3)
Multiple	7 (1.1)	9 (1.4)	6 (0.9)	8 (1.3)
Others [a]	60 (9.3)	58 (9.2)	60 (9.4)	62 (9.8)
Weight (kg)	104.8 ± 21.4	102.9 ± 20.7	105.8 ± 23.3	105.6 ± 22.9
BMI (kg/m^2)	38.2 ± 6.9	37.4 ± 6.6	38.2 ± 7.0	38.1 ± 6.7
BMI Categories, n (%)				
<30	24 (3.7)	38 (6.0)	38 (6.0)	40 (6.3)
≥30 to <35	227 (35.3)	241 (38.3)	209 (32.9)	199 (31.6)
≥35 to <40	180 (28.0)	174 (27.6)	187 (29.4)	179 (28.4)
≥40	212 (33.0)	177 (28.1)	202 (31.8)	212 (33.7)
Waist circumference (cm)	114.0 ± 14.9	113.2 ± 14.3	114.8 ± 15.8	114.4 ± 15.6
Prediabetes, n (%)	270 (42.0)	247 (39.2)	262 (41.2)	253 (40.2)

Duration of obesity (year)	14.0 ± 10.7	14.0 ± 10.8	14.7 ± 11.1	14.8 ± 10.8
SBP (mmHg)	122.9 ± 12.8	123.6 ± 12.5	123.8 ± 12.8	123.0 ± 12.9
HbA1c (mmol/mol)	37.4 ± 4.1	37.3 ± 3.96	37.1 ± 4.0	37.2 ± 4.4
HbA1c (%)	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4
Comorbidities, n (%)				
Hypertension	199 (30.9)	205 (32.5)	208 (32.7)	207 (32.9)
Dyslipidaemia	186 (28.9)	201 (31.9)	188 (29.6)	182 (28.9)
ASCVD	21 (3.3)	16 (2.5)	20 (3.1)	21 (3.3)
PCOS	13 (2.0)	7 (1.1)	13 (2.0)	6 (1.0)
OSA	59 (9.2)	41 (6.5)	51 (8.0)	46 (7.3)
Osteoarthritis	76 (11.8)	87 (13.8)	86 (13.5)	77 (12.2)
Anxiety or Depression	108 (16.8)	119 (18.9)	101 (15.9)	94 (14.9)
NAFLD	46 (7.2)	42 (6.7)	44 (6.9)	48 (7.6)
Asthma or COPD	78 (12.1)	72 (11.4)	64 (10.1)	53 (8.4)
Gout	35 (5.4)	35 (5.6)	34 (5.3)	32 (5.1)
Concomitant medications, n (%)				
Participants using ≥1 Lipid-lowering Medication	115 (17.9)	116 (18.4)	99 (15.6)	99 (15.7)
Participants using ≥1 Antihypertensive Medication	181 (28.1)	196 (31.1)	191 (30.0)	189 (30.0)

Adapted from CS Tables 8, 9, and 10.

[a]American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander combined by EAG

Abbreviations: ASCVD: Atherosclerotic Cardiovascular Disease; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Oedema; HbA1c: Haemoglobin A1c; NAFLD: Non-alcoholic Fatty Liver Disease; OSA: Obstructive Sleep Apnoea; PCOS: Polycystic Ovary Syndrome; SBP: Systolic Blood Pressure

2.2.5 SURMOUNT-1 ROB assessment

The company states that risk of bias was assessed using the Cochrane risk of bias assessment tool, but in fact they used questions from CRD Report 2009, as referenced in CS Table 13. These are the minimum criteria recommended by NICE. A comparison of the company assessment and EAG assessment of risk of bias in SURMOUNT-1 is presented in Appendix 1. The EAG notes there is higher drop out

in the placebo arm, which is not explained by the reasons for discontinuation. The EAG requested further details of the reasons for discontinuation due to protocol deviations, withdrawal by participant and 'other', in clarifications A2 but these could not be provided as they were not available in aggregate form. A higher proportion in the placebo arm discontinued treatment due to protocol deviations and from participant withdrawal and more in the placebo arm also discontinued the study, most commonly due to withdrawal. The EAG also undertook a risk of bias assessment using the Cochrane RoB 2 tool. Overall, the EAG considers the overall risk of bias in SURMOUNT-1 to be of some concern due to the unexplained imbalance in discontinuations.

2.2.6 Description and critique of the results of SURMOUNT-1 trial

An overview of the key clinical outcomes specified by the NICE scope for the overall population is presented in Table 11. No data were available for the NICE scoped outcomes of Type 2 diabetes, cardiovascular events or mortality (presented in Section 1.3). Surrogate outcome measures were reported in the CS (systolic blood pressure, triglycerides, non-HDL cholesterol, HDL cholesterol, FSG, HbA1c and fasting insulin) but these are not presented here as they are not specified by the NICE scope (with the exception of those used in the model, see NMA results section 2.3.6).

A statistically significant greater improvement was found for each dose of tirzepatide compared with placebo for all key outcome measures at 72 weeks follow-up (Table 11). The difference from placebo in the co-primary endpoint of mean percent change in body weight from baseline was -13.5% (95% CI -14.6 to -12.5), -18.9% (95% CI -20.0 to -17.8) and -20.1 (95% CI -21.2 to -19.0) for the 5 mg, 10 mg and 15 mg dose arms, respectively. The portion of participants achieving ≥5% body weight reduction (co-primary endpoint) was 89.4%, 96.2% and 96.3%, respectively, compared with 27.9% of the placebo group. A body weight reduction of ≥20% was achieved by 31.6%, 55.5% and 62.9%, respectively, compared with 1.3% of the placebo arm. The difference from placebo in mean change in BMI from baseline was −5.1 (95% CI −5.5 to −4.6), -7.2 (95% CI −7.7 to −6.8) and −7.7 (95% CI −8.2 to −7.3) for the 5 mg, 10 mg and 15 mg dose arms, respectively. For change from baseline in waist circumference, the difference from placebo was −11.2 cm (95% CI −12.3 to −10.0), −16.0 cm (95% CI −17.2, −14.9) and −16.5 cm (95% CI −17.7,

−15.4), respectively. The portion of participants with a change in glycaemic states from prediabetes to normoglycaemia was [redacted] and [redacted] respectively, compared with [redacted] of the placebo group.

Table 11. Overview of key clinical outcomes at 72 weeks, efficacy analysis set

Parameters	**Placebo (N=643)**	**Tirzepatide 5 mg (N=630)**	**Tirzepatide 10 mg (N=636)**	**Tirzepatide 15 mg (N=630)**
Percent change in body weight (co-primary endpoint for 10 and 15 mg doses)				
Percent change from baseline (%)	−2.4[a]	−16.0[a]	−21.4[a]	−22.5[a]
Percent change difference from placebo (%) (95% CI)	N/A	−13.5[b] (−14.6,−12.5)	−18.9[b] (−20.0,−17.8)	−20.1[b] (−21.2,−19.0)
Percentage of participants achieving body weight reduction of:				
≥5% (co-primary endpoint for 10 and 15 mg doses)	27.9	89.4 [b]	96.2 [b]	96.3 [b]
≥10%	13.5	73.4 [b]	85.9 [b]	90.1 [b]
≥15%	6.0	50.2 [b]	73.6 [b]	78.2 [b]
≥20%	1.3	31.6 [b]	55.5 [b]	62.9 [b]
BMI				
Change from baseline	−0.9 [a]	−5.9 [a]	−8.1 [a]	−8.6 [a]
Change difference from placebo (95% CI)	N/A	−5.1 [b] (−5.5, −4.6)	−7.2 [b] (−7.7, −6.8)	−7.7 [b] (−8.2, −7.3)
Waist circumference, cm				
Change from baseline	−3.4 [a]	−14.6 [a]	−19.4 [a]	−19.9 [a]
Change difference from placebo (95% CI)	N/A	−11.2 [b] (−12.3,−10.0)	−16.0 [b] (−17.2, −14.9)	−16.5 [b] (−17.7,−15.4)
Glycaemic status				

Proportion with prediabetes at baseline to normoglycaemia at 72-weeks, n (%) (exploratory endpoint)	[redacted]	[redacted]	[redacted]	[redacted]

[a] p<0.001 versus baseline.

[b] p<0.001 versus placebo for superiority.

[c] Proportions calculated by EAG based on values from CS Tables 8 and 20.

2.2.7 Surrogate outcomes used in the economic model

The CS use the surrogate outcomes of CfB weight (%), SBP, HDL cholesterol and total cholesterol in their economic model**Error! Reference source not found.**. CS Table 17 and CS Table 18 present comparisons for secondary outcomes of SBP, triglycerides, non-HDL cholesterol and HDL cholesterol pooling all tirzepatide doses compared with placebo as per the SURMOUNT-1 protocol. Clinical advice to the EAG was that the assumption for this pooling, that CV parameters would improve in a similar magnitude was not reasonable because with increasing doses of tirzepatide there are differences in weight loss and there are close links between body weight and CV outcomes. The EAG also comment that in the NMA comparisons these outcomes were analysed by treatment dose arms (See 2.3.6). The company provided the results for these outcomes by arm of SURMOUNT-1 in clarification response A29.

2.2.8 HRQoL

SURMOUNT-1 evaluated the following PROMs (CS Table 7), which are reported in CS Appendix M.3:

Mean change in SF-36v2 acute form Physical Functioning domain score for pooled tirzepatide 10 mg and 15 mg (key secondary endpoint). Analysis for tirzepatide 5mg was an additional secondary endpoint, but data were not presented in the CS (available in CSR Table GPHK.5.17 for all doses separately). A statistically significant greater improvement from baseline to week 72 was found for the combined 10/15mg arm compared with placebo (difference 2.3, 95% CI 1.6, 2.9) (CS

Appendix Table 125). This was also the case for each separate dose (CSR Table GPHK.5.17) The CS does not discuss the MCID.

Mean change in IWQOL-Lite-CT Physical Function Composite score for tirzepatide 5 mg, 10 mg and 15 mg (key secondary endpoint). The Physical Composite score, Psychosocial Composite score and Total score were also presented (CS Appendix Table 124). Compared with placebo, a statistically significant greater improvement from baseline to week 72 was found with each dose of tirzepatide for all scores reported.

Change from baseline in EQ-5D-5L scores at 72 weeks (exploratory endpoint). Compared with placebo, a statistically significant greater improvement from baseline to week 72 was found with each dose of tirzepatide (Table 12). This was also the case for the EQ VAS (CS Appendix Table 126). The CS does not discuss the MCID. The EAG notes the MCID is reported to be 0.03 [26, 27] for the EQ-5D-5L, and the differences in Table 12 achieve this.

The company does not use the EQ-5D data in their economic model; further clarification was requested from the company regarding the justification for this, see Section 3.1.18.

Table 12. EQ-5D-5L health index score at baseline and 72 weeks; EAS

Parameters	**Placebo (N=643)**	**Tirzepatide 5 mg (N=630)**	**Tirzepatide 10 mg (N=636)**	**Tirzepatide 15 mg (N=630)**
EQ-5D-5L health state index (UK; valued using Van Hout value set)				
n	473	537	532	532
Baseline	0.85	0.85	0.84	0.85
Change from baseline	0.02[a]	0.04[b]	0.05[b]	0.07[b]
Change difference from placebo (95% CI)	N/A	0.03[c] (0.01, 0.04)	0.03[c] (0.01, 0.05)	0.05[d] (0.03, 0.06)

From CS Appendix Table 126.

[a]p-value <0.01, [b]p-value <0.001 versus baseline, [c]p-value <0.01, [d]p-value <0.001 versus placebo.

2.2.9 Adverse events

An overview adverse events (AE) from the overall population of SURMOUNT-1 is summarised in Table 13. Treatment emergent adverse events (TEAEs) and TEAEs related to study treatment (as judged by the investigator) were more common in the tirzepatide treatment groups than the placebo groups. The rates between tirzepatide arms were generally similar suggesting there may not be a dose relationship. However, this may be a reflection of the dose escalation which was performed up to 20 weeks for the 15 mg tirzepatide dose. As reported in the CS Section B.2.10 the actual dose of tirzepatide that the participant was taking at the time of an AE may have been lower than the final assigned dose by treatment group.

Serious adverse events occurring in >2 participants are presented in CS Appendix Table 78. Individual serious adverse events occurred in ≤1% of participants. There were 11 deaths in SURMOUNT-1, none of which were considered to be related to tirzepatide, apart from one which was uncertain due to a number of confounding factors (CS Appendix F.4).

Table 13. Overview of adverse events in the safety analysis set, mITT population

Category n (%)	Placebo (N=643)	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)
Deaths	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)
SAEs	44 (6.8)	40 (6.3)	44 (6.9)	32 (5.1)
Discontinuations from study due to AE	17 (2.6)	16 (2.5)	18 (2.8)	21 (3.3)
Discontinuations from study treatment due to AE	21 (3.3)	30 (4.8)	46 (7.2)	40 (6.3)
TEAEs	463 (72.0)	510 (81.0)	520 (81.8)	497 (78.9)
TEAEs related to study treatment	196 (30.5)	350 (55.6)	395 (62.1)	386 (61.3)

Modified from CS Appendix Table 75

AE: adverse event; TEAE: SAE: Serious adverse event; Treatment emergent adverse event

Table 14 provides an overview of adverse events from the safety population of the integrated SURMOUNT-1 and SURMOUNT-2 trials (provided in the CS reference pack) for context (there was no 5 mg group in SURMOUNT-2) and those from the SURMOUNT-3 publication. In the integrated safety analysis the proportions reported were similar to those in SURMOUNT-1 above, although TEAEs related to study treatment were not reported in the company integrated safety analysis. In SURMOUNT-3 the dose of tirzepatide was the maximum dose a participant tolerated (10 or 15 mg). Although the proportions of key adverse events were generally similar, the discontinuation from study treatment was high at 10% in the tirzepatide arm. This may be because a feature of the study was that participants who were unable to tolerate 2.5 or 5 mg discontinued treatment and participants unable to tolerate up to 10 mg after de-escalation and re-escalation also discontinued treatment. All remained on study for follow-up.

Table 14. Overview of adverse events in the integrated safety analysis alongside those from SURMOUNT-3

Category n (%)	**Placebo** **(N=958)**	**Tirzepatide** **10 mg** **(N=948)**	**Tirzepatide** **15 mg** **(N=941)**
Deaths	[redacted]	[redacted]	[redacted]
Deaths SURMOUNT-3	Placebo (n = 292) 1 (0.3)	Tirzepatide MTD (n = 287) 1 (0.3)	
SAEs	[redacted]	[redacted]	[redacted]
SAEs SURMOUNT-3	Placebo (n = 292) 14 (4.8)	Tirzepatide MTD (n = 287) 17 (5.9)	
Discontinuations from study due to AE	[redacted]	[redacted]	[redacted]
Discontinuations from study due to AE SURMOUNT-3	Placebo (n = 292) 2 (0.7)	Tirzepatide MTD (n = 287) 4 (1.4)	
Discontinuations from study treatment due to AE	[redacted]	[redacted]	[redacted]

Discontinuations from study treatment due to AE SURMOUNT-3	Placebo (n = 292) 6 (2.1)	Tirzepatide MTD (n = 287) 30 (10.5)
TEAEs	[redacted]	[redacted] [redacted]
TEAEs SURMOUNT-3	224 (76.7)	250 (87.1)

Adapted from CS Ref 122, Eli Lilly. Data on File. Integrated Summary of Safety Information Addendum Tirzepatide (LY3298176). Chronic Weight Management. 2023.

AE: adverse event; MTD: Maximum tolerated dose SAE: Serious adverse event; TEAE: Treatment emergent adverse event

2.2.9.1 Discontinuations due to adverse events

As seen in Table 14 above, discontinuations from study treatment due to AE varied between the treatment groups, from 3.3% of participants in the placebo group to 4.8%, 7.2%, and 6.3% participants in the tirzepatide 5, 10 and 15 mg groups, respectively. There are some slight discrepancies in the rates of discontinuations from the study due to AEs between the different sources provided by the company. Presented above are those reported in CS Appendix Table 75 which aligns with the CSR. Rates presented in the Jastreboff publication of SURMOUNT-1 [23] and CS Table 72 for the tirzepatide 5mg, 10mg and 15 mg arms respectively were 27/630 (4.3%), 45/636 (7.1%), 39/630 (6.2%). For the placebo arm Jastreboff presents the rate as 17/643 (2.6%). The CSR states that these differences are because the definition of completion status differed. The values used in the economic model are those from CS Table 72.

Discontinuations from the study due to AEs were more balanced.

The CS reports that AEs in the gastrointestinal disorders system organ class (SOC) were the most common AEs that led to study drug discontinuation. The Jastreboff publication [23] reports the proportions discontinuing treatment for nausea, diarrhoea, abdominal pain and vomiting. The CS states that compared with the placebo group, more participants in the tirzepatide groups discontinued study drug due to AEs in the gastrointestinal disorders SOC. Study discontinuation due to gastrointestinal disorders (all types) were [redacted]

2.2.9.2 Dose De-scalations

The CS does not report proportion having de-escalation of the dose of tirzepatide. The CSR (Table GPHK 8.16) reports the following in the mITT population:

- The proportion of participants missing ≥3 consecutive doses were [redacted]. These participants were required to [redacted] (CSR 4.6.3)

The proportion of participants having dose de-escalation were [redacted]Given the escalation and potential de-escalation in the SURMOUNT-1 trial, particularly at the higher doses, it is unclear if this would have an impact on the relative effectiveness of the doses because no data were identified on the mean treatment exposure (average doses) given in the SURMOUNT-1 arms over the duration of the trial. It is also unclear when these de-escalations occurred as no data are available. For comparison, data for the proportions having de-escalation from the SURMOUNT-2 CSR were[redacted]

In addition, as discussed in Section 2.2.9.1 discontinuations due to GI AEs ranged from 4.8-7.2 %; it is unclear if any of these had dose de-escalations before discontinuing. The aim of the dose titration is to minimise GI effects, however, GI effects were the most common reason for drug discontinuation.

2.2.9.3 Treatment emergent AEs

The CS reports individual TEAEs occurring in at least 5% of participants in CS Table 53 and reproduced in Table 13 below. With the exception of COVID-19 the most frequently reported TEAEs in the tirzepatide arms were gastrointestinal related (nausea, diarrhoea, constipation, dyspepsia, vomiting and decreased appetite). COVID-19, headache and abdominal pain were similar between placebo and the tirzepatide arms; the other events occurred more frequently with tirzepatide. Higher doses of tirzepatide led to more nausea and diarrhoea, other events were more similar across the three tirzepatide arms. As the actual dose of tirzepatide when a TEAE occurred may have been lower than the final assigned dose by treatment group it is difficult to establish whether there was a dose response relationship. It may be possible that there is an interaction with the GI effects and weight loss. The

proportions with these TEAEs in the integrated analysis of SURMOUNT-1 and SUMROUNT-2 were similar (not reproduced here).

GI TEAEs are of special interest for tirzepatide and the GI SOC (serious adverse events of Grade 3 or 4) is used in the economic model. The CS reports a summary of individual GI TEAEs of any grade occurring in ≥2% of participants in any treatment group in the safety analysis set in CS Table 54 (not reproduced here as mostly an overlap with CS Table 53). The CS states (CS B.2.10.4) that other adverse events of special interest include hepatobiliary disorders and exocrine pancreas safety, however, these are not reported in the CS or Appendices. Where reported in the CSR the proportions were low across all treatment groups.

Table 15. Treatment-emergent adverse events occurring in ≥5% of participants in the safety analysis set, SURMOUNT-1

Preferred Term n (%)	**Placebo (N=643)**	**Tirzepatide 5 mg (N=630)**	**Tirzepatide 10 mg (N=636)**	**Tirzepatide 15 mg (N=630)**
Nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)
Diarrhoea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)
COVID-19	90 (14.0)	94 (14.9)	98 (15.4)	82 (13.0)
Constipation	37 (5.8)	106 (16.8)	109 (17.1)	74 (11.7)
Dyspepsia	27 (4.2)	56 (8.9)	62 (9.7)	71 (11.3)
Vomiting	11 (1.7)	52 (8.3)	68 (10.7)	77 (12.2)
Decreased appetite	21 (3.3)	59 (9.4)	73 (11.5)	54 (8.6)
Headache	42 (6.5)	41 (6.5)	43 (6.8)	41 (6.5)
Abdominal pain	21 (3.3)	31 (4.9)	34 (5.3)	31 (4.9)
Alopecia	6 (0.9)	32 (5.1)	31 (4.9)	36 (5.7)
Dizziness	15 (2.3)	26 (4.1)	35 (5.5)	26 (4.1)
Eructation	4 (0.6)	24 (3.8)	33 (5.2)	35 (5.6)
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)

Adapted from CS Table 53

2.2.9.4 Compliance

Compliance was defined in SURMOUNT-1 as taking at least 75% of the required doses of the study drug. The proportion of participants who did not meet this criterion was similar between arms ([redacted]). The proportion of participants missing 3 or more consecutive doses was [redacted] respectively.

2.2.1 SURMOUNT-1 apriori subgroups

The NICE scope did not identify any subgroups of interest. The SURMOUNT-1 trial examined the following pre-specified subgroups:

- Age group (<65, ≥65 years)
- Race
- Sex
- Ethnicity
- Region of enrolment (US, outside the US)
- BMI group (<30, ≥30 and <35, ≥35 and <40, ≥40 kg/m2)
- Glycaemic status at randomisation (normoglycemia vs prediabetes)

Analyses were planned for the outcomes of percent change in body weight and percentage of participants achieving ≥5% change from baseline in body weight at 72 weeks. P-values are presented in CS Appendix E.2, Tables 71 to 74, but effect estimates are not reported.

The treatment-by-subgroup interactions for percent change in body weight at 72 weeks were statistically significant for sex, ethnicity, and BMI for the treatment regimen estimand, and for race, sex, ethnicity, region of enrolment and BMI for the efficacy estimand. The company's observations on the significant interactions are summarised in Table 16.

There were no statistically significant treatment-by-subgroup interactions for the proportion of participants achieving ≥5% change from baseline in body weight at 72 weeks for any subgroup for the treatment regimen estimand, whereas interactions were statistically significant for ethnicity and BMI for the efficacy estimand (see Table 16).

Table 16. Statistically significant treatment-by-subgroup interactions and company observations

Subgroup	Observation by company
Percent change in body weight at week 72	
Sex (treatment regimen estimand and efficacy estimand)	This interaction may be related to the greater weight reduction observed for female participants and the relatively smaller mean weight at baseline in the placebo and tirzepatide 5 mg treatment groups for male participants.
Ethnicity (treatment regimen estimand and efficacy estimand)	This interaction may be related to the greater weight reduction observed in the tirzepatide 15 mg treatment group for the subset of ethnicity = “Not Hispanic or Latino” compared with those in the same treatment group for the subset of “Hispanic or Latino.”
BMI group (treatment regimen estimand and efficacy estimand)	This interaction may be related to the similar weight reduction observed for all 3 tirzepatide treatment groups at 72 weeks from the subset of BMI <30 kg/m2, and the larger but similar weight reduction observed in the tirzepatide 10 and 15 mg treatment groups from the subset of BMI ≥30 kg/m2 to <35 kg/m2.
Race (efficacy estimand only)	This interaction may be related to the variability from the subset of race = “Multiple” with a much smaller sample size and imbalanced baseline weights. The small sample size of race = “Multiple” also limited the interpretation of the results.
Region of enrolment (efficacy estimand only)	This interaction may be related to the relatively smaller baseline weight of participants in the US versus OUS, and the smaller weight reduction observed in the tirzepatide 10-mg treatment group from the subset of region = “OUS” compared with those in the same treatment group from the subset of “US.”

Percentage of participants achieving ≥5% change from baseline in body weight at 72 weeks	
Ethnicity (efficacy estimand only)	The interaction may be related to the smaller percentage of participants achieving the ≥5% target in the category of "Not Hispanic or Latino" in the placebo group.
BMI group (efficacy estimand only)	The interaction may be related to the relatively smaller percentage of the placebo group in the category of BMI ≥35 kg/m^2 to 40 kg/m^2 and the percentage of the tirzepatide 5 mg group in the category of BMI ≥40 kg/m^2.

OUS: outside the United States.

2.2.1.1 CS subgroup analyses of SURMOUNT-1

The CS considers five groups in total, including the whole trial population and four post-hoc subgroups. A summary of these groups, the data reported in the CS, and how they are dealt with in the company's NMA and economic analysis is presented in Table 17 below.

The EAG has summarised the baseline characteristics and results for the company's base case population (BMI ≥30 with ≥1 weight-related comorbidity) in 2.2.1.2. Limited results were provided in the CS for the other three subgroups (change from baseline percent body weight, HDL cholesterol, total cholesterol, SBP). Baselines for the subgroup BMI ≥35 with prediabetes and high CVD risk can be seen in Clarification response A4.

Table 17. Summary of groups considered in the CS

Population / subgroup	Baselines / results available	Included in NMA?	Economic model?
Whole trial population (BMI ≥30 or BMI ≥27 with ≥1 weight-related comorbidity)	Baselines: Yes Results: Yes	Yes – for transparency and to allow comparison with subgroup analyses	Subgroup analysis (vs diet and exercise

BMI ≥30 with ≥1 weight-related comorbidity	Baselines: Yes[a] Results: Yes[b]	Yes – population defined in Decision Problem	Base case (vs semaglutide, diet and exercise)
BMI ≥35 with prediabetes and high CVD risk	Baselines: Yes[a] Results: some[c]	Yes – subgroup analysis	Subgroup analysis (vs semaglutide, liraglutide, diet and exercise)
BMI ≥30 with/without comorbidities	Baselines: No Results: some[c]	No: only comparator is diet and exercise	Subgroup analysis (vs diet and exercise)
BMI ≥35 with/without comorbidities	Baselines: No Results: some[c]	No: only comparator is diet and exercise	Subgroup analysis (vs diet and exercise)

[a] Provided in response to clarification A4.

[b] NICE scoped outcomes provided in response to clarification A1, percent change in body weigh not provided.

[c] Change from baseline in percent body weight, HDL cholesterol, total cholesterol, SBP

2.2.1.2 SURMOUNT-1 subgroup results; those with BMI ≥30 kg/m2 and ≥ one weight-related comorbidity

As described in Sections 1.3 and 2.2.4 the population in SURMOUNT-1 is wider than the population considered in the company DP. The results from the subgroup with BMI ≥30 kg/m2 and ≥ one weight-related comorbidity were requested at clarification as these are pivotal to the economic analysis.

2.2.1.3 Baseline characteristics subgroup BMI ≥30 with ≥ one weight-related comorbidity

Baseline characteristics of the subgroup BMI ≥30 with ≥ one weight-related comorbidity were reported in clarification response A4. The EAG presents the key baseline characteristics in Table 18. The EAG assessed these to be balanced across the treatment arms. The EAG considered these baseline characteristics against those seen in the whole SURMOUNT-1 trial populations. Although there were some differences seen, these were all characteristics that are related to the

differences in the degree of overweight and obese (e.g BMI, weight, waist circumference, pre-diabetes) between the whole trial population and the subgroup which would be expected. The lipid profile (Total, HDL, LDL cholesterols, and Triglycerides) was very similar between those in the whole trial population and the subgroup. A possible reason for this similarity may be related to more intensive management of lipid-lowering with increased disease severity across the groups, but the EAG are unable to verify this with the available data.

Table 18. Key baseline characteristics from the subgroup BMI ≥30 + ≥1 weight-related comorbidity

	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
Attribute	(n = 435)	(n = 423)	(n = 433)	(n = 414)
Mean ± SD unless stated otherwise				
Age (years), mean ± SD	47.0 ± 12.2	48.1 ± 12.0	47.1 ± 11.8	47.4 ± 11.9
Female, n (%)	289 (66.4)	281 (66.4)	285 (65.8)	274 (66.2)
Age Category 1, n (%)				
<65	405 (93.1)	379 (89.6)	406 (93.8)	386 (93.2)
≥65	30 (6.9)	44 (10.4)	27 (6.2)	28 (6.8)
Race, n (%)				
Asian	41 (9.4)	36 (8.5)	40 (9.2)	38 (9.2)
Black or African American	42 (9.7)	35 (8.3)	34 (7.9)	36 (8.7)
White	312 (71.7)	304 (71.9)	311 (71.8)	300 (72.5)
Multiple	6 (1.4)	9 (2.1)	5 (1.2)	6 (1.4)
Others[a]	34 (7.8)	39 (9.2)	43 (9.9)	34 (8.2)
Weight (kg)	106.5 ± 21.7	104.9 ± 21.1	108.5 ± 23.5	108.3 ± 23.5
BMI (kg/m^2)	38.8 ± 6.9	38.2 ± 6.6	39.0 ± 6.9	39.1 ± 6.8
BMI Categories, n (%)				
<30	N/A	N/A	N/A	N/A
≥30 to <35	150 (34.5)	171 (40.4)	150 (34.6)	134 (32.4)
≥35 to <40	134 (30.8)	119 (28.1)	126 (29.1)	122 (29.5)
≥40	151 (34.7)	133 (31.4)	157 (36.3)	158 (38.2)
Waist circumference (cm)	115.7 ± 15.0	114.8 ± 14.4	117.0 ± 15.6	116.7 ± 15.6
Prediabetes, n (%)	260 (59.8)	234 (55.3)	248 (57.3)	239 (57.7)
Duration of obesity (year)	15.1 ± 11.5	15.4 ± 11.3	16.1 ± 11.8	15.9 ± 11.2
SBP (mmHg)	124.2 ± 12.7	125.0 ± 12.3	125.3 ± 13.2	124.5 ± 12.9

HbA1c (mmol/mol)	NR	NR	NR	NR
HbA1c (%)	5.7 (0.4)	5.7 (0.3)	5.6 (0.4)	5.6 (0.4)
Comorbidities, n (%)				
Hypertension	193 (44.4)	187 (44.2)	181 (41.8)	181 (43.7)
Dyslipidaemia	169 (38.9)	175 (41.4)	165 (38.1)	160 (38.6)
ASCVD	20 (4.6)	15 (3.5)	18 (4.2)	18 (4.3)
PCOS	7 (2.4)	4 (1.4)	9 (3.2)	3 (1.1)
OSA	58 (13.3)	41 (9.7)	47 (10.9)	45 (10.9)
Osteoarthritis	54 (12.4)	60 (14.2)	62 (14.3)	62 (15.0)
Depression[b]	44 (10.1)	47 (11.1)	42 (9.7)	35 (8.5)
NAFLD	9 (2.1)	4 (0.9)	9 (2.1)	4 (1.0)
Asthma or COPD[c]	69 (15.8)	54 (12.8)	55 (12.7)	45 (10.9)
Gout	6 (1.4)	8 (1.9)	6 (1.4)	10 (2.4)
Concomitant medications, n (%)				
Participants using ≥1 Lipid-lowering Medication	NR	NR	NR	NR
Participants using statins	84 (19.3)	86 (20.3)	65 (15.0)	69 (16.7)
Participants using ≥1 Antihypertensive Medication	NR	NR	NR	NR

adapted from Clarification question responses, A4, Tables 9, 10, and 11

[a] American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander combined by EAG

[b] Clarification Question Responses document *Table 14*. Reports only 'Depression' for the subgroup. Jastreboff et. al 2022, the company submission, clinical study report and National Clinical Trials supply a 'Depression or Anxiety' measure for the all Randomised Participants in addition

[c] Asthma and COPD combined by EAG

Abbreviations: ASCVD: Atherosclerotic Cardiovascular Disease; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Oedema; HbA1c: Haemoglobin A1c; NAFLD: Non-alcoholic Fatty Liver Disease; NR: Not reported; OSA: Obstructive Sleep Apnoea; PCOS: Polycystic Ovary Syndrome; SBP: Systolic Blood Pressure

2.2.1.4 Key results subgroup BMI ≥30 with ≥ one weight-related comorbidity

The results for the population specified in the decision problem were provided in clarification response A1 and are summarised in Table 19 below. Data for the key outcome of percent change in body weight were not provided. Clarification response A1 also presents data for FSG and HbA1c (not summarised here).

Weight loss outcomes and adverse events for the BMI ≥ 30 with weight related comorbidity group were consistent with the whole trial population results (Table 19,

and Table 20). Results for the EQ-5D-5L health index score were also similar, although the difference from placebo in the change from baseline was statistically significant for the 15 mg tirzepatide group only (Table 20).

Table 19. BMI ≥30 with ≥1 weight-related comorbidity: key clinical outcomes at 72 weeks, EAS

Parameters	**Placebo**	**Tirzepatide 5 mg**	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**
Percentage of participants achieving body weight reduction of:				
Number of participants in imputed data	[redacted]	[redacted]	[redacted]	[redacted]
≥5% (imputed values)	[redacted]	[redacted]	[redacted]	[redacted]
≥10% (imputed values)	[redacted]	[redacted]	[redacted]	[redacted]
≥15% (imputed values)	[redacted]	[redacted]	[redacted]	[redacted]
≥20% (imputed values)	[redacted]	[redacted]	[redacted]	[redacted]
BMI				
Number with baseline and post-baseline value at Week 72	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Waist circumference, cm				
Number with baseline and post-baseline value at Week 72	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Glycaemic status				
Number in the specified treatment group	[redacted]	[redacted]	[redacted]	[redacted]
Proportion with prediabetes at baseline to normoglycaemia at 72-weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

From Clarification response A1. Imputed data includes observed value and imputed value if endpoint measure is missing. Missing endpoint measures are imputed by predictions using observed data in the efficacy analysis set from the same treatment group through an MMRM analysis model for post-baseline measures.

[a] p<0.001 versus placebo for superiority.

[b] p<0.001 versus baseline.

[c] Proportions calculated by EAG

Table 20. BMI ≥30 with ≥1 weight-related comorbidity: EQ-5D-5L health index score at baseline and 72 weeks, EAS

Parameters	**Placebo** [redacted]	**Tirzepatide** [redacted]	**Tirzepatide** [redacted]	**Tirzepatide** [redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 72 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Change difference from placebo at 72 weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

From Clarification response A1. [redacted] [a] p<0.001 versus placebo for superiority.

[b] p<0.001 versus baseline.

[c] As stated in Clarification A1 Table 7, appears to be typographical error.

Table 21. BMI ≥30 ≥1 with weight-related comorbidity: overview of adverse events, SAS

Category	n (%)			
	Placebo [redacted]	**Tirzepatide 5mg** [redacted]	**Tirzepatide 10mg** [redacted]	**Tirzepatide 15mg** [redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations from study due to an AE	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations from study treatment due to an AE	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]

From Clarification response A1.

2.2.2 Ongoing trials

The company lists five ongoing studies of tirzepatide in CS Table 55 and provides the trial record numbers for these in Clarification response C1. The company states that the SURMOUNT-CN trial (NCT05024032) and SURMOUNT-J (NCT04844918), which are in Chinese and Japanese populations respectively and with lower BMI criteria for obesity or overweight, are therefore not generalisable to this appraisal. The EAG notes that NICE guidance in previous appraisals allow for lower BMI criteria for some ethnic minority groups, so these may be potentially of relevance.

The EAG conducted additional searches in the WHO ICTRP trial register search portal for records of trials of tirzepatide in obesity/overweight people. The additional ongoing studies identified by the EAG as of relevance from these additional searches are listed in Table 22.

Table 22. Additional ongoing trials of possible relevance

Main ID	Public Title	Completion date	Population
NCT06047548 SURMOUNT-MAINTAIN	A study of LY3298176 (tirzepatide) for the maintenance of body weight reduction in participants who have obesity or overweight with weight-related comorbidities	May 2026	Weight maintenance study
NCT06009653	Effect of tirzepatide plus intensive lifestyle therapy on body weight and metabolic health in Latinos with obesity	November 2025	Hispanic/Latino population
NCT05536804	A study of tirzepatide (LY 3298176) in participants with overweight or obesity and chronic kidney disease with or without type 2 diabetes	February 2026	Chronic kidney disease

NCT04847557 SUMMIT	A study of tirzepatide (LY 3298176) in participants with heart failure with preserved ejection fraction and obesity	July 2024	Heart failure

2.2.3 Generalisability

The company notes in CS B.2.12.2 that the limitations of the SURMOUNT-1 include the absence of any trial sites in UK or England, but state that the results still remain generalisable to UK clinical practice. This is expanded on in Clarification response A28, citing subgroup analysis results, generalisability of healthcare systems and standard of care arm, and supporting data from the SURPASS trial programme.

However, the EAG has a number of concerns regarding the generalisability of the evidence presented in the CS.

In clinical practice, the maintenance dose of 5 mg, 10 mg or 15 mg is decided by an individual's response on weight measures and adverse events, although guidance on the amount of weight loss that should occur for a decision to maintain at 5mg or to increase to 10 mg and then to 15 mg is not provided in the draft SmPC. In SURMOUNT-1, on the other hand, participants in each of the three dose arms could only receive the maximum maintenance dose they were allocated to. It is also unclear whether the same escalation and de-escalation protocol as in the trial would occur in clinical practice.

The NICE scope includes people with BMI ≥27 to <30 and at least one weight-related comorbidity. The whole trial population of SURMOUNT-1 included people with BMI ≥27 to <30, but limited to those with at least one of hypertension, dyslipidaemia, OSA or cardiovascular disease. CS Table 10 presents comorbidities of all randomised participants, but the distribution of these comorbidities for the population with BMI ≥27 to <30 is unclear. This subgroup was excluded from the company's base case and was not analysed as a separate subgroup. In addition, the SmPC lists prediabetes as an example of a weight-related comorbidity for those with BMI ≥27 to <30, however these people were not eligible for the trial unless they also had one of the four specified comorbidities. People with BMI ≥27 to <30 and other

weight-related comorbidities, such as chronic kidney disease, would also not have been eligible for SURMOUNT-1, and people with T2DM were excluded from the trial.

In previous NICE guidance (TA 664, TA 875), the BMI thresholds were reduced for people from some ethnic backgrounds. The eligibility for SURMOUNT-1 did not allow for this, therefore there is no evidence available for these subgroups.

2.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

Section B.2.9 of the CS describes the indirect treatment comparisons methods used by the company. The population under review in the ITC was the base case subgroup identified in the company's decision problem: adults with a BMI≥30 kg/m^2 and at least one weight-related comorbidity. NMAs of the whole trial population and the participants with BMI ≥35 kg/m^2 with prediabetes and a high CVD risk subgroup using the efficacy estimand were included as inputs scenario analyses in the economic model. NMAs were not relevant for the BMI ≥35 kg/m2 and BMI ≥30 kg/m2 subgroups (each irrespective of comorbidities) subgroups. An NMA of the whole trial population using the treatment regimen estimand was also included as inputs in economic scenario analyses. These subgroups are explained in 2.3.6**.**

2.3.1 Feasibility assessments of indirect treatment comparison methods

The only study which assessed the use of tirzepatide in the subgroup defined above was SURMOUNT-1, therefore no meta-analyses or pairwise meta-analyses were conducted.

The company opted for an anchored NMA to compare the efficacy of tirzepatide to semaglutide and liraglutide. The treatments were anchored by placebo across all the studies included in the NMA.

2.3.2 Search strategy

The company conducted a clinical SLR to identify RCTs that were related to the efficacy and safety of tirzepatide and its comparators for weight management. Studies were included if they evaluated approved FDA/EMA, approved in Japan, or non-approved (off label use) doses of the included treatments. The full eligibility criteria is presented in Table 7 of CS appendix D.1.3.

Searches were conducted on June 2, 2022, with an updated search conducted on March 1, 2023 using the same strategies and databases as outlines in CS section D.1.1. Databases included the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE®, and grey literature (conference abstracts from relevant conferences during 2020-2023).

The original SLR identified 6,355 records. After duplicates were removed, 3,873 remained. After title and abstract and full-text screening, 205 publications remain (figure 1 of D.1.5). The updated search in March 2023 identified a further seven publications (figure 2 of D.1.5).

CS section B.2.9.3.2 chronicled the eligibility assessment (section 2.1) of studies identified in the SLR for the NMA. Of the relevant comparators included in this submission, a total of six studies were eligible for inclusion in the NMA.

2.3.3 Heterogeneity of studies included in the ITC

Table 27 of CS B.2.9.3.4 present the treatment groups and eligible population of the studies included in the NMA. All studies included people aged 18 years and over who did not have diabetes. Eligibility for O'Neil 2018 included people with BMI ≥30 kg/m^2 and ≥1 nonsurgical weight-loss attempt. The other five studies included either patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with a weight-related comorbidity, such as hypertension, dyslipidaemia, obstructive sleep apnoea, or CVD. The EAG considers that the eligible populations were comparable, especially since all of the studies recruited adults without diabetes with BMI ≥30 kg/m^2.

2.3.3.1 Characteristics and background therapies

Tables 28 and 29 of CS B.2.9.3.4 and Table 24 of the EAG report compare the study design, demographic characteristics, and the background therapies of the studies included in the company's NMA as part of this submission. The six studies were:

- Liraglutide 3.0 mg QD vs placebo: O'Neil et al. 2018[28] and SCALE Obesity and Prediabetes.[29]
- Semaglutide 2.4 mg QW vs placebo: STEP 1[11] and STEP 5. [30]
- Semaglutide 2.4 mg QW vs liraglutide 3.0 mg QD vs placebo: STEP 8[31]
- Tirzepatide 5, 10, 15 mg QW vs placebo: SURMOUNT-1.[23]

CS Table 28 describes the descriptive statistics of patient characteristics across studies for the whole trial population of the six included studies. Although there were some differences observed with the percentage female lower in SURMOUNT-1 and in O'Neil 2018 and the percentage White was higher in SCALE and Step 5 studies were broadly similar. Mean BMI was around 37-39.5 kg/m^2, mean HbA1c was around 5.5-5.7%, and none had T2DM at baseline. One thing to note is that these descriptive statistics were provided for the whole cohort of each trial, not by treatment group. The EAG was unable to compare the characteristics of intervention groups only or the placebo groups only.

Table 29 of the CS describes the background therapies of the included studies. These consisted of a combination of diet advice, exercise recommendations, and other lifestyle intervention. The diet advice was consistent throughout. Participants were instructed to reduce calorie intake by 500 kcal per day with respect to their estimated energy requirements. Exercise recommendations included at least 150 minutes per week of exercise, except for SCALE Obesity and Prediabetes where pedometers were provided. Lifestyle intervention included regular dietary and/or exercise counselling, or completion of three-day food diaries. Three studies (SCALE Obesity and Prediabetes,[29] STEP 1,[11] and SURMOUNT-1[23]) included all three (diet plus exercise plus lifestyle intervention) as background therapies. The remaining studies (O'Neil 2018, [28] STEP 5,[30] and STEP 8[31]) included diet plus exercise as background therapies, not lifestyle intervention. However, the company stated in the table that STEP 5 included individual dietary counselling every 4 weeks. The EAG asked the company to clarify why STEP 5 was deemed to offer only diet plus exercise as background therapies given that it also included the lifestyle intervention of dietary counselling. From the clarification responses question A15, the company clarified the error and confirmed that the background therapies of STEP 5 were diet plus exercise plus lifestyle intervention (reference to Section 2.3.3.4 to add here).

Comorbidities at baseline were presented in clarification response A14 Table 21 for the key comorbidities of hypertension, dyslipidaemia and CVD. Rates of hypertension were similar, in the STEP 8 trial the rate of dyslipidaemia was higher than the other studies included in the NMA. There were limited data on which to compare rates of CVD across the included studies. Concomitant medications were presented in clarification response A19, Table 22. Rates were broadly in line across

the included trials with the exception of the proportion receiving anti-hypertensives which was lower in Step-1

2.3.3.2 Analysis timepoint

The company reported the timepoints of efficacy and safety outcomes of studies included in the NMA in CS section B.2.9.3.3. The timepoints eligible were between 52-72 weeks as this would mean patients would have been receiving full treatment dose for at least 52 weeks. In SURMOUNT-1, participants in the tirzepatide 15 mg group received this dose continuously for 52 weeks by week 72. In contrast, those in the 5 mg group remained on the 5 mg dose from week 5, accumulating a total duration of 68 weeks, while participants in the 10 mg group stayed on the 10 mg dose for 60 weeks.

The EAG requested the timepoint analysed for each study in the NMA during clarifications which was provided in responses to question A21. O'Neil 2018 and STEP 5 analysed data at 52 weeks, SCALE Obesity and Prediabetes at 56 weeks, STEP 1 and STEP 8 at 68 weeks.

Time on treatment at the point of analysis ranges from 52 weeks to 68 weeks, which is comparable, thus the EAG has no concerns regarding analysis timepoint.

2.3.3.3 Analysis set and estimands

The EAG requested details on the analysis sets for each study included in the NMA during the clarification stage. The main analysis of O'Neil 2018 was based on the ITT population, SURMOUNT-1 was based on the efficacy analysis set, and the remaining were based on the full analysis set.

As SURMOUNT-1 used the efficacy and treatment regimen estimand, and as it was possible to align the other studies to these estimands if they did not report it themselves, the company considered it more appropriate to compare the heterogeneity with regards to estimands, not analysis sets.

Generally, it is more appropriate to compare estimands in NMAs as they are defined to address specific research questions, ensuring that the analysis is directly aligned with the objectives of the NMA. They also provide a common framework for estimating treatment effects across different studies, even if design or population differ, and are designed to capture clinically meaningful outcomes.

The SCALE study did not report an estimand comparable to the efficacy estimand of SURMOUNT-1 given the relatively recent emergence of estimands in health research. It was assumed that the analysis of change from baseline (cfb) in weight (%) more closely aligned with the treatment regimen estimand as patients were asked to return at week 56 even if they withdrew. The other three outcomes aligned more to the efficacy estimand. The company deemed this more appropriate than removing the study of the network altogether.

Table 31 of CS B.2.9.3.6 presents the estimand definition of each study in the NMA, how they are comparable to the treatment regimen and efficacy estimands of SURMOUNT-1. The EAG agree with the company on taking the approach comparing the estimands and considers the alignment of estimands with that of SURMOUNT-1 to be appropriate given the evidence base and definitions provided.

2.3.3.4 Placebo response comparability

The company presented the placebo responses for the studies included in the NMA of the whole trial population and the BMI ≥30kg/m2 with at least one weight-related comorbidity subgroup in Figure 24 and Figure 25, respectively, of CS B.2.9.3.4. The EAG further asked for this data to be tabulated in clarification question A17. The company provided the placebo responses for the whole trial population using the efficacy estimand and the treatment regimen estimand, but not for the BMI ≥30kg/m2 with at least one weight-related comorbidity subgroup, in Table 23.

Table 23. Placebo responses of the studies included in the NMA

		Percent Body Weight		HDL		Total Cholesterol		SBP	
Estimand	**Trial**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Whole Population Efficacy Estimand	O'Neil, 2018	-2.30	0.71	0.00	1.00	-3.00	1.00	-1.58	1.04
	SCALE Obesity and Prediabetes	-2.60	0.16	0.70	0.52	-1.00	0.44	-1.50	0.35
	STEP 1	-2.44	0.32	2.00	0.71	0.00	0.60	-1.14	0.50
	STEP 5	-2.30	0.70					-0.72	2.54
	STEP 8	-1.80	1.02	-0.50	1.68	-0.20	1.56	4.50	1.45
	SURMOUNT-1	-2.40	0.41	0.20	0.74	-1.10	0.69	-1.20	0.47
	O'Neil, 2018	-2.30	0.74	0.00	1.00	-3.00	1.00	-1.58	1.04

Whole Population Treatment Regimen Estimand	SCALE Obesity and Prediabetes	-2.60	0.16	0.70	0.70	-1.00	0.55	-1.50	0.35
	STEP 1	-2.41	0.37	1.00	0.95	0.00	0.75	-1.06	0.54
	STEP 5	-3.30	0.56					-0.72	2.54
	STEP 8	-1.90	1.07	-0.90	1.89	-3.30	2.40	3.20	1.48
	SURMOUNT-1	-3.10	0.61	-0.68	1.12	-1.78	0.97	-1.00	0.68

The placebo responses across the studies in the network meta-analysis exhibit good consistency, with confidence intervals for each study demonstrating overlapping ranges. This suggests a high degree of homogeneity in the observed placebo effects, strengthening the robustness of the NMA.

2.3.3.5 Outcome definition

Of the four outcomes of the NMA (change from baseline in body weight, HDL, total cholesterol, and SBP), change in SBP was reported as absolute change across all studies. Change in body weight was reported as either percentage or ratio change and thus was comparable across studies.

Change in HDL and total cholesterol were reported as either absolute, percentage or ratio change. SURMOUNT-1 reported these outcomes as percentage change, which is comparable to ratio change. Where results were reported as absolute change, these were not included in the analysis as they were not comparable to the other two outcome types.

Only weight loss was included in the NICE scope, the other three outcomes were not specified in the scope.

2.3.3.6 Statistical heterogeneity

Statistical heterogeneity was calculated from the RE models for all of the analyses using the posterior between-study SD, presented in CS D.3. Additionally, where more than one study was included for a comparator, pairwise meta-analyses were conducted to calculate I-squared values. The EAG was unable to locate the results of this in the CS, therefore it was calculated using the codes and data provided.

2.3.3.7 Other points of heterogeneity

Table 24 of the EAG report describes the study design of the six included studies. All studies except O'Neil 2018 were phase III RCTs, and all are double-blind with the

exception of STEP 8. In STEP 8, active treatment groups are double-blind vs placebo, but are open-label between active treatment groups, due to the difference in dose timing (semaglutide once a week vs liraglutide once a day).

In responses to clarification question A21, the company provided data on the geographic location of each study included in the NMA. SCALE, STEP 1 and STEP 5 did not report the location of the studies, which is a major limitation. STEP 8 was only conducted in the United States of America. O'Neil 2018 and SURMOUNT-1 were conducted worldwide. The EAG was able to find the locations of SCALE, STEP 1, and STEP 5 in the NCT records. SCALE was conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, Former Serbia and Montenegro, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Mexico, the Netherlands, Norway, Poland, Russian Federation, Serbia, South Africa, Spain, Switzerland, Turkey, UK, and the USA. STEP 1 was conducted in Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puerto Rico, Russian Federation, Taiwan, UK, and the USA. STEP 5 was conducted in Canada, Hungary, Italy, Spain, and the USA.

2.3.4 Dose escalations and de-escalations

Pre-specified dose-escalation schemes were similarly used in the comparator trials for semaglutide and liraglutide, however, the time before participants reached maintenance doses were different for both comparator drugs.

Semaglutide doses are titrated from 0.25 mg every four weeks to reach the 2.4 mg maintenance dose at 16 weeks. In the STEP trials dose escalation could be individualised with a total delay of up to 7 days and dose reductions were permitted if the recommended target dose of 2.4 mg was not tolerated with the participant staying at 1.7 mg once weekly if otherwise they would have had to discontinue treatment completely. It was recommended that the participant make at least one attempt to re-escalate to 2.4 mg. No data on dose reductions (how many, how long or when occurred) were identified by the EAG.

Liraglutide doses are escalated from 0.6 mg per day and escalated by 0.6 mg each week (at least 1-week intervals depending on gastrointestinal tolerability) to the maintenance dose of 3 mg reached in week five. After reaching target dose no

changes were permitted and if a participant did not tolerate the dose they were withdrawn from the trial. The exception was for suspected acute pancreatitis which led to discontinuation until results of a confirmatory test were known, where those without pancreatitis could remain on the trial with re-initiation of titration until the target dose is reached. No details of numbers but likely small as the number of acute pancreatitis was n=4.

To conclude, the EAG picked up on the following points of concern regarding outcome definition and geographic diversity. Change from baseline in HDL and total cholesterol exhibited a mixture of definitions, including absolute change, percentage change, or ratio change. This was due to the absence of necessary data, as converting absolute change to percentage change required data not available in the related studies.

The included studies in the NMA exhibit notable heterogeneity in terms of geographic location. SCALE was conducted in a wide array of countries spanning multiple continents, including Europe, the Americas, and Asia. In comparison, STEP 1, O'Neil 2018, and SURMOUNT-1 were carried out in a diverse set of countries, with representation in North America, Europe, and Asia. Notably, STEP 5 had a more focused scope, primarily encompassing Canada, Hungary, Italy, Spain, and the USA. Conversely, STEP 8 was conducted exclusively within the United States. This geographic variance highlights the need for careful consideration of the distinct regional characteristics and healthcare systems in the interpretation and generalizability of the NMA results.

However, while the geographic diversity in the studies may introduce heterogeneity in the results, it is worth noting that the baseline demographic characteristics of key treatment effect modifiers were similar across the included studies. This suggests that while the study's findings may be influenced by the varied geographic settings, the fundamental factors influencing treatment outcomes remained consistent, providing a basis for comparative analysis. Nevertheless, for more direct applicability to the NHS population, it is crucial to consider the country-specific healthcare and demographic variations, necessitating localised data and potential adjustments in interpretation.

Table 24. Characteristics of the studies included in the company's NMA

Studies	Phase and design	Interventions	Control	Background therapy	Blinding	Geographic location
O'Neil, 2018	Phase 2 RCT	Liraglutide 3 mg QD	Placebo	Diet + Exercise	Double	Australia (5.7%) Belgium (9.4%) Canada (8.6%) Germany (9.8%) Israel (9.6%) Russia (15.6%) UK (11.7%) USA (40.2%)
SCALE Obesity and Prediabetes	Phase 3 RCT	Liraglutide 3 mg QD	Placebo	Diet + Exercise + Lifestyle Intervention	Double	Not reported
STEP 1	Phase 3 RCT	Semaglutide 2.4 mg QW	Placebo	Diet + Exercise + Lifestyle Intervention	Double	Not reported
STEP 5	Phase 3 RCT	Semaglutide 2.4 mg QW	Placebo	Diet + Exercise + Lifestyle Intervention[1]	Double	Not reported
STEP 8	Phase 3 RCT	Semaglutide 2.4 mg QW Liraglutide 3 mg QD	Placebo	Diet + Exercise	Double/open-label[2]	USA (100%)
SURMOUNT-1	Phase 3 RCT	Tirzepatide 5 mg QW	Placebo		Double	Argentina (14.4%)

		Tirzepatide 10 mg QW		Diet + Exercise + Lifestyle Intervention		Brazil (9.4%) China (1.2%) India (1.3%) Japan (4.9%) Mexico (17.0%) Russia (4.7%) Taiwan (2.3%) USA (44.9%)
		Tirzepatide 15 mg QW				

[1] Lifestyle intervention of STEP 5 added from clarification response A15

[2] STEP 8 is double-blind vs placebo and open-label vs active comparators

2.3.5 NMA methods

The company use the Bayesian Markov Chain Monte Carlo method to perform the NMA in OpenBUGS (version 3.2.3; revision 1012) and R (version 4.2.1) using the R2OpenBUGS package. The different models that were fitted include: unadjusted fixed effects model, unadjusted random effects model, fixed effects adjusted for baseline risk, random effects adjusted for baseline risk, and a further inconsistency model based on which of the previous four models fit the best.

The best-fitting model by way of the deviance information criterion (DIC) and total residual deviance was chosen. If these criteria were similar, the fixed effects model was chosen over the random effects model for ease of interpretation, the baseline risk model over the standard model, and the inconsistency model if an inconsistency was possible in the network (existence of at least one closed loop).

For each analysis, three chains with differing sets of initial values were used with an initial 20,000 burn-in iterations and then a further 60,000 iterations per chain. Vague priors were specified for all of the basic models (Table 35 of CS B.2.9.4.7). If the posterior distribution of tau, usually representing between-study heterogeneity or variance, informative priors were used, based on the approach by Turner et al.

The main analysis that informs the company's economic model base case is the subgroup NMA on participants whose BMI ≥30 kg/m^2 with at least one comorbidity from the efficacy estimand, participants with BMI ≥35 kg/m^2 with prediabetes and a high CVD risk were also considered in economic analyses. The NMA of the whole trial population did not inform the economic model but was included in the submission to allow for comparison with the subgroups. NMAs for the BMI ≥35 kg/m^2 and BMI ≥30 kg/m^2 (irrespective of comorbidities) were not conducted as the only head-to-head evidence for these comparisons were from SURMOUNT-1. Analyses conducted using the treatment regimen estimand were done for scenario analyses in the economic assessment of this submission.

The outcomes analysed in the submission were change from baseline in body weight, SBP, HDL, and total cholesterol. As outcomes were continuous, normal distribution with an identity link was specified, as recommended in NICE TSD 2. Baseline risk was adjusted for using meta-regression models as mentioned in NICE

TSD 3 using the study-level baseline risk. For random effect analyses, multi-arm adjustments were incorporated.

During the clarification stage, the company provided the data necessary to replicate all of the NMAs that were presented in this submission. The EAG also asked the company why the NMAs for discontinuation due to adverse effects, discontinuation due to primary treatment failure, and reversal of prediabetes were not included in the submission when these outcomes were included in the economic model. The company stated in clarification response A22 that discontinuation data for comparator studies were not available for the subgroups considered in the economic analysis in CS B.3.3.3. The economic modelling requires estimates of prediabetes reversal and discontinuations due to primary treatment failure, taking these from the active treatment arms of SURMOUNT-1, STEP-1 and SCALE without any adjustment for the placebo effect. The placebo effects differed quite noticeably between the trials, particularly the rates of prediabetes reversal:

The EAG performed its own NMA for reversal of prediabetes and achieving a minimum of 5% weight loss, results of which are presented in section 2.5.2.

Results were presented as relative treatment effects (median of mean difference) and corresponding 95% credible intervals.

2.3.6 NMA results

The main results of the company's NMA are presented in CS section B.2.9.5 with the remaining results presented in CS appendix D.5-6, a breakdown of which is presented in Table 36 of CS document B.

2.3.6.1 BMI ≥30 kg/m2 with ≥1 weight-related comorbidity subgroup

The results relevant to the base case of the economic model, participants BMI ≥30 kg/m2 with ≥1 weight-related comorbidity using the efficacy estimand is presented in section B.2.9.5.1 and summarised below in Table 25. All active treatments achieved statistical superiority over placebo for all four outcomes. Furthermore:

- Change from baseline in weight (%): tirzepatide 15 mg achieved statistical superiority over all other treatment arms, followed by tirzepatide 10 mg.

- Change from baseline in HDL (%): tirzepatide 15 mg achieved statistical superiority over semaglutide and placebo, but only numerical superiority over the other tirzepatide doses.
- Change from baseline in total cholesterol (%): tirzepatide 15 mg achieved statistical superiority over the other tirzepatide doses and placebo, but only numerical superiority over semaglutide.
- Change from baseline in SBP (mmHg): tirzepatide 10 mg achieved statistical superiority over placebo, and numerical superiority over the other treatment arms.

The fixed effects unadjusted model was chosen for all analyses as there were no differences between the fixed effects and random effects models in terms of DIC or residual deviance, and the interaction between baseline risk and treatment effect was not statistically significant. The results of this NMA were used in the economic model (Tables 64-67 of CS document B).

Table 25. Results of the NMA in participants BMI ≥30 kg/m2 with ≥1 weight-related comorbidity using the efficacy estimand

Outcome	Model	N trials	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg
CfB in weight (%)	FE unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CfB in HDL (%)	FE unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CfB in total cholesterol (%)	FE unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CfB in SBP (mmHg)	FE unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reference treatment = placebo, CfB Change from baseline, FE: fixed effect.						

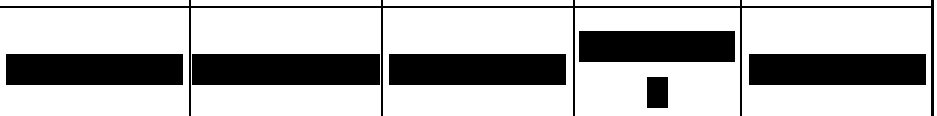
2.3.6.2 Whole trial population

Results for the whole trial population, which was used as a scenario in the economic model are presented in Table 26. Briefly:

- Change in weight (%): tirzepatide 15 mg achieved statistical superiority over all other treatment arms.
- Change in HDL (%): tirzepatide 10 mg achieved statistical superiority over liraglutide, semaglutide and placebo, and numerical superiority over tirzepatide 5 mg and 15 mg.
- Change in total cholesterol (%): tirzepatide 15 mg achieved statistical superiority over all other treatment arms except semaglutide, where it achieved numerical superiority.

Change in SBP (mmHG): tirzepatide 10 mg achieved statistical superiority over liraglutide, semaglutide and placebo, and numerical superiority over tirzepatide 5 mg and 15 mg.

Table 26. Results of the NMA of the whole trial population using the efficacy estimand

Outcome	Model	N trials	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Liraglutide 3 mg	Semaglutide 2.4 mg
CfB in weight (%)	FE unadjusted	6					
CfB in HDL (%)	FE unadjusted	5					
CfB in total cholesterol (%)	FE unadjusted	5					
CfB in SBP (mmHg)	FE baseline risk	6					

Reference treatment = placebo, CfB: FE: fixed effect.

Results of the other NMAs that are presented in appendix D of the CS generally favour tirzepatide over the other comparators. Tirzepatide 10 mg and 15 mg were usually superior (statistically or numerically) compared to the other treatments.

The company economic modelling uses the subgroup specific NMA estimates for change in body weight, SBP, HDL and total cholesterol. NMAs for the proportion of those with at least 5% weight loss, the proportion of those with prediabetes having this reversed to normal glycaemia, adverse events or discontinuations due to adverse events are not undertaken. The estimates for these are taken from the treatment arms of SURMOUNT-1 for placebo and tirzepatide 5mg, 10mg and 15mg, and from the active treatment arms of SCALE and STEP-1 for liraglutide and semaglutide respectively.

The EAG was able replicate the heterogeneity tests and NMA for the whole trial cohort and the subgroup used in the economic base case and were able to arrive at the same pooled results and conclusions, albeit with minor changes to the 95% credible intervals, however this is expected due to the nature of the Bayesian approach to statistics, such as differences in prior specifications or computational methods which can lead to very slightly different results.

2.3.6.3 Additional outcomes

2.3.6.3.1 Adverse events

No NMA was undertaken of the adverse events in the included trials (clarification A12). The EAG examined the adverse events reported in the NICE technology assessments of liraglutide (TA664 [17]) and semaglutide (TA 875 [1]). The adverse events in SURMOUNT-1 were broadly in line with those in the studies of liraglutide and semaglutide, with no additional concerns noted. The discontinuations owing to adverse events were also similar to those in SURMOUNT-1.

2.3.6.4 Pre-diabetes

Reversal of pre-diabetes across the comparator trials was not analysed in an NMA, this is discussed in more detail in Section 2.5.2.2. The EAG checked the definitions of prediabetes used in the trials. The trials all used the same criteria, although O'Neil 2018 [28] had an additional option that could be used to categorise diabetes. O'Neil 2018 also did not report the proportion with prediabetes at baseline, or report changes in glycaemic category, despite this being a secondary outcome.

2.4 *Critique of the indirect comparison and/or multiple treatment comparison*

The company's NMA feasibility assessment was presented in CS Section B.2.9.3. Six eligible RCTs evaluating the efficacy and safety of tirzepatide as well as specific treatment comparators (liraglutide and semaglutide) along with outcomes of interest were included in the feasibility assessment for conducting the NMA. The company assessed the feasibility of the NMA by examining:

- The treatment network connectivity.
- Loop consistency.
- Transitivity and heterogeneity assumption.

The three points above will be expanded more in this section, but, to summarise, the EAG considers the company's overall approach for assessing the feasibility of the NMA to be appropriate and in line with current NMA recommendations.

2.4.1 Treatment network connectivity

The network connectivity was examined through the characteristics of treatments, outcomes, and the existence of a common treatment. In all of the studies included in the NMA, placebo was the comparator, therefore placebo was the anchoring treatment arm connecting all treatments to each other except for the STEP 8 trial which include both a semaglutide and liraglutide arm compared to placebo. Figure 1 presents an illustration of the connectivity of the company's NMA when specific outcome is not taken into account.

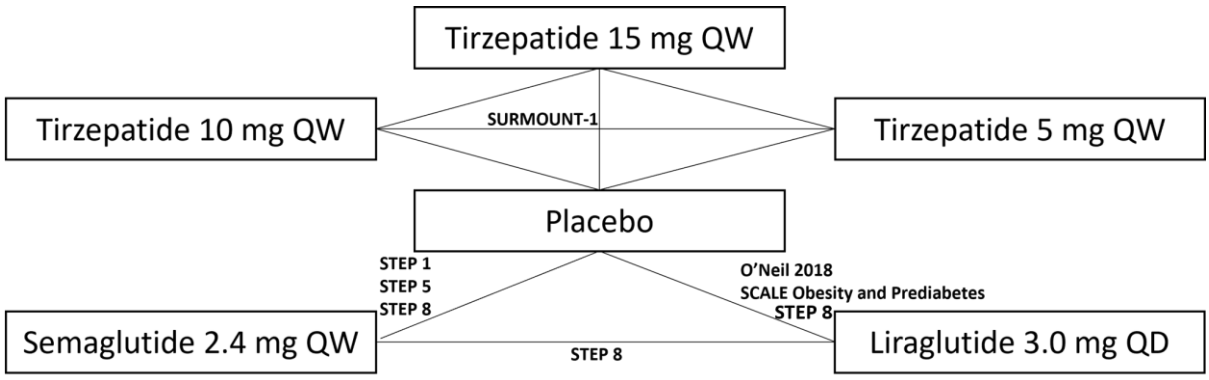


Figure 1. The full network connectivity of the six studies included in the company's NMA irrespective of outcome

Where studies did not report on different outcomes, they were removed from the network map, but this did not change the fact that placebo was the only comparator linking the active treatments together, unless STEP 8 was included in this network where there would be a closed loop between placebo, liraglutide and semaglutide. The EAG notes that the treatment nodes were connected correctly in all of the NMA plots.

2.4.2 Loop consistency

The STEP 8 trial had three treatment groups: liraglutide, semaglutide, and placebo. When this study was included in a network, a closed loop appeared in the network map. This trial was included in the NMA for the following populations and outcomes:

- Whole trial population: change from baseline in weight, HDL, total cholesterol, and SBP.
- (Base case) BMI ≥ 30 kg/m^2 with at least one weight-related comorbidity: Not included.
- BMI ≥ 35 kg/m^2 prediabetes and high CV risk: Not included.

In the company's NMA results, the consistency models were favoured over the inconsistency model as the DIC for both models were similar, suggesting no evidence of loop inconsistency.

The EAG tested loop consistency by removing one of the links in the network and comparing the direct estimates to the indirect estimates and found it consistent with the overall NMA result. Therefore, the EAG concludes that the network is internally consistent and the model accurately reflects the relationship between the treatments.

2.4.1 Transitivity and Heterogeneity

Transitivity was assessed in this submission by comparing the distribution of population characteristics that are effect modifiers across the treatment comparisons in the presented network.

The heterogeneity assumption of the NMA was examined by conducting a heterogeneity test on a set of pooled studies that compared the same treatments to determine if there was any clinical, methodological or statistical heterogeneity between the studies.

The company provided the I-squared values for the NMA of the whole trial population for both the efficacy and treatment regimen estimands in Table 14 of CS appendix D.3 and is presented below in Table 27. Except the change from baseline in weight for both estimands, and change from baseline in SBP for the treatment regimen estimand, the I-squared values may represent moderate to substantial heterogeneity, according to section 9.5.2 of the Cochrane Handbook for Systematic Reviews of Interventions. The company stated in section B.2.9.4.4 that "I-squared analyses indicate limited heterogeneity in the networks where this analysis could be conducted; however, the wide 95% CIs mean this conclusion is subject to some uncertainty." However, an I-squared of 45%, 67% and 72% indicate substantial heterogeneity. This suggests the studies included in the analysis are not consistent with their results and this variability may stem from the factors of concern that were noted in section 2.3.3 of the EAG report, namely differences in outcome definitions and the diversity in geographic region within- and between-studies.

Table 27. I-squared (95% CI) values for the NMA of the whole trial population; from Table 14 of CS appendix D.3

Outcome	Efficacy Estimand	Treatment Regimen Estimand
Cfb in weight (%)	[redacted]	[redacted]
Cfb in HDL (%)	[redacted]	[redacted]
Cfb in total cholesterol (%)	[redacted]	[redacted]
Cfb in SBP (mmHG)	[redacted]	[redacted]

2.5 *Additional work on clinical effectiveness undertaken by the EAG*

2.5.1 Statistical heterogeneity I-squared

The company did not include the I-squared values for the NMAs of the BMI≥30 kg/m^2 with weight-related comorbidities subgroup, which was used as the base case in the economic model. Using the codes and data the company provided to the EAG, the EAG calculated the I-squared values for the subgroup used in the economic base case. I-squared was calculated to be under 20% across the four NMAs, indicating that heterogeneity was not an issue. It should be noted that there are only two

studies in the NMA of the BMI ≥30 kg/m2 with ≥1 weight-related comorbidity subgroup. The results are reliable due to the low I-squared values and the use of a fixed-effects model is justified due to the lack of significant heterogeneity.

When calculating the I-squared and Cochrane's Q using pairwise fixed and random-effects meta-analyses for liraglutide, semgalutide, and placebo, the results are presented in Table 28 for the full cohort and the main subgroup (BMI ≥30 kg/m^2 with at least one comorbidity).

Table 28. Statistical heterogeneity pairwise meta-analysis

	Whole cohort							
	Cfb Weight (%)		**Cfb HDL**		**Cfb cholesterol**		**Cfb SBP**	
	I-squared	**Cochrane's Q P-value**	**I-squared**	**Cochrane's Q P-value**	**I-squared**	**Cochrane's Q P-value**	**I-squared**	**Cochrane's Q P-value**
Liraglutide	58.3%	0.091	57.7%	0.094	58.1%	0.092	0.0%	0.390
Placebo	0.0%	0.956	16.2%	0.311	42.8%	0.136	69.5%	0.006
Semaglutide	0.0%	0.897	94.4%	< 0.001	91.2%	0.001	0.0%	0.931
	BMI ≥30 kg/m^2 with at least one comorbidity subgroup							
Placebo	0.0%	0.930	76.6%	0.039	69.9%	0.068	0.0%	0.991
Cfb change from baseline								

The majority of pairwise comparisons have little to no heterogeneity, as confirmed through the small I-squared value and non-significant Cochrane's Q p-value. However, there are a few of concern with either a high I-squared value, such as cfb HDL and total cholesterol for the semaglutide comparison in the whole cohort, and statistically significant p-values. This signifies that the studies included in the analysis exhibit substantial variability in their effect sizes, indicating a significant level of heterogeneity. The statistically significant p-values for Cochrane's Q test further confirm that the observed variability in these outcomes is unlikely to have occurred by chance alone, emphasising the need to explore and understand the potential

sources of heterogeneity and consider alternative statistical approaches in the meta-analysis.

2.5.2 Prediabetes and 5% weight loss NMA

The EAG conducted a series of NMAs for two outcomes: prediabetes reversal and minimum 5% weight loss. There were four NMAs for prediabetes reversal and one for 5% weight loss.

2.5.2.1 Statistical analysis of NMAs

Data for the tirzepatide vs placebo comparisons were taken from the CS Document B which featured results of the SURMOUNT-1 trial. Data for the semaglutide vs placebo comparisons were taken from publications of the STEP-1 trial, and data for the liraglutide vs placebo comparisons were taken from NICE TA664 which were the committee papers of the STA "Liraglutide for managing overweight and obesity". The inputs of the NMAs are presented in Table 29.

The analyses were conducted using the R2OpenBUGS package in R, using Bayesian fixed effects models. The models were 10,000 burn-in samples and then three chains of 60,000 iterations for a total of 180,000 iterations. Vague priors were utilised. Results are presented as median of mean differences with corresponding 95% credible intervals.

2.5.2.2 Prediabetes reversal NMAs

The populations analysed in the four NMAs for this outcome were the whole trial population, the subgroup of patients with a BMI ≥30 kg/m^2 in the presence of at least one comorbidity, the subgroup of patients with a BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD, and a scenario analysis on the whole trial population where the input of the liraglutide group was for early responders only.

The tirzepatide 15 mg group was the best performing of the three tirzepatide groups across the four NMAs of this outcome. However compared to placebo, semaglutide performed the best (highest median and mean), then liraglutide, and then tirzepatide 15 mg.

In the BMI ≥ 30 kg/m^2 with at least one comorbidity subgroup, compared to a weighted mean placebo response rate of 51.6%, over 95% of the semaglutide group achieved prediabetes reversal, 90% of the liraglutide group, 84% of the tirzepatide

15 mg group, 81% of the 10 mg group, and 79% of the 5 mg group. Semaglutide was superior to all the tirzepatide groups (95% CrIs did not overlap).

2.5.2.3 Minimum 5% weight loss NMA

One NMA of this outcome was conducted by the EAG using the whole trial populations where available.

The tirzepatide 10 mg and 15 mg groups had the highest median estimates from the fixed-effects NMA model which, when compared to a weighted mean response placebo rate of 28%, resulted in a 96.2% response rate for this outcome. The tirzepatide 5 mg was third best (89.2%), then semaglutide (87%), and then the liraglutide group (68%).

Results of the NMAs are presented in Table 30.

Table 29. Data inputs for the prediabetes and weight loss NMA

Intervention	Placebo	Intervention rates	Placebo rates	Intervention N	Placebo N	Source
NMA1: Prediabetes in the whole trial population						
TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
LIRA	Placebo	75.5%	35.2%	400	95	TA664
SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1
NMA2: Prediabetes in the whole trial population scenario analysis using results of liraglutide early responders						
TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
LIRA	Placebo	82.8%	40.7%	314	55	TA664
SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1
NMA3: Prediabetes in the BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup						
TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
LIRA	Placebo	75.5%	35.2%	400	95	TA664
SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1
NMA4: Prediabetes in the BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD subgroup						
TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B
LIRA	Placebo	75.5%	35.2%	400	95	TA664
SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1
NMA5: Primary responders: Minimum 5% weight loss in full trial population						
TIRZ 5mg	Placebo	89.4%	27.9%	630	643	CS Doc B
TIRZ 10mg	Placebo	96.2%	27.9%	636	643	CS Doc B
TIRZ 15mg	Placebo	96.3%	27.9%	630	643	CS Doc B
LIRA	Placebo	59.9%	20.3%	531	271	TA664
SEMA	Placebo	92.4%	33.1%	1059	499	STEP 1

Table 30. Results of the NMAs for prediabetes and weight loss with 95% credible intervals

	Median	2.5% CrI	97.5% CrI	Median plus weighted mean of placebo
Prediabetes reversal				
NMA 1				
Tirzepatide 5 mg	32.9%	28.5%	37.3%	86%
Tirzepatide 10 mg	32.0%	27.6%	36.3%	85%
Tirzepatide 15 mg	34.9%	30.6%	39.3%	88%
Liraglutide	40.9%	30.3%	51.5%	94%
Semaglutide	44.0%	39.6%	48.4%	97%
NMA 2				
Tirzepatide 5 mg	32.9%	28.5%	37.3%	56%
Tirzepatide 10 mg	32.0%	27.6%	36.3%	56%
Tirzepatide 15 mg	34.9%	30.6%	39.3%	56%
Liraglutide	41.8%	27.5%	56.1%	61%
Semaglutide	44.0%	39.6%	48.4%	56%
NMA 3				
Tirzepatide 5 mg	30.9%	26.5%	35.3%	54%
Tirzepatide 10 mg	31.0%	26.6%	35.3%	54%
Tirzepatide 15 mg	33.9%	29.6%	38.3%	54%
Liraglutide	40.9%	30.3%	51.5%	57%
Semaglutide	44.0%	39.6%	48.4%	54%
NMA 4				
Tirzepatide 5 mg	29.6%	20.8%	38.6%	54%
Tirzepatide 10 mg	31.7%	23.0%	40.6%	54%
Tirzepatide 15 mg	34.7%	26.7%	42.8%	53%
Liraglutide	40.9%	30.3%	51.5%	55%
Semaglutide	44.0%	39.6%	48.4%	51%
Minimum 5% weight loss				
NMA 5				
Tirzepatide 5 mg	60.9%	56.5%	65.3%	31%
Tirzepatide 10 mg	67.9%	63.5%	72.3%	31%
Tirzepatide 15 mg	67.9%	63.5%	72.3%	31%
Liraglutide	40.0%	34.4%	45.5%	31%
Semaglutide	59.0%	54.6%	63.4%	31%

2.5.3. Conclusions of the clinical effectiveness section

- The CS provided evidence comparing tirzepatide one weekly maintenance doses of 5 mg, 10 mg and 15 mg in addition to diet and exercise with placebo in addition to diet and exercise. One study was identified in the company SLR, SURMOUNT-1, which is an international double-blind placebo-controlled phase III RCT. SURMOUNT-1 is ongoing but the primary efficacy analysis at 72 weeks has been undertaken.
- The EAG considers the overall risk of bias in SURMOUNT-1 to be of some concern due to an unexplained imbalance in discontinuations between the trial groups.
- The population specified in the NICE scope was adults with a BMI of ≥30 kg/m2 (obesity) or ≥27 kg/m2 to <30 kg/m2 (overweight) and at least one weight-related comorbidity. The SUMOUNT-1 eligibility criteria were more strict for people with a BMI ≥27 kg/m2 to <30 kg/m2 , specifying that the weight-related comorbidity had to be one of hypertension, dyslipidaemia, OSA or cardiovascular disease. The company decision problem focused on a narrower population than defined in the NICE scope. This was on adults who have a BMI of ≥30 kg/m2 (obesity) and at least one of the four weight-related comorbidities. The results from SURMOUNT-1 were presented for the whole trial population, however, at clarification the company provided summary results for the clinical efficacy of the decision problem subgroup.
- In SURMOUNT-1 there was a statistically significant difference favouring all doses of tirzepatide versus placebo at 72 weeks follow-up for key outcomes including in body weight, BMI and waist circumference. Health-related quality of life measures echoed the results of the clinical effectiveness outcomes. There was also evidence of higher doses of tirzepatide achieving better responses on key clinical effectiveness outcomes, although this was less marked between tirzepatide 10 mg and tirzepatide 15 mg. Weight loss outcomes for the BMI ≥ 30 kg/m2 with at least one weight-related comorbidity subgroup (company decision problem population) were generally consistent with the whole trial population results.

- Adverse events were generally more common in the tirzepatide treatment groups than the placebo group. The most commonly reported adverse events with tirzepatide were GI. The rates of adverse events between the tirzepatide arms were generally similar suggesting there may not be a dose relationship. Discontinuations from the study treatment due to AEs in the tirzepatide arms ranged from 4.8-7.2%. However, a pre-specified dose escalation scheme was used in SURMOUNT-1, which may have had an effect on the adverse event rates seen. Dosing started at 2.5 mg once weekly and increased by 2.5 mg every 4 weeks, taking four weeks to reach 5 mg, 12 weeks to reach 10 mg and 20 weeks to reach 15 mg. Therefore, the actual dose of tirzepatide that the participant was taking at the time of an adverse may have been lower than the final assigned dose. There was also a dose de-escalation strategy for those reporting intolerable GI symptoms. The aim of the dose-escalation and de-escalation scheme was to minimise GI effects, however, the EAG notes that GI effects were the most common reason for drug discontinuation.
- The EAG has concerns regarding the generalisability of the evidence provided in terms of the alignment of the doses with how tirzepatide would be used in clinical practice, the differences between the trial population and the NICE scope, and the lack of evidence or use of appropriate BMI thresholds for people with some ethnic backgrounds.
- The EAG did not identify any concerns with regards to the statistical analyses of the outcomes presented in section B.2.6 of the CS. In the absence of head-to-head trials comparison tirzepatide to the active treatments outlined in the NICE scope, the company performed an NMA which was anchored by the common comparator across all of the eligible studies, placebo. The EAG agreed with the company's feasibility assessment which concluded that the NMA was the most appropriate ITC method given the availability of studies and data. Results of the NMA was used in the economic assessment of tirzepatide 10 mg and 15 mg by showing superiority over semaglutide, thereby allowing the company to focus on the tirzepatide vs semaglutide vs diet and exercise alone in the economic analyses.
- The EAG had a few concerns regarding the NMA methodology. Namely, issues surrounding statistical heterogeneity where the I-squared of the base

case NMA and NMA of the whole trial population were, for some outcomes, in the moderate to high presence of heterogeneity range. Additional issues were concerning differences in definitions of the change from baseline in HDL and total cholesterol outcomes between studies, and the notable heterogeneity in terms of geographic location between studies.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

Overall, the search strategy was appropriate. Fewer comparators were included in the cost-effectiveness search in comparison to the clinical searches. There was a very limited attempt to search for diet and exercise (only two indexing terms, no free-text). Database searches were undertaken in October 2022.

HRQoL and CRU SLR searches included two SLRs from SRs/HTAs that included HSUV and CRU data for individuals with obesity or obesity related comorbidity. Database searches (undertaken in Dec 2022) were limited to SRs and HTAs published in 2017 and onwards. For all database search strategies, lines 1-3 for 'disease area and interventions' were not very sensitive. Appropriate study type filters were applied. There were some discrepancies between the CS Doc B and the CS appendices that were resolved in clarification questions. It was unclear if the literature sources for utilities used in the CS model were identified from the HRQoL SLR or from studies identified from cost-effectiveness SLR or other sources. Targeted searches were used for the CRU literature sources (CS Doc B section B.3.2.5.1).

3.1.1 NICE reference case checklist

Table 31: NICE reference case checklist

Element	Reference case	EAG comment
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Yes.
Perspective on costs	NHS and PSS	NHS costs are applied. There is no consideration of PSS costs.

Element	Reference case	EAG comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No. A cost utility analysis is presented. Results for the mutually exclusive alternatives are presented as pairwise comparisons. A fully incremental analysis is not presented in the company submission.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. A lifetime horizon is applied.
Synthesis of evidence on health effects	Based on systematic review	Yes. But only a subset of the clinical effect estimates is drawn from the NMA. The estimates of prediabetes reversal, the proportion losing at least 5% body weight and discontinuations due to adverse events are taken from the individual arms of the relevant studies and do not control for placebo.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. But the EQ-5D data of SURMOUNT-1 is ignored. The main source of quality of life values used the EQ-5D-3L.

Element	Reference case	EAG comment
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. The main source of quality of life values used the Health Survey for England. It estimated the effects of age, BMI and comorbidities upon quality of life. As such it relates to the general population rather than the patient group under consideration. This function is not applied for those with a BMI of more than 35 kgm^{-2}, but a linear function is extrapolated from it as in TA664.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. The standard UK tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.1.2 Model structure

The company presents an individual patient model programmed in visual basic for applications. This employs a 4 week cycle length for the first 2 years of the model in order to be able to simulate the different time points for initial effects and also for discontinuations due to not achieving a 5% weight loss at the relevant time points. Thereafter an annual cycle length is applied.

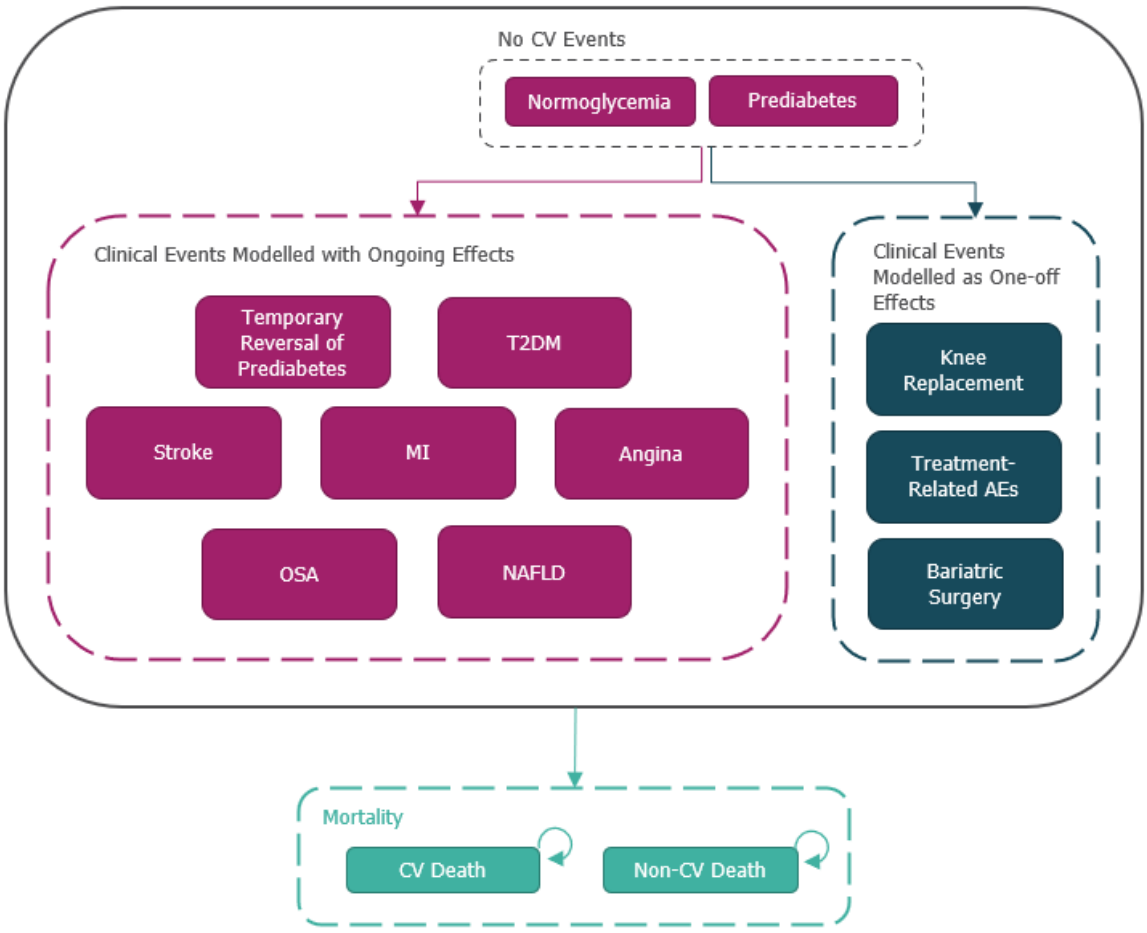


Figure 2: Model structure: © Eli Lilly and Company (2023). All rights reserved

The company base case models placebo, semaglutide, tirzepatide 5mg, 10mg and 15mg, all in addition to diet and exercise. A scenario analysis includes liraglutide for the patient population approved under TA664, as outlined below.

The treatment effects taken from the company NMA are:

- Weight change
- SBP change

- HDL change
- Total cholesterol change

Treatment effects taken from the individual arms of SURMOUNT-1, STEP-1 and SCALE are:

- Proportion of patients achieving a 5% weight loss
- Prediabetes reversal
- Severe and serious GI adverse events
- Discontinuations due to AEs

For these effects, the estimate for placebo is taken from SURMOUNT-1 trial, the values for placebo in STEP-1 and SCALE being disregarded.

The model estimates the following events:

- CVD events, myocardial infarction, stroke and angina 1st events and recurrent events
- Obstructive sleep apnoea (OSA)
- Non-alcoholic fatty liver disease (NAFLD)
- Type 2 diabetes (T2DM)
- Knee replacement
- Bariatric surgery
- Death

The risk equations for these are briefly summarised below.

Adverse events are also modelled.

3.1.3 Population

The company base case presents a comparison with semaglutide as assessed in TA875 using the NMA data, so for a population without T2DM, a BMI ≥ 30kgm^{-2} and at least 1 comorbidity associated with obesity.

The company presents four further comparisons:

- A comparison with liraglutide as assessed in TA664, so for a population without T2DM, a BMI ≥ 35kgm^{-2}, prediabetes and a high risk of CVD,
- A population without T2DM and a BMI ≥ 30kgm^{-2} for a comparison with placebo,
- A population without T2DM and a BMI ≥ 35kgm^{-2} for a comparison with placebo, and
- The SURMOUNT-1 trial population.

The EAG mainly focusses upon the target population subgroup and the TA664 population subgroup of SURMOUNT-1, also presenting the all patient population main baseline characteristics in Table 32.

For reasons of space, Table 32 and Table 36 use the headers “Target pop” to denote the patient group with BMI ≥ 30 kgm^{-2} with at least one comorbidity and “TA664 pop” to denote the patient group with BMI ≥ 35 kgm^{-2}, pre-diabetes and a high CVD risk.

Table 32: Baseline patient characteristics: SURMOUNT-1

	All patients	Target pop	TA664 pop
Age	45	47	47
Female	68%	66%	66%
BMI	38.0	38.8	42.6
SBP	123.3	124.8	126.5
TC	187.9	194.0	158.8
HDL	47.3	48.7	45.3
Pre-diabetes	41%	58%	100%

3.1.4 Interventions and comparators

The company base case compares tirzepatide 5mg, 10mg and 15mg with semaglutide 2.4mg and placebo, all in conjunction with diet and exercise.

For the scenario analyses:

- The TA664 based analysis compares tirzepatide 5mg, 10mg and 15mg with liraglutide, semaglutide and placebo, all in conjunction with diet and exercise.

- For the populations with (a) a BMI ≥ 30kgm^{-2}, (b) BMI ≥ 35kgm^{-2} and (c) the SURMOUNT-1 ITT population tirzepatide 5mg, 10mg and 15mg are compared to placebo, all in conjunction with diet and exercise.

3.1.5 Perspective, time horizon and discounting

These are broadly aligned with the NICE reference case. The stated perspective is patient benefits for quality of life and NHS/PSS for costs, though no PSS costs are included. A lifetime horizon and 3.5% discount rate are applied.

3.1.6 Treatment effectiveness estimates from the NMA

The company uses the EAS NMA clinical effect estimates for BMI, SBP, HDL and total cholesterol, these being the percentage change from baseline except for SBP which is the change in mmHg from baseline. The timing of these effects within the model differs between treatments: 56 weeks for placebo and liraglutide, 68 weeks for semaglutide and 72 weeks for tirzepatide.

Table 33: EAS NMA efficacy data: All patients

	Weight	SBP	HDL	TC
PLAC	[redacted]	[redacted]	[redacted]	[redacted]
LIRA	[redacted]	[redacted]	[redacted]	[redacted]
SEMA	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 5mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 10mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 15mg	[redacted]	[redacted]	[redacted]	[redacted]

The values in Table 33‡ for weight, SBP, HDL and TC largely correspond with the fixed effect model estimates reported in Tables 46, 52, 48 and 50 of the company submission Document B for placebo, liraglutide and semaglutide. But there are some discrepancies between Table 33 and the company submission in the weight, SBP, HDL and TC changes for tirzepatide 5mg, 10mg and 15mg, though these discrepancies are typically relatively small. There is also a small discrepancy in the TC value for placebo.

The values for the reversal of prediabetes correspond with those implied in the company submission Document B Table 20 and reported in Table 69.

‡ Taken from the model *Subgroup Data* worksheet

Table 34: EAS NMA efficacy data: BMI ≥ 30kgm^{-2} and 1 comorbidity

	Weight	SBP	HDL	TC
PLAC	[redacted]	[redacted]	[redacted]	[redacted]
SEMA	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 5mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 10mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 15mg	[redacted]	[redacted]	[redacted]	[redacted]

Within the position sought of BMI ≥ 30kgm^{-2} liraglutide is not considered a relevant comparator.

The values in Table 34 for weight, SBP, HDL and TC correspond with the fixed effect model estimates reported in Tables 38, 44, 40 and 42 of the company submission Document B.

Table 35: EAS NMA efficacy data: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk

	Weight	SBP	HDL	TC
PLAC	[redacted]	[redacted]	[redacted]	[redacted]
LIRA	[redacted]	[redacted]	[redacted]	[redacted]
SEMA	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 5mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 10mg	[redacted]	[redacted]	[redacted]	[redacted]
TIRZ 15mg	[redacted]	[redacted]	[redacted]	[redacted]

The values in Table 35 for weight, SBP, HDL and TC correspond with the fixed effect model estimates reported in Tables 24, 30, 26 and 28 of the company submission Appendix D.5.

The model also has the facility to use the ITT NMA data as presented in the company submission Appendix D.6.

3.1.7 Reversal of pre-diabetes

The company NMA does not consider the proportions of patients having their pre-diabetes reversed to normal glycaemia. This is instead sourced from SURMOUNT-1 for placebo and tirzepatide 5mg, 10mg and 15mg. For liraglutide and semaglutide the company states that it sources these from TA875, these not being differentiated by subgroup.

TA875 reports prediabetes reversal of 90.4% for semaglutide and 45.8% for diet and exercise for the STEP-1 trial. TA875 also applied a value of 83.6% for liraglutide. TA664 reports prediabetes reversal of 82.8% for liraglutide and 40.7% for diet and exercise in the SCALE trial.

Table 36: Pre-diabetes reversal estimates by patient subgroup

Group	All	Target pop	TA664 pop
PLAC	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
SEMA	[redacted]	[redacted]	[redacted]
TIRZ 5mg	[redacted]	[redacted]	[redacted]
TIRZ 10mg	[redacted]	[redacted]	[redacted]
TIRZ 15mg	[redacted]	[redacted]	[redacted]

3.1.8 Severe or serious GI events

Adverse events are limited to severe or serious GI events, sourced from the single arms of SURMOUNT-1, STEP-1 and SCALE, with the placebo rate being taken from the placebo arm of SURMOUNT-1.

Table 37: Severe or serious GI events

	Annual rate
PLAC	0.80%
TIRZ 5mg	1.23%
TIRZ 10mg	2.26%
TIRZ 15mg	2.40%
SEMA	4.90%
LIRA	7.10%

It appears that these are assumed to occur at the same annual rate for the duration of treatment.

3.1.9 Discontinuations due to lack of primary efficacy.

Despite 28% of the EAS placebo arm patients of SURMOUNT-1 achieving a weight reduction of at least 5% the model assumes that all those in the placebo arm in effect discontinue at week 72 and see their weight loss reversed.

For the active treatments, it is assumed that a proportion of patients have their treatment withdrawn. This proportion is based upon the estimated proportions of patients not achieving a weight loss of at least 5%. But the current EAG understanding is that for a given treatment the model applies the same percentage weight loss to all patients. A proportion of these patients have their treatment withdrawn as per the values in Table 38.

Table 38: Discontinuations due to lack of primary efficacy

	Discontinuations	Modelled (wks)
PLAC	100%	
LIRA	17.00%	16
SEMA	10.00%	26
TIRZ 5mg	9.65%	30
TIRZ 10mg	3.77%	38
TIRZ 15mg	3.74%	46

The values for tirzepatide are based upon SURMOUNT-1 72 week data. The 10% estimate for semaglutide is based upon expert opinion, while the 17% estimate for liraglutide is taken from that reported in TA875.

It appears that the values for placebo and tirzepatide may be taken from SURMOUNT-1 all patient data and so not be specific to the target group of those with a BMI ≥ 30 kgm^{-2} and at least one comorbidity. They are not varied by subgroup within the modelling.

The reason for the different modelled timepoints for tirzepatide is that the company has allowed for the up-titration period; i.e. for tirzepatide the primary efficacy estimates are assumed to be applied after 6 months maintenance dosing. The draft SmPC states that

“[redacted]”.

Allowing for up titration does not appear to apply to semaglutide. Its SmPC notes that dose up-titration should occur over 16 weeks but it also notes assessing response at 6 months in identical wording to that of the draft tirzepatide SmPC. The FAD of TA875 suggests stopping treatment if a weight loss of at least 5% has not

been achieved after 6 months on the maintenance dose. The EAG will increase the time for assessment of response for semaglutide to 42 weeks.

3.1.10 Discontinuations due to adverse events

Discontinuations due to adverse event rates are taken from the individual arms of the relevant trials and annualised based upon the trial follow up period. These are applied during every model cycle, suitably adjusted for the initial shorter model cycles.

Table 39: Discontinuations due to adverse events

	AE Disc	Weeks	Annual
TIRZ 5mg	4.29%	72	3.11%
TIRZ 10mg	7.08%	72	5.16%
TIRZ 15mg	6.19%	72	4.51%
SEMA	7.04%	56	6.56%
LIRA	9.89%	68	7.59%

3.1.11 Discontinuations due to stopping rules

TA875 specifies a maximum 2 year treatment duration for semaglutide. TA664 specifies that liraglutide can only be used in SWMS, the company noting that access to an SWMS is limited to a maximum of 2 years. As a consequence, the company applies a 2-year stopping rule for semaglutide and liraglutide.

The company Appendix M page 354 notes that SURMOUNT-4 shows that withdrawal of maximum tolerated 10/15mg tirzepatide at 36 weeks results in the 36 week 21.1% mean weight loss falling to only 6.3% at 88 weeks, whereas ongoing maximum tolerated 10/15mg tirzepatide further increased the weight loss to 27.8% at 88 weeks and a net effect of 21.4%.

It has not yet been stipulated whether tirzepatide should be provided within an SWMS or not. The company assumes it will not, and so does not apply a stopping rule for tirzepatide at 2 years.

3.1.12 Discontinuations and loss of treatment effect

For the active treatments, after treatment discontinuation due to the treatment stopping rule or due to adverse events a linear loss of treatment effect is assumed.

Patients' risk factors return to the placebo arm values after 3 years, thereafter following the placebo arm values. For a male patient with a baseline BMI of 33 kgm^{-2} and a weight of 91.2kg who does not discontinue due to stopping rules or adverse events the modelled evolution of his weight is shown below, based upon information supplied by the company at clarification.

3

For the evolution of weight the initial treatment effect is assumed to occur over the first 68 weeks of the model for semaglutide and 72 weeks for tirzepatide.

For semaglutide this weight loss is retained for 36 weeks to week 104 at which point the stopping rule applies. The patient returns to the placebo curve linearly over a period of 3 years, after which it follows the placebo curve. The placebo curve increases due to the natural history annual increase in BMI of +0.145 kgm^{-2} for men, and +0.175 kgm^{-2} for women.

For tirzepatide, because no stopping rule is applied the initial treatment effect at 72 weeks is retained for the remainder of the model time horizon. This also means that the net gain for tirzepatide relative to placebo and semaglutide increases each year by a BMI of 0.145 kgm^{-2} for men and by a BMI of 0.175 kgm^{-2} for women.

The evolution of the other NMA risk factors, SBP, HDL and total cholesterol, broadly parallels that of weight as presented above. The main difference is that there is no natural history annual worsening of these and as a consequence after the initial treatment effect for placebo its trajectory is parallel to the x-axis, in common with semaglutide and tirzepatide.

The proportion of those with prediabetes who have their pre-diabetes reversed to

4

The loss of prediabetes reversal occurs at year two for placebo but is apparently a step change at year five for semaglutide, this corresponding to the stopping rule plus three years for loss of effect.

At clarification the company states that discontinuations due to the stopping rule, adverse events and a lack of primary efficacy are all modelled, only with cessation of treatment occurring at different time points. The company submission Document B states that treatment discontinuations due to a lack of primary efficacy are treated differently, with weight and the other risk factors immediately returning to baseline values. The EAG thinks that the company clarification response is correct.

3.1.13 Event risk equations

The model simulates a number of events, mortality being addressed in section below.

- The CVD events of myocardial infarction, stroke and angina 1st events and recurrent events
- The onset of T2DM
- The onset of NAFLD
- The onset of OSA
- Knee replacement surgery
- Bariatric surgery

Many of these are from relatively standard, well established risk functions, the development of T2DM and CVD events and recurrence being based upon the QDiabetes function of Hippisley-Cox et al,[32] the QRisk3 function of Hippisley-Cox [33] and the UKPDS 82 of Hayes et al,[34] with recurrence for those without T2DM being based upon D'Agosino et al.[35]

The onset of NAFLD is based upon the hazard ratios derived by the company from Loomis et al [36] from their study of 1,133,525 UK THIN database patients with median follow-up of 5 years. These are applied to a baseline annual risk of 0.12/1,000 sourced from the Vurisikala et al [37] study of the UK THIN database. This is briefly reviewed in the section below.

The onset of OSA applies the odds ratio function that Erridge et al [38] derived from 276,600 obese patients sampled from the UK CPRD data base, with those with a BMI of 30 to 35 kgm^{-2} being the reference group for the BMI coefficient. These odds ratios are applied to the five year 7.5% risk for moderately severe Sleep Disordered Breathing taken from the Tishler et al [39] study of the 1,149 participants in the Cleveland Family Study. This is briefly reviewed in section below.

The incidence of knee replacement is based upon the US study of Wendelboe et al [40] which estimated odds ratios and provided the baseline incidence rates for those under 65 years of age, 53.52 per 100,000 patient years, and over 65 years of age,

120.22 per 100,000 patient years. This is reported as being the same source as was used in TA664 and TA875.

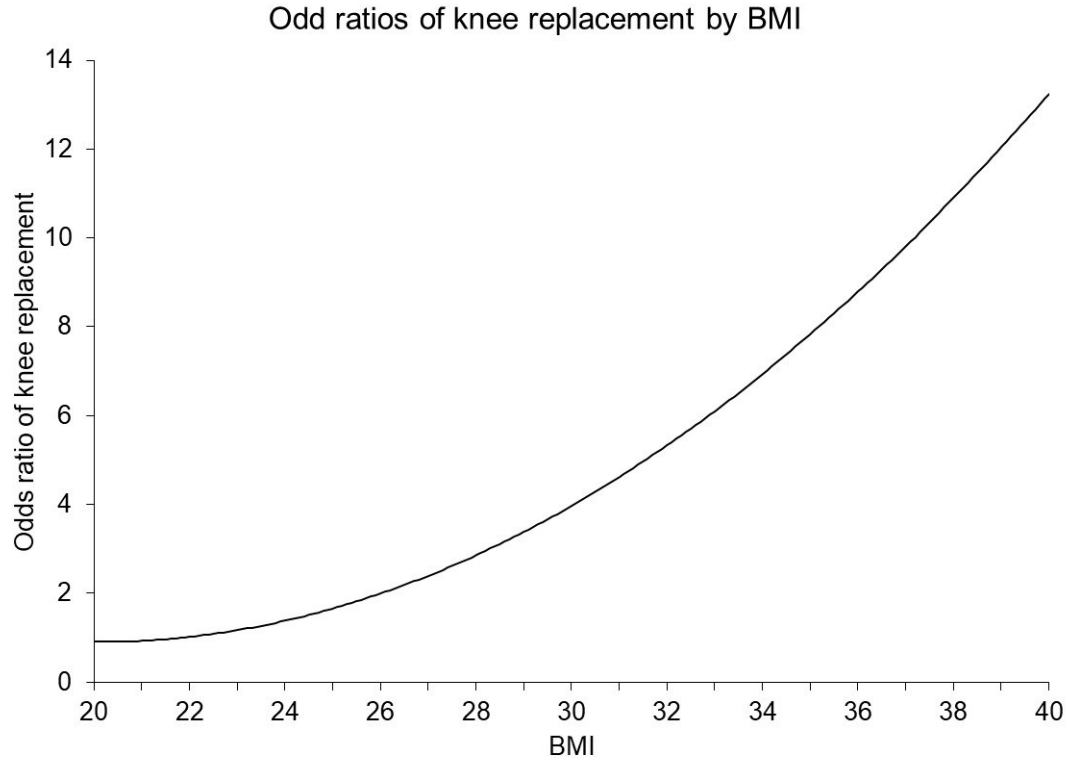


Figure 5: Odd ratios of knee replacement by BMI

The function of Figure 5 may underestimate the effects of BMI towards the upper end of the range, Wendelboe et al noting an odds ratio of 16.4 for men with a BMI between 37.5 and 40.0 kgm^{-2} and of 19.1 for women with a BMI of more than 40.0 kgm^{-2}.

The EAG has not been able to source a risk function for bariatric surgery. It appears that it may be a constant 0.2% annual proportion independent of BMI, based upon the 3rd UK National Bariatric Surgery Registry Report§.[41] Bariatric surgery is associated with an average weight loss of around 30% for RYGB, sleeve gastrectomy and OAGB and 16% for gastric band and rates of prediabetes reversal and OSA remission of around 31-68%. Given the low incidence rate it has minimal effect upon the modelling and is not reviewed by the EAG.

§ https://e-dendrite.com/Publishing/Reports/Bariatric/NBSR2020.pdf

3.1.14 Mortality introduction

There are a number of mortality elements within the model.

- All cause general population mortality
- Mortality multipliers by BMI
- Mortality multipliers for those with:
  - A history of myocardial infarction or ongoing angina
  - Ongoing NAFLD
  - A history of stroke
- Event mortality probabilities for:
  - Myocardial infarction
  - Stroke

The general approach is that cardiovascular deaths are removed from the all cause general population mortality. The non-CVD mortality risk is then qualified by the relevant BMI related mortality multiplier and any other relevant mortality multipliers.

Cardio-vascular event mortality is separately modelled and added to the mortality multiplier adjusted non-CVD mortality.

3.1.15 Mortality: all cause and mortality multipliers

All-cause mortality is first adjusted to remove the age specific mortality proportions associated with cardio-vascular events, as sourced from ONS 2018 data on myocardial and stroke deaths. This results in the non-CVD mortality probabilities.

While simplifying slightly, BMI specific mortality multipliers** sourced from the Bhaskaran et al [42] analysis of UK CPRD data are applied to the non-CVD mortality probabilities.

Table 40: BMI mortality multipliers

BMI	Multiplier
<18.5	1.56

** The BMI related mortality multipliers are hazard ratios and are actually applied as 1-(1-P)^HR but since the mortality probabilities are typically small this is very little different from treating them as multiplicative relative risks. The NAFLD mortality multiplier is also a hazard ratio and is treated in a like manner.

18.5–19.9	1.29
20.0–22.4	1.11
22.5–24.9	1.00
25.0–27.4	0.98
27.5-29.9	1.01
30.0–34.9	1.12
35.0–39.9	1.36
≥40.0	1.88

Those with angina or a history of MI have an additional mortality multiplier of 1.30 sourced from the Johansson et al [43] systematic literature review, while those with NAFLD have a 1.93 mortality multiplier sourced from the Simon et al [44] analysis of Swedish liver biopsy data. Those with a history of stroke have SMRs specific to the time since their stroke source from the Brønnum-Hansen et al [45] analysis of 1982 to 1991 data from Copenhagen.

Table 41: History of stroke SMRs

	Aged 25 – 69 years		Aged over 70 years	
Time since stroke	Male	Female	Male	Female
t ≤ 1 yr	4.64	9.27	3.70	5.18
1 yr < t ≤ 5 yr	3.01	3.52	1.92	2.05
5 yr < t ≤ 10 yr	2.75	3.32	1.89	1.99
10 yr < t ≤ 15 yr	2.50	2.45	2.49	1.67

The probabilistic modelling applies the 95% confidence intervals of Bhaskaran et al. It appears that the 95% confidence intervals of Simon et al and Brønnum-Hansen et al are not applied. Within Johansson et al there is no obvious 95% confidence interval for the 1.30 estimate.

3.1.16 Mortality: cardio-vascular

The mortality associated with myocardial infarction events is taken from the 30 day English case fatality rates from 2001-2010 reported in Smolina et al.[46]

Table 42: Myocardial infarction 39 day fatality rates

Age	Male	Female
30–54 Years	13.8%	13.3%

55–64 Years	14.2%	17.4%
65–74 Years	19.5%	25.3%
75–84 Years	28.0%	35.8%
≥85 Years	37.9%	45.7%

The mortality associated with stroke events is taken from the 30 day English HES case fatality rates based upon 2010 data as reported in Seminog et al.[47]

Table 43: Stroke 30 days fatality rates

Age	Male	Female
20–34 Years	11.2%	9.3%
35–54 Years	11.5%	11.4%
55–64 Years	12.5%	15.0%
65–74 Years	17.1%	18.0%
75–84 Years	23.4%	25.9%
≥85 Years	34.3%	38.3%

It appears that the probabilistic modelling does not apply the 95% confidence intervals of Seminog et al. There are no corresponding 95% confidence intervals reported in Smolina et al.

3.1.17 Mortality: compounding of effects

To clarify the above, the general population annual mortality risk for a 45 year old man is 0.25%. Around 13% of these deaths are either stroke or myocardial infarction which results in a non-CVD mortality risk of 0.25% * (1-13%) = 0.21%.

Again simplifying slightly and treating the hazard ratios as relative risks, a patient with a BMI of 35 kgm^{-2} has the BMI mortality multiplier of 1.36 applied to this. If they have NAFLD they have the 1.93 mortality multiplier applied as well. A stroke during the year appears to have a double impact: the immediate 11.5% event mortality and also the first year stroke history mortality multiplier of 4.64 applied. The subsequent year would see only the 3.01 stroke history mortality multiplier applied.

So a 45 year old man with a BMI of 35 kgm^{-2} and NAFLD who has a stroke has a probability of dying that year of (0.21% * 1.36 * 1.93 * 4.64) + 11.5% = 14.1%. The next year his probability of dying, ignoring the slight increase due to age, is 0.21% *

1.36 * 1.93 * 3.01 = 1.69% or around seven times that of someone with a healthy weight, no NAFLD and no history of stroke.

Angina would further increases these probabilities by 30% from 14.1% to 18.3% and from 1.69% to 2.20%.

3.1.18 Health related quality of life

3.1.18.1 Main BMI and complications quality of life values

SURMOUNT-1 collected EQ-5D data but this is not used in the health economic model. For the direct association between BMI and quality of life the company relies upon the function of Søltoft et al.[48] This is an analysis of the large scale Health Survey for England (HSE) which provided data for 14,416 adult, using the EQ-5D to evaluate quality of life. This was also used in TA875 and TA664.

Table 44: Main quality of life functions

	BMI ≤ 35 kgm^{-2}		BMI > 35 kgm^{-2}	
	Male	Female	Male	Female
Intercept	-0.023	0.401	1.324	1.463
Age 25–34	..	..	As per BMI ≤ 35 kgm^{-2}	
Age 35–44	-0.003	-0.021		
Age 45–54	-0.008	-0.034		
Age 55–64	-0.043	-0.043		
Age 65–74	-0.022	-0.062		
Age 75–100	-0.057	-0.075		
BMI	0.099	0.057	-0.105	-0.147
BMI²	-0.003	-0.002	..	..
BMI³	0.00003	0.00002	..	..
T2DM	-0.053	-0.033	As per BMI ≤ 35 kgm^{-2}	
Musculoskeletal	-0.172	-0.201		
Respiratory problems	-0.024	-0.043		
Heart problems	-0.049	-0.028		
Cancer	-0.095	-0.072		
General Health Questionnaire (GHQ)				
0	..	..		
1-3	-0.073	-0.070		
4+	-0.251	-0.219		

Education finishing age		
<15	-0.020	-0.020
15-18	..	..
18+	0.023	0.023
Unfinished	0.010	0.018
Non-manual work	0.024	0.027

The company applies the intercept, age coefficients, BMI coefficients and coefficients for T2DM, musculoskeletal problems and respiratory problems, the latter two being used for knee replacement and OSA respectively. Knee replacement is assumed to only affect quality of life in the year it occurs. The other coefficients of Søltoft et al are not applied.

As reviewed in greater detail in section 5.3.2 below, due to sample data not extending to the higher BMI values, for those with a BMI > 35 kgm^{-2} the company augments the function of Søltoft et al with the TA664 linear extension of Søltoft et al. The company reports that this was also used in TA875.

The above quality of life functions are augmented by additional quality of life decrements from Sullivan et al [49] of -0.035 for stroke and post stroke, -0.063 for MI or angina and -0.037 for post MI or angina and -0.096 for NAFLD. An additional one off decrement of -0.220 for bariatric surgery is taken from Campbell et al.[50]

Adverse events are assumed to have a disutility of -0.040 taken from the Kim et al [51] cost effectiveness study of semaglutide.

3.1.18.2 Severity

The model contains quality of life values to enable severity modifiers to be applied. There is no obvious setting within the model that enables this to be explored. Document B Section B.3.6 on page 192 states that no severity weights were used in the evaluation of quality adjusted life expectancy. Setting these values to zero has no effect upon the modelled base case.

3.1.19 Resources and costs

3.1.19.1 Direct drug costs

The model assumes that after initial up titration those on treatment are treated with tirzepatide 5mg, 10mg or 15mg weekly, semaglutide 2.4mg weekly or liraglutide 3.0mg daily. Liraglutide is available in two pack sizes, each with the same cost per mg.

Table 45: Treatment prices

Tirzepatide		Semaglutide		Liraglutide	
2.5mg	£92.00	0.25mg	£73.25	3 x 18mg	£117.72
5.0mg	£92.00	0.50mg	£73.25	5 x 18mg	£196.20
7.5mg	£107.00	1.00mg	£73.25		
10.0mg	£107.00	1.70mg	£73.25*		
12.5mg	£122.00	2.40mg	£73.15*		
15.0mg	£122.00				
* Company assumed due to TA875 redactions					

This results in annual costs of £1,200, £1,396 and £1,591 for tirzepatide 5mg, 10mg and 15mg, £956 for 2.4mg semaglutide and £2,389 for 3.0mg liraglutide. Semaglutide and liraglutide have confidential prices, the effects of which are presented in the cPAS appendix.

3.1.19.2 Administration and monitoring costs

It is assumed that patients require two nurse appointments to be trained in subcutaneous injections at a cost of £24.

Quarterly GP visits and blood tests, and twice quarterly nurse visits are assumed together with one prescription, yielding an annual cost of £234. This is based upon the Ara et al study of using drugs to treat obesity in primary care.[52] This presupposes that the active treatments are administered in primary care rather than in an SWMS. At error check the company confirmed that these costs are applied to all patients, regardless of treatment status.

3.1.19.3 Adverse event costs

The adverse events of **Error! Reference source not found.** are costed at £148, b ased upon the weighted average of NHS reference costs for gastroenterology outpatients visits.

3.1.19.4 Complication costs

The costs of events and ongoing complications are taken from a variety of sources.

Table 46: Complication costs

	Incidence	Year 1	Years 2+
Angina	£2,173	£1,006	£762
MI	£3,120	£1,121	£781
Stroke	£6,089	£1,270	£880
T2DM	..	£1,771	£1,771
OSA	..	£288	£288
NAFLD	..	£3,108	£3,108
Knee replacement	£8,186	..	..
Bariatric surgery	£7,286	..	..

Incidence costs are taken from weighted averages of NHS inpatient costs.

The ongoing costs of T2DM are an average of a variety of NHS reference costs as reviewed in greater detail in section 5.4.2 below. Most of the other ongoing costs are sourced from the UKPDS 84 Alva et al.[53]

The ongoing cost of OSA is taken from undocumented Sharples reference. The company notes that during TA875 the EAG preferred a cost of £274 based upon the annual cost of a continuous airways pressure machine. The current EAG is unclear whether all new OSA patients are treated with a continuous airways pressure machine. The company also reports that during TA875 the experts preferred a £1,018 annual cost based upon averaging unspecified reference costs.

The ongoing £3,108 cost of NAFLD is based upon averaging liver failure disorder reference costs, which are driven by inpatient admissions.

4 COST EFFECTIVENESS RESULTS

4.1 *Cost basis*

There are commercial agreements in place for semaglutide and liraglutide. All results in this document are based upon list prices. A cPAS appendix is provided that applies the relevant discounts.

4.2 *Company base case cost effectiveness results*

The deterministic model estimates the following costs by arm, the EAG only reporting the more important comorbidities and one off events and omitting elements that have little effect upon net costs, such as MI and stroke. Note that, e.g. the comorbidities costs is the total cost of all ongoing comorbidities with the EAG reporting the more important elements of these such as T2DM.

Table 47: Company base case cost estimates: Deterministic

	Tirzepatide				
	5mg	10mg	15mg	SEMA	PLAC
Drug Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One off events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Knee replace	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAFLD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These yield the following net cost estimates for tirzepatide.

Table 48: Company base case net cost estimates: Deterministic

	Tirzepatide vs Semaglutide			Tirzepatide vs Placebo		
	5mg	10mg	15mg	5mg	10mg	15mg
Drug Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One off events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Knee replace	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comorbidities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAFLD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
* Angina, MI, Stroke and bariatric surgery						

Due to tirzepatide being used for the patient lifetime unless there are discontinuations due to lack of primary efficacy or adverse events the model estimates substantial additional drug costs, these being notably higher for tirzepatide 15mg. Administration costs are the same for tirzepatide and semaglutide despite the 2-year stopping rule for semaglutide due to patient administration. Monitoring costs are also essentially the same,

There are quite substantial cost offsets due to reduced comorbidities, this mainly being due to reduced T2DM which is in turn appears to be mainly due to the reversal of prediabetes ceasing for semaglutide due to the 2-year stopping rule and for placebo due to modelling assumptions. There are some additional cost offsets from reduced adverse events, most notably knee replacements and adverse events.

The model estimates the following quality of life effects, the overall totals including the effects of the one off events and ongoing comorbidities.

Table 49: Company base case QALY estimates: Deterministic

	Tirzepatide				
	5mg	10mg	15mg	SEMA	PLAC
BMI and LYG	17.332	17.274	17.363	16.886	16.773
One off events	-0.050	-0.051	-0.050	-0.057	-0.056
Knee replace	-0.031	-0.029	-0.028	-0.038	-0.040
Other	-0.006	-0.009	-0.010	-0.003	0.000

Comorbidities	-0.602	-0.570	-0.546	-0.676	-0.731
T2DM	-0.169	-0.154	-0.145	-0.229	-0.270
MI	-0.018	-0.018	-0.017	-0.021	-0.023
OSA	-0.328	-0.315	-0.308	-0.337	-0.349
NAFLD	-0.036	-0.033	-0.028	-0.039	-0.040
Total	16.680	16.653	16.767	16.153	15.986

These yield the following net QALY estimates for tirzepatide.

Table 50: Company base case net QALY estimates: Deterministic

	Tirzepatide vs Semaglutide			Tirzepatide vs Placebo		
	5mg	10mg	15mg	5mg	10mg	15mg
BMI and LYG	0.446	0.388	0.478	0.559	0.501	0.590
One off events	0.007	0.006	0.006	0.006	0.005	0.006
Knee replace	0.007	0.008	0.010	0.009	0.011	0.012
Other	-0.002	-0.006	-0.007	-0.006	-0.009	-0.010
Comorbidities	0.074	0.106	0.130	0.129	0.161	0.185
T2DM	0.060	0.075	0.084	0.101	0.115	0.124
MI	0.003	0.003	0.004	0.005	0.005	0.006
OSA	0.010	0.022	0.030	0.022	0.034	0.042
NAFLD	0.003	0.006	0.011	0.003	0.006	0.011
Total	0.527	0.500	0.614	0.695	0.667	0.781

While there are some QALY gains from reduced complications, most notably reduced T2DM, most of the modelled QALY gains arises from patient BMI and increased life expectancy. But the direct quality of life net gains from events in the above are not the whole story. For instance, the direct net quality of life effects and net cost effects from NAFLD appear minor. This might suggest that NAFLD is unimportant in the modelling. But NAFLD is assumed to have a 1.93 mortality multiplier. If this is set to 1.00 the net QALY gain from tirzepatide 5mg relative to placebo increases from 0.695 QALYs to 0.730 QALYs, and relative to semaglutide increases from 0.527 QALYs to 0.540 QALYs. This may initially appear counterintuitive, but the company has clarified that it is because if fewer patients die due to NAFLD they remain at risk of CVD events, with there being a net QALY benefit to tirzepatide arising from this.

The company presents results separately for 5mg, 10mg and 15mg tirzepatide. Due to these being mutually exclusive alternatives, the EAG groups these into an incremental analysis in Table 51 as required by the NICE methods guide, also presenting the pairwise cost effectiveness estimates for the individual treatments with semaglutide and with placebo.

Table 51: Company base case cost effectiveness estimates: Deterministic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	[redacted]	15.986	..	..	..
SEMA	[redacted]	16.153	£785	..	£785
TIRZ 10mg	[redacted]	16.653	Ext. Dom	£15,454	£11,777
TIRZ 5mg	[redacted]	16.680	£14,910	£14,910	£11,510
TIRZ 15mg	[redacted]	16.767	£23,076	£16,062	£12,792

Semaglutide is estimated to have an excellent cost effectiveness compared to placebo at conventional willingness to pay thresholds. Within the fully incremental analysis tirzepatide 10mg is estimated to have a slightly worse cost effectiveness estimate when compared with semaglutide than tirzepatide 5mg and is extendedly dominated.

Tirzepatide 5mg increases treatment costs by [redacted] compared to semaglutide but cost offsets of [redacted] reduce the total net cost to £7,863. A gain of 0.527 QALYs results in a cost effectiveness estimate of £14,910 per QALY.

Tirzepatide 15mg has a cost effectiveness estimate of £23,076 per QALY compared to tirzepatide 5mg.

The probabilistic estimates and ICERs are similar to the deterministic estimates[††].

Table 52: Company base case cost effectiveness estimates: Probabilistic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	[redacted]	15.985	..	..	..

[††] These estimates are based upon EAG revisions to the VBA. Given the difficulty of confidently revising the VBA within the time constraints of the assessment the EAG urges the company to check the EAG revisions for errors. All EAG changes in the VBA can be identified by searching the project for “EAG”.

SEMA	[redacted]	16.140	£725	..	£725
TIRZ 10mg	[redacted]	16.652	Ext. Dom	£15,254	£11,876
TIRZ 5mg	[redacted]	16.672	£14,811	£14,811	£11,629
TIRZ 15mg	[redacted]	16.760	£24,683	£16,227	£13,127

Both the deterministic estimates and probabilistic central estimates suggest that the most cost effective use of tirzepatide may be to limit its use to tirzepatide 5mg due to tirzepatide 10mg being extendedly dominated and tirzepatide 15mg having a cost effectiveness estimate greater than £20,000 per QALY. However, the differences in costs and QALYs between tirzepatide 5mg and 10mg are small and perhaps the extended dominance should not be over stressed. More reliable may be that tirzepatide 15mg involves higher costs for relatively small gains so may not be cost effective. This does not address possible sequencing of treatments.

The CEAC is presented in Figure 6 below.

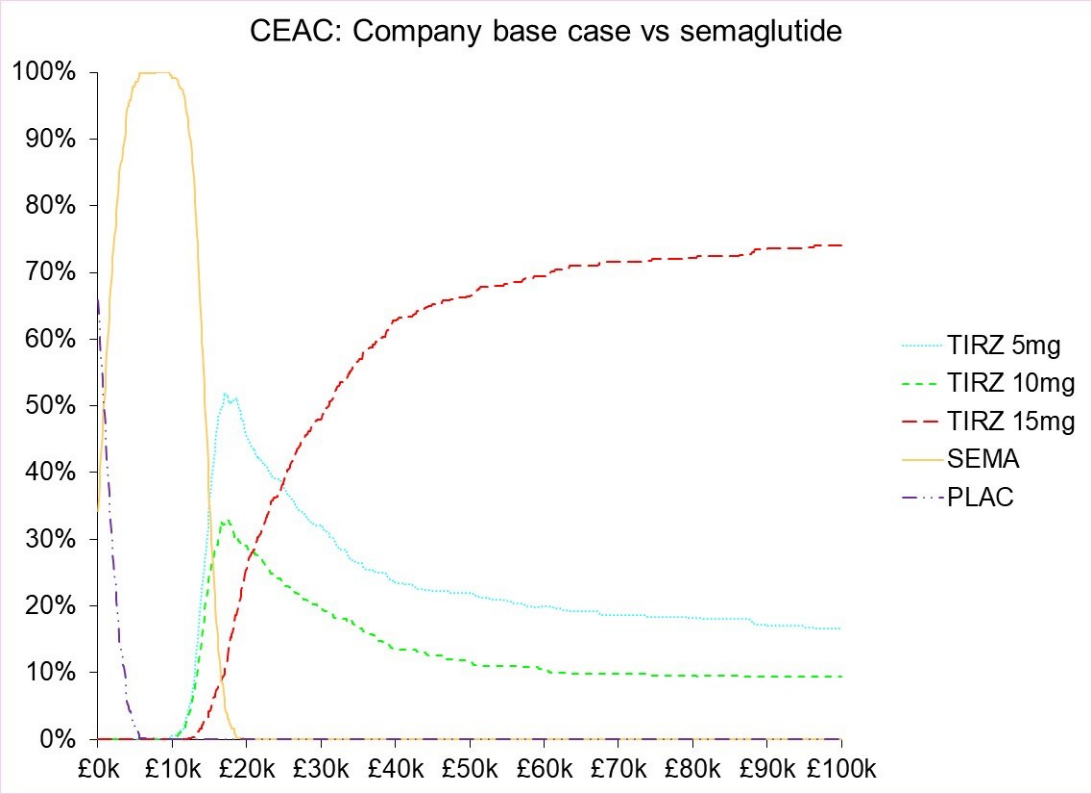


Figure 6: Company base case CEAC

At low willingness to pay values semaglutide is estimated to be the most likely to be cost effective. Tirzepatide 5mg overtakes it at a willingness to pay of £15,000 per

QALY, with tirzepatide 15mg overtaking tirzepatide 5mg at a willingness to pay of £24,700 per QALY. At a willingness to pay of £15,000 per QALY the probability of tirzepatide 10mg being the most cost effective is around two thirds that of tirzepatide 5mg. This gradually declines to become around half the probability of tirzepatide 5mg being the most cost effective from a willingness to pay of £50,000 per QALY.

4.3 *Company subgroup analysis: BMI ≥ 35kgm^{-2}, prediabetes, high CVD risk*

For the modelling of those with a higher BMI of at least 35kgm^{-2}, prediabetes and a high CVD risk the company base case deterministic estimates are presented in Table 53.

Table 53: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk: Deterministic

			ICER			
	Cost	QALY	Incr.	vs SEMA	vs LIRA	vs PLAC
SEMA	[redacted]	15.719	..	..	Dominant	Dominant
PLAC	[redacted]	15.541	Dominated	..	..	..
LIRA	[redacted]	15.628	Dominated	..	..	£28,853
TIRZ 10mg	[redacted]	16.362	£8,865	£8,865	£3,455	£6,148
TIRZ 5mg	[redacted]	16.325	Dominated	£9,595	£3,805	£6,585
TIRZ 15mg	[redacted]	16.480	£21,176	£10,778	£5,914	£8,040

The corresponding central estimates from the probabilistic modelling of Table 54 are similar to the deterministic results of Table 53.

Table 54: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk: Probabilistic

			ICER			
	Cost	QALY	Incr.	vs SEMA	vs LIRA	vs PLAC
SEMA	[redacted]	15.734	..	..	..	Dominant
PLAC	[redacted]	15.575	Dominated	..	..	..
LIRA	[redacted]	15.663	Dominated	..	..	£28,449
TIRZ 10mg	[redacted]	16.336	Ext. Dom	£9,797	£4,039	£6,864
TIRZ 5mg	[redacted]	16.390	£9,261	£9,261	£3,982	£6,627
TIRZ 15mg	[redacted]	16.496	£22,433	£11,088	£6,324	£8,441

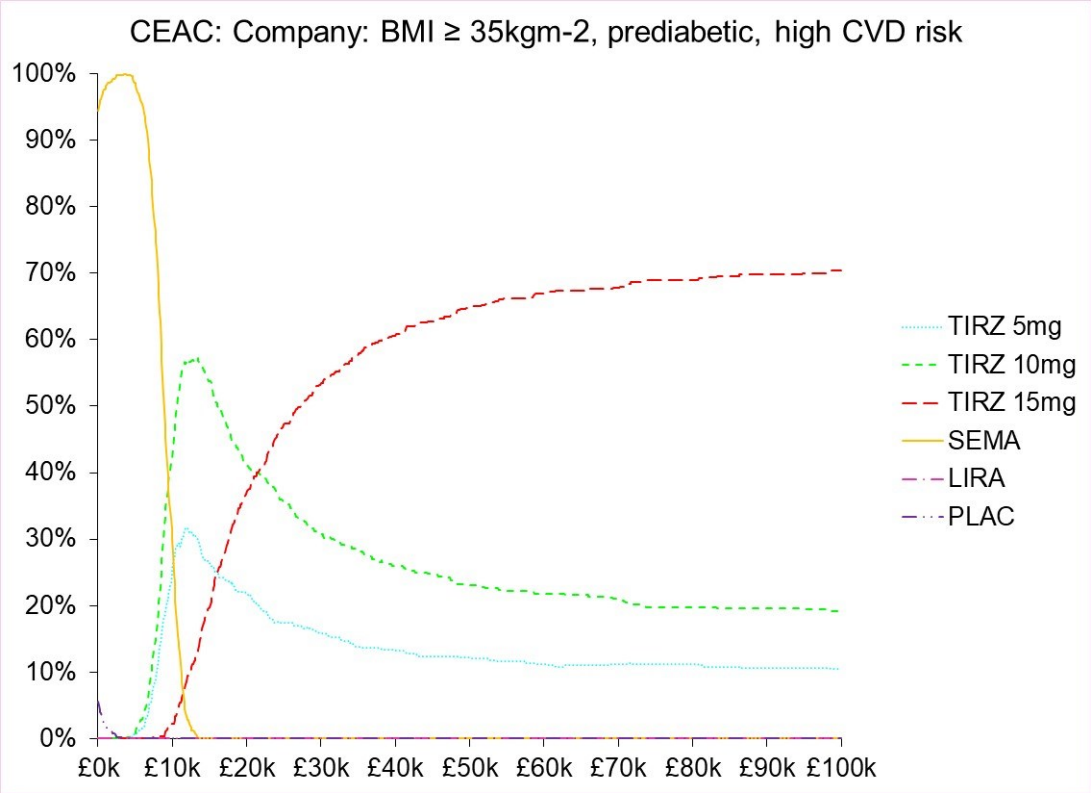


Figure 7: CEAC: Company: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk

Placebo and liraglutide are never estimated as being likely to be cost effective. At low willingness to pay values semaglutide is the most likely to be cost effective. Tirzepatide 10mg becomes the most likely to be cost effective above a willingness to pay of £9,500 per QALY, with tirzepatide 15mg becoming the most likely to be cost effective above a willingness to pay of £21,300 per QALY.

4.4 *Company subgroup analysis: BMI ≥ 30kgm^{-2}*

The deterministic cost effectiveness estimates for the modelling of those with a BMI of at least 30kgm^{-2} are presented in Table 55 below.

Table 55: BMI ≥ 30kgm^{-2}: Deterministic

			ICER	
	Cost	QALY	Incr.	vs PLAC
PLAC	[redacted]	16.702	..	..
TIRZ 10mg	[redacted]	17.385	Ext. Dom	£13,822

TIRZ 5mg	[redacted]	17.402	£13,757	£13,757
TIRZ 15mg	[redacted]	17.462	£36,982	£15,589

Among those with a BMI of at least 30kgm^{-2} tirzepatide 5mg is estimated to have a relatively good cost effectiveness compared to placebo of £13,757 per QALY.

It can be noted that tirzepatide 15mg is estimated to provide relatively small patient gains over tirzepatide 5mg but at somewhat higher cost, resulting in an ICER of £36,982 per QALY.

4.5 *Company subgroup analysis: BMI ≥ 35kgm^{-2}*

The deterministic cost effectiveness estimates for the modelling of those with a BMI of at least 30kgm^{-2} are presented in Table 56 below.

Table 56: BMI ≥ 35kgm^{-2}: Deterministic

			ICER	
	Cost	QALY	Incr.	vs PLAC
PLAC	[redacted]	16.440	..	..
TIRZ 10mg	[redacted]	17.203	£11,700	£11,700
TIRZ 5mg	[redacted]	17.162	Dominated	£12,682
TIRZ 15mg	[redacted]	17.311	£21,697	£12,940

The main point of interest for those with a BMI of at least 35kgm^{-2}, a subgroup of those with a BMI of at least 30kgm^{-2}, is that the ICER for tirzepatide 15mg compared to tirzepatide 5mg is much improved at £21,697 per QALY compared to the £36,982 per QALY of Table 55.

4.6 *Company analysis: SURMOUNT-1 all patients*

The deterministic cost effectiveness estimates for the modelling of the SURMOUNT-1 all patient group are presented in Table 57 below.

Table 57: SURMOUNT-1 all patient analysis: Deterministic

			ICER	
	Cost	QALY	Incr.	vs PLAC
PLAC	[redacted]	16.764		
TIRZ 10mg	[redacted]	17.351	Ext. Dom	£16,265

TIRZ 5mg	[redacted]	17.393	£15,386	£15,386
TIRZ 15mg	[redacted]	17.423	£74,754	£18,095

The main result of interest is that tirzepatide 15mg is estimated to provide very few patient gains compared to tirzepatide 5mg but at somewhat higher cost, resulting in an ICER of £74,754 per QALY.

4.7 *Model validation and face validity check*

4.7.1 QALY gains compared to previous assessments

Assessing the structural model uncertainty can in part be addressed by comparing the current cost effectiveness estimates for semaglutide and liraglutide with the TA875 and TA664 cost effectiveness estimates. Due to uncertainty around the treatment costs that were applied in these analyses, the EAG focusses upon the modelled QALYs.

The company submission for TA875 for the target group of those with a BMI ≥ 30kgm^{-2} and at least one comorbidity estimated 15.239 QALYs for diet and exercise and 15.330 QALYS for semaglutide resulting in a net gain of 0.091 QALYs. The EAG preferred base case estimated 15.562 QALYs for diet and exercise and 15.656 QALYS for semaglutide resulting in a net gain of 0.094 QALYs. The current modelling estimates 15.986 QALYs for diet and exercise and 16.153 QALYS for semaglutide resulting in a net gain of 0.167 QALYs. The company base case estimates a net QALY gain for semaglutide compared to diet and exercise that is around 80% higher than that of TA875.

The company submission for TA875 for those with a BMI ≥ 35kgm^{-2}, prediabetes and at high risk for CVD estimated 14.401 QALYs for liraglutide and 14.444 QALYS for semaglutide resulting in a net gain of 0.043 QALYs. The EAG preferred base case estimated 14.745 QALYs for liraglutide and 14.788 QALYS for semaglutide resulting in a net gain of 0.043 QALYs. The current modelling estimates 15.628 QALYs for liraglutide and 15.719 QALYS for semaglutide resulting in a net gain of 0.091 QALYs. The company base case estimates a net QALY gain for semaglutide compared to liraglutide that is around 110% higher than those within TA875.

The company submission for TA664 for those with a BMI ≥ 35kgm^{-2}, prediabetes and at high risk for CVD estimated 15.216 QALYs for diet and exercise and 15.336 QALYS for liraglutide resulting in a net gain of 0.120 QALYs. The EAG presented two main analyses, one that assumed that those with prediabetes who had a CVD event immediately progressed to diabetes and one that did not assume this. The former estimated 15.329 QALYs for diet and exercise and 15.387 QALYS for liraglutide resulting in a net gain of 0.059 QALYs. The latter estimated 15.397 QALYs for diet and exercise and 15.453 QALYS for liraglutide resulting in a net gain of 0.056 QALYs. The EAG presented a variety of scenarios, within which the net gain varied from 0.026 QALYs to 0.066 QALYs. The current modelling estimates 15.541 QALYs for diet and exercise and 15.628 QALYS for liraglutide resulting in a net gain of 0.087 QALYs. The company base case estimates a net QALY gain for liraglutide compared to diet and exercise that is around 27% lower than the company estimates of TA875, but it is around 50% higher than the EAG estimates.

4.7.2 Modelled overall survival compared to BMI SMRs

The modelled undiscounted overall survival for placebo assuming no treatment effect and no worsening of BMI over time can be compared with those estimated through the simple application of the BMI related SMRs to life table data to a maximum age of 100 years, weighted 33% male and 66% female. For a baseline age of 45 years across all ITT patients this yields the following.

Table 58: Model vs BMI SMRs estimates of overall survival: Target group

	Model		Only BMI SMRs		
BMI	OS	Net vs BMI of 42	OS	Net vs 42	Net Diff.
18	35.051	1.369	34.295	1.619	18%
19	36.713	3.031	35.933	3.258	7%
21	37.867	4.184	37.219	4.543	9%
24	38.481	4.799	38.104	5.429	13%
26	38.650	4.968	38.275	5.600	13%
32	37.549	3.866	37.142	4.467	16%
38	36.203	2.521	35.479	2.804	11%
42	33.682	..	32.675	..	..

Within the modelling the above only varies patients' BMI, applying this over the patient lifetime with no annual increase, and applies a baseline age of 45 years. It retains the other SURMOUNT-1 ITT patient baseline characteristics. This is imperfect due to the SURMOUNT-1 ITT patient baseline characteristics relating to patients with a BMI ≥ 27kgm^{-2} with one weight related comorbidity or with a BMI ≥ 30kgm^{-2}. Consequently, the modelling of those with a BMI < 27kgm^{-2} is likely to model them as being in worse health at baseline than they would be and consequently is likely to underestimate their survival compared to the general population with the same BMI.

The model estimates slightly higher overall survival compared to the simple application of the SMRs to life table data. The EAG finds this surprising given that the model includes the BMI SMRs and a range of other mortality multipliers. The EAG cannot state why this does occurs, but it may be related to the model stripping out CVD mortality from general mortality and estimating CVD mortality separately.

But other factors may be at play which suggests examining the net effects upon overall survival from moving from a BMI of 42 kgm^{-2} to the other values for the lifetime of the patient. The model appears to suggest a smaller net effect for improvements from a BMI of 42kgm^{-2} than simply applying the BMI SMRs which again seems counterintuitive given the additional mortality multipliers within the model.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *EAG critique of economic modelling compared to position sought*

TA875 recommended semaglutide for those with a:

- BMI ≥ 35kgm^{-2} and at least 1 weight related comorbidity, or
- BMI between 30kgm^{-2} and 35kgm^{-2} who are eligible for referral to an SWMS.

The base case modelling for the comparison with semaglutide is of those with a:

- BMI ≥ 30kgm^{-2} and at least 1 weight related comorbidity.

The EAG is unclear quite how specific the criteria for referral to an SWMS are within CG189 but notes that Section 1.3.7 includes when "*conventional treatment has been unsuccessful*". It remains unclear to the EAG whether the modelling for the

comparison with semaglutide should have been restricted to those with a BMI ≥ 35kgm^{-2} and at least 1 weight related comorbidity The availability of clinical effect estimates for semaglutide for the NMA may also be an issue.

The EAG thinks that the modelled position for the comparison with semaglutide is reasonable provided that any recommendation limits tirzepatide to the same population as that recommended for semaglutide.

TA664 recommended liraglutide for those with a BMI ≥ 35kgm^{-2}, prediabetes and a high risk of CVD. The scenario modelling for the comparison with liraglutide is aligned with this.

An aspect that the modelling does not address is the possibility of sequencing treatments. The company is seeking a price premium over the prices it assumed for semaglutide and liraglutide. It may consequently be more cost effective to trial semaglutide or liraglutide first and to reserve the more costly tirzepatide for non or poor responders to semaglutide or liraglutide. Similarly, the company price structure means that annual costs of tirzepatide increase with the dose. This may mean that it may be more cost effective to trial tirzepatide 5mg first and to reserve the more costly tirzepatide doses for non or poor responders to tirzepatide 5mg. This is reviewed in slightly more detail in section 5.2.8 below.

The trials of the NMA all had T2DM as an exclusion criterion. The position sought by the company in its economic modelling is among patients who:

- Have previously failed at least one dietary attempt to lose weight,
- Have a BMI ≥ 30 kgm^{-2},
- Have at least one BMI related comorbidity, and
- Do not have diabetes.

Within this quite large cost offsets and some additional QALY gains are modelled to arise from the prevention of T2DM. The model does not provide any guide to the likely cost effectiveness of tirzepatide for the treatment of T2DM patients.

5.2 *EAG critique of elements of the company model*

5.2.1 Underestimation of BMI related mortality and possible bias

The BMI mortality multipliers are grouped into BMI bands, the worst being for those with a BMI ≥ 40 kgm^{-2} and a mortality multiplier of 1.88 which is somewhat above the 1.36 for those with a BMI between 35 kgm^{-2} and 40 kgm^{-2}.

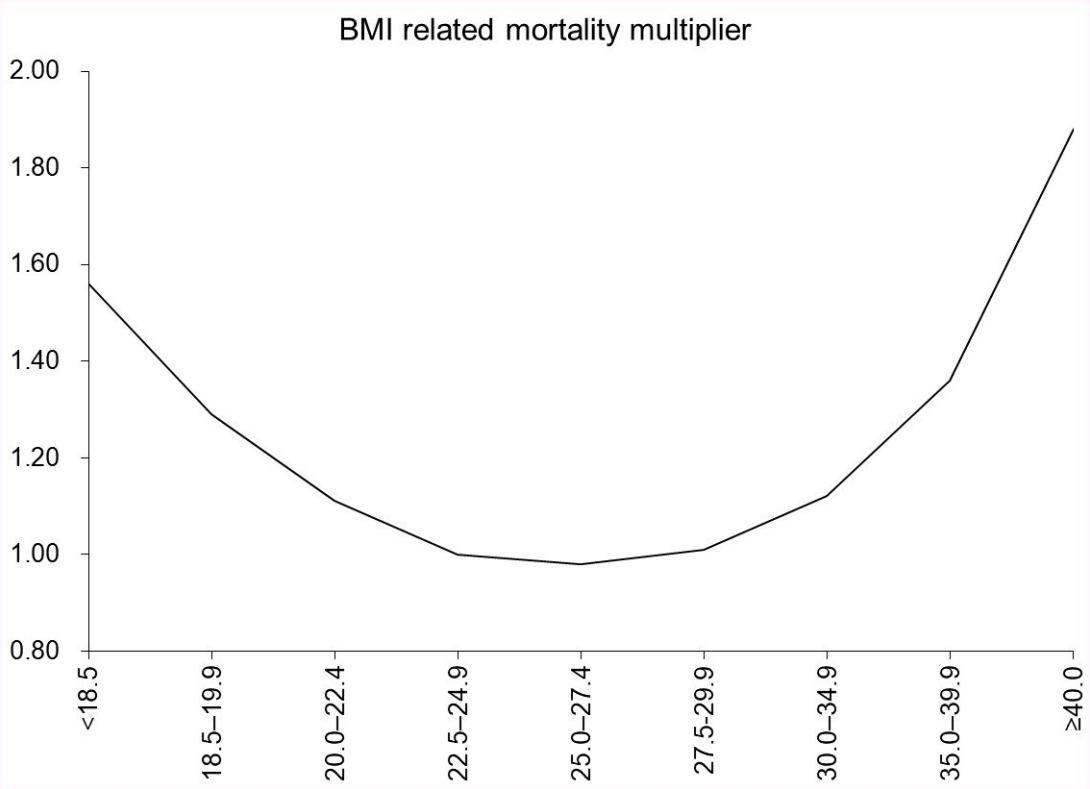


Figure 8: BMI related mortality multipliers

Within the model the 1.88 mortality multiplier applies to all those with a BMI ≥ 40 kgm^{-2}. But it seems likely that those with a BMI ≥ 45 kgm^{-2} or a BMI ≥ 50 kgm^{-2} will have a worse mortality. While speculation it seems possible that the BMI mortality multiplier for values higher than 40 kgm^{-2} increases non-linearly with the greatest effect upon mortality being among those with the worst BMI.

Due to the mean (sd) baseline BMI for the target group being 38.7 (6.8) kgm^{-2} a non-trivial proportion of patients are modelled as having a BMI ≥ 40 kgm^{-2}: 34%, 16% and 8% having a baseline BMI greater than 40, 45 and 50 kgm^{-2} respectively.

The base case estimate is that semaglutide causes a 16.5% weight loss. For those with, e.g., a BMI of 50 kgm^{-2} this causes their BMI to fall to 41.7 kgm^{-2}. For these

patients, despite their considerable weight loss, the model assumes that there are no direct BMI related mortality benefits. Intuition suggests that the mortality benefits might be greatest for these patients.

Applying the central weight loss estimates for placebo, semaglutide, tirzepatide 5mg, 10mg and 15mg to the target patient distribution results in the following proportions of patients remaining with a BMI ≥ 40 kgm^{-2} while on treatment.

Table 59: Proportion of patients with BMI ≥ 40 kgm^{-2}

	Weight loss	Remaining BMI ≥ 40 kgm^{-2}
PLAC	-2.5%	29%
SEMA	-16.5%	10%
TIRZ 5mg	-15.9%	11%
TIRZ 10mg	-20.7%	7%
TIRZ 15mg	-22.3%	5%

Despite the quite large weight losses from the active treatments significant proportions of patients are modelled as having no direct BMI related mortality benefits from this weight loss due to them remaining with a BMI ≥ 40 kgm^{-2} throughout. The model underestimates the benefits of treatment for these patients. For treatments with a smaller effect upon BMI this applies to a greater proportion of patients. This may cause the model to be biased in favour of the more effective treatments.

Without better BMI related mortality data for those at the upper end of the BMI distribution this modelling bias cannot be addressed. This should be read in conjunction with the data presented in section 5.2.2 below.

5.2.2 BMI mortality multipliers from the cited paper

The source of the BMI mortality multipliers, Bhaskaran et al,[42] is based upon an analysis of UK CPRD data. Within their data set the full study population included 3,632,674 people, but results are reported mainly for the 1,969,648 people who had never smoked among whom there were 188,057 deaths. The paper may provide estimates with a finer gradation than the tabulated results, though it is not clear to the EAG whether the analyses are based upon the WHO classification categories, the finer Global BMI Mortality Collaboration categories or a restricted spline smooth

application of BMI values. For all-cause mortality results are presented for all patients and for those who had never smoked.

Figure 9: BMI related mortality multipliers: All patients and never smoked

Given that 45% of patients had smoked the above suggests a somewhat lower mortality risk and lesser association between BMI and mortality for those who have smoked compared to those who have not.

Bhaskaran et al note that the association between BMI and mortality was stronger at younger ages than at older ages, the figures also suggesting an association with sex with both relationships being statistically significant. Unfortunately, these only appear to be reported for the never smokers.

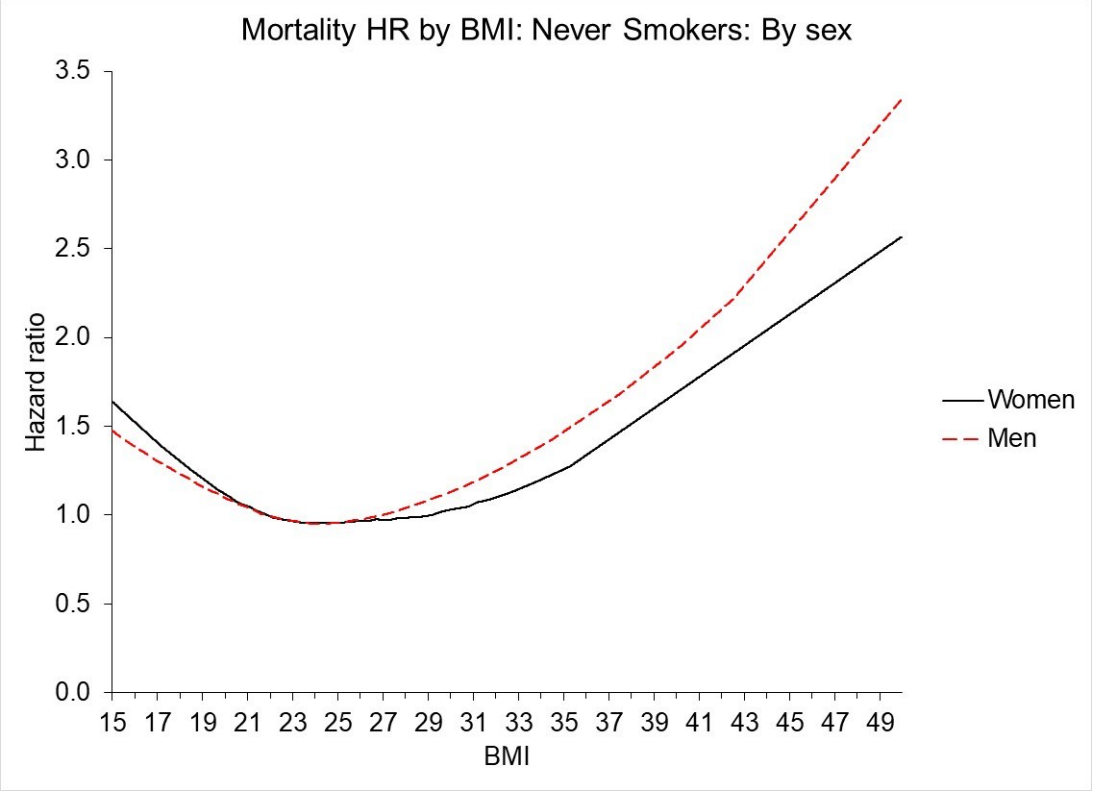


Figure 10: BMI related mortality multipliers: Never smokers: By sex

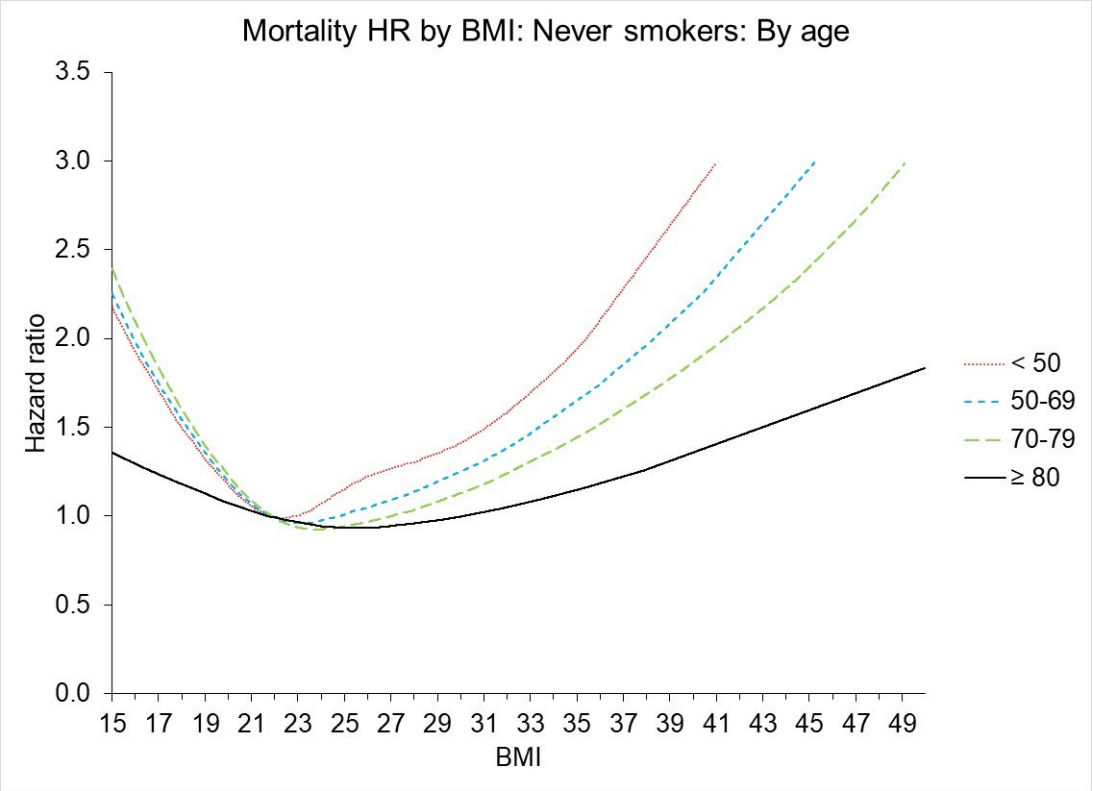


Figure 11: BMI related mortality multipliers: Never smokers: By age

While there are differences by sex in the BMI related mortality hazard ratios and it would be better if the model could reflect these, it is debatable whether the model needs to incorporate these.

Of more concern are the effects of age, older patients having a much weaker relationship between BMI and the mortality hazard ratio than younger patients. This is in the context of the annual general population mortality risk increasing strongly in age.

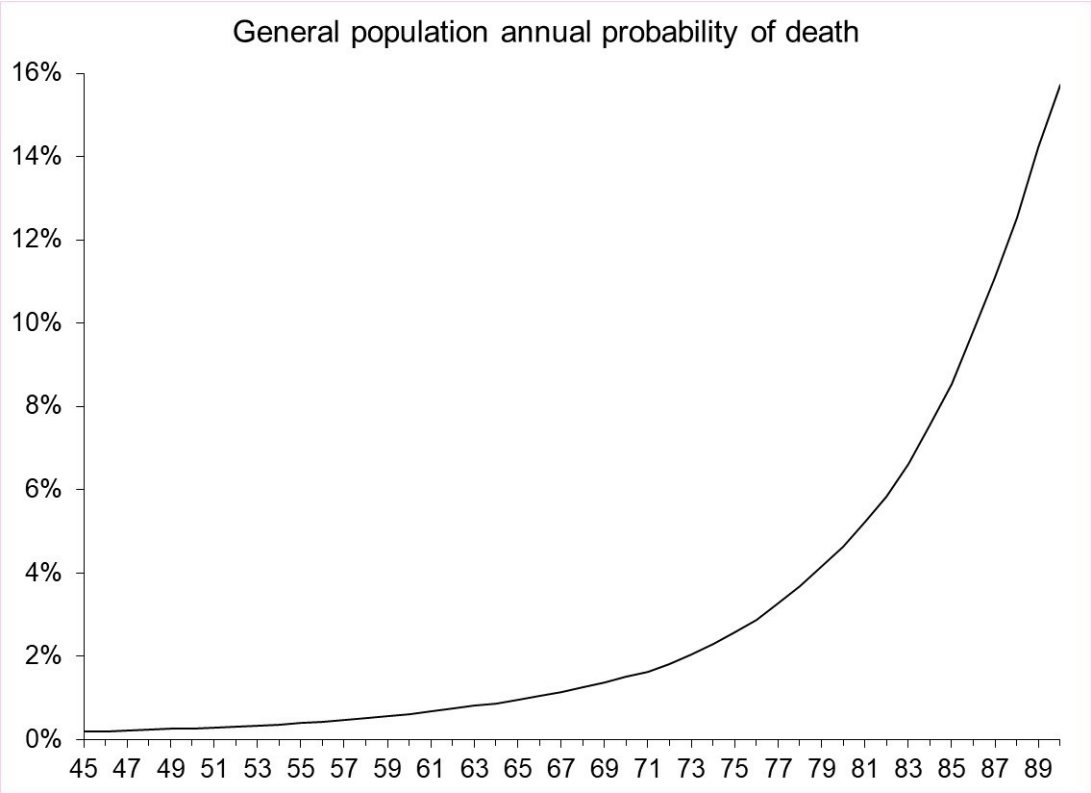


Figure 12: General population annual probability of death by age

General mortality increasing with age seems likely to be due to other non-BMI related events increasing the overall mortality risk, underlining the need to apply age specific BMI related mortality hazard ratios. Applying too low a hazard ratio of, say, 1.88 to an annual probability of death of 0.2% for a 45 year old will result in some bias but applying the same 1.88 to an annual probability of death of 4.6% for an 80 year old may result in more bias.

For instance, among those who have never smoked Figure 9 suggests a hazard ratio of around 1.765 for those with a BMI of 40 kgm^{-2}, while Figure 12 suggests hazard ratios of 2.818, 2.207, 1.867 and 1.355 for those under 50, 50 to 69, 70 to 70 and 80 plus respectively‡‡. Applying 1.765 for a patient 45 years old at baseline suggests a life expectancy of 33.0 years whereas applying the age specific values suggests a life expectancy of 32.1 years, a difference of 0.88 years, or when discounted 19.3 years and 18.8 years respectively, a difference of 0.48 years. This is in the context of the company base case estimating an undiscounted survival gain from tirzepatide 15mg over semaglutide of 0.71 years and a discounted gain of 0.27 years.

The EAG cannot revise the model to apply age specific BMI related hazard ratios. The possibility of this may be limited by only data for those who have never smoked being available, though the data of Figure 9 could be used to adjust for this given an assumption of a constant smoker effect by BMI for each of the four age bands.

The EAG thinks that the above implies quite considerable unquantified and possibly unquantifiable uncertainty around the cost-effectiveness estimates of the model.

5.2.3 Double counting within mortality multipliers

The mortality multiplier for those with a history of angina or MI are based upon the systematic literature review of Johansson et al [43] which notes an increase of at least 30%. But they also note that risk factors leading to worse outcomes after an MI included diabetes, hypertension, peripheral artery disease, reduced renal function and a history of stroke.

The mortality multipliers for those with a history of stroke are from Copenhagen data from 1982 to 1991 and so are relatively dated. It can be noted that within the Copenhagen data the 28 day stroke fatality rate was 28%, with roughly two thirds of fatal strokes being among those aged over 70 years. This is somewhat higher than the more recent English 2001 to 2010 data from for 30 day stroke event fatality rates which ranged between 9.3% and 15.0% for those aged up to 64 years, and 17.1% and 25.9% for those age between 65 and 84 years. The English 30 day stroke event

‡‡ The latter hazard ratios are not easily reconciled with the all patient hazard ratio given a patient distribution across all patients of 63.4%, 29.4%, 5.9% and 1.3% among the obese which when applied as a simple weighted average suggest a pooled hazard ratio of 2.563 which is somewhat higher than the reported pooled value of 1.765. These are the proportions for patients with a BMI ≥ 30 kgm^{-2} and while 1.3% may appear low it still amounts to 7,376 patients, though the number of patients over 80 years patients with a BMI of around 40 kgm^{-2} would be somewhat less.

fatality rate only exceeded 28% for those aged over 85 years. Seminog et al also noted from the English stroke data that between 2001 and 2021 stroke case fatality rates declined by 40%. The history of stroke mortality multipliers from the Copenhagen data may be too high.

The mortality multipliers for those with a history of stroke do not appear to have controlled for other comorbidities. Brønnum-Hansen et al note that two thirds of deaths subsequent to a non-fatal stroke were due to vascular diseases, this being split roughly equally between ischaemic heart disease and cerebrovascular disease.

In general it can be observed that there is likely to be double counting in the treatment of the mortality multipliers. Due to their multiplicative effect any double counting will compound these effects. If the BMI related mortality multipliers are reliable, while the model may be correctly modelling the incidences of the various complications associated with BMI for cost and quality of life purposes, it is not obvious why any additional mortality multipliers are required for them.

The main caveat to this is that the BMI mortality multipliers are pooled for those with a BMI ≥ 40 kgm^{-2}. As already noted, when relying upon Bhaskaran et al [42] for those who remain with a BMI ≥ 40 kgm^{-2} throughout there will be no mortality effects from changes in their BMI.

Given the above the EAG revised base case will only apply the BMI mortality multipliers of Bhaskaran et al. A scenario analysis that follows the method of the company base case will be presented.

5.2.4 Mortality multipliers within the wider literature

The company base case uses Bhaskaran et al,[42] which is based upon an analysis of the large UK CPRD data set. It is a reasonable source to use. But other values are reported in the literature based upon systematic reviews and larger data sets.

Aune et al [54] in a systematic review of studies covering over 30 million patients and 3.7 million deaths applied a random effects model to estimate a similar J-curve relationship to that of Bhaskaran et al.

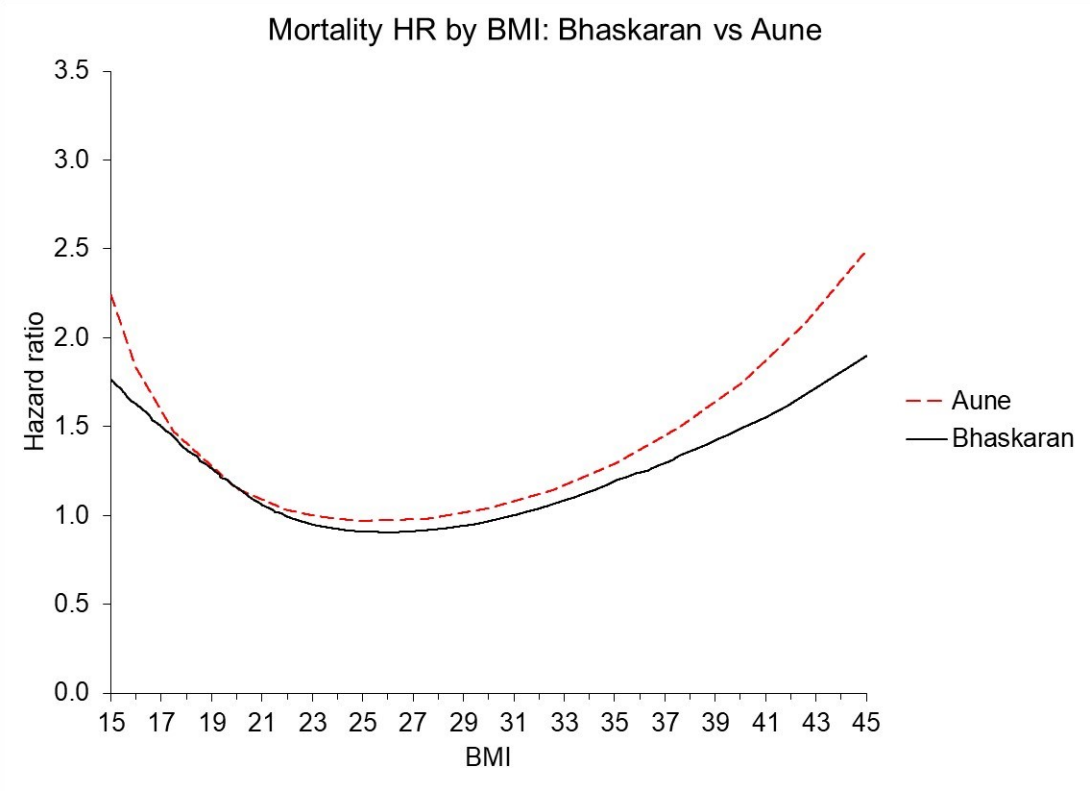


Figure 13: General population annual probability of death by age

The systematic review of Aune et al estimates a stronger relationship between BMI and the mortality hazard ratio[§§].

The EAG agrees with the company that Bhaskaran et al is to be preferred for the base case due to it being UK specific. The EAG will present a scenario analysis that applies the values of Aune et al.

5.2.5 Stopping rules

The TA875 FAD limits semaglutide to a maximum of 2 years and that it be used within an SWMS. This is aligned with the position sought by the company during TA875. The TA664 FAD limits liraglutide to being prescribed within a tier 3 SWMS, though it is unclear whether referral to an SWMS is necessarily restricted to a maximum of 2 years. The TA664 company proposed within its modelling that liraglutide is used for a maximum of 2 years. The TA664 FAD notes that the

[§§] To be strictly correct, the estimates of Aune et al are relative risks but at moderate mortality risks their effects are much the same.

commercial agreement is only available through provision of liraglutide through a secondary care tier 3 weight management service.

This needs to be read in conjunction with Document B Section B.1.3 page 20, which states that due to increasing criticism of the tiered obesity management system HM government is piloting a two year study of the use of incretin based therapies within primary care. It also notes that it is anticipated that there will be substantial changes to the NICE guidelines for the management of obesity.

The use of incretin based therapies is not obviously directly addressed by any of the September 2023 review questions, though it could be interpreted to be within some of them. The economic plan is limited to examining "*partial diet replacements, intermittent fasting, plant-based and low carbohydrate diets*". The current anticipated publication date of the guidelines is the same as that of this assessment: 27 March 2024.

At error check the company highlighted the publication of NICE HTE14 on 26 October 2023. This provides guidance on digital technologies that may be able to deliver SWMS to manage weight management medicine, instead of requiring face to face SWMS services. HTE14 recognises the potential for digital technologies to meet unmet need in areas where SWMS are not available. HTE14 permits 5 out of 8 digital weight management technologies to be used for 4 years in order to generate more evidence. HTE14 recognises that their cost-effectiveness will also be driven by the costs of face to face SWMS services, which are also poorly enumerated and require further research. NICE will review results and make a recommendation on whether they should be adopted at the end of the 4 year evidence generation period.

It can be further noted that SURMOUNT-1 appears to have been mainly if not exclusively conducted in secondary care rather than primary care. All arms included a diet and exercise programme. Patients were also required to have a history of "*at least one self-reported unsuccessful dietary effort to lose body weight*" which may accord to some extent with the CG189 referral to SWMS criterion of when "*conventional treatment has been unsuccessful*". As a consequence, this may mean that the SURMOUNT-1 setting was more akin to an SWMS referral than to treatment in primary care, with its clinical effectiveness estimates being most directly relevant to treatment within an SWMS.

At error check the company noted that the frequency of weight management advice in SURMOUNT-1 was four weekly for the first quarter and quarterly thereafter, which is less frequent than the minimum fortnightly fisits during the 1st quarter for tier 2 weight management services. It also noted that SURMOUT-1 did not include support from a multidisciplinary team as required for Tier 2 and Tier 3/4 weight management services. The EAG will include scenario analyses that removes the SWMS costs from (A) placebo, (B) placebo and tirzepatide, and (C) all arms.

Given the cost-effectiveness estimates it is possible that a commercial agreement may be agreed for tirzepatide. If so, this may mirror that of liraglutide and only be available through a secondary care tier 3 weight management service. It is also unclear to the EAG whether approval of GLP-1s in primary care would have implications for the confidential liraglutide and semaglutide prices.

If the revised NICE guidelines do not recommend use of incretin based therapies in primary care, it is not known whether NICE will within the current review specify that, in common with semaglutide and liraglutide, tirzepatide can only be used within an SWMS.

In the light of the above, in terms of stopping rules the EAG prefers treating tirzepatide, semaglutide and liraglutide on the same basis. The EAG revised base case will apply a common stopping rule at 2 years. The EAG will provide scenario analyses of (A) tirzepatide, semaglutide and liraglutide not having any stopping rule, and (B) as per the company base case only semaglutide and liraglutide having a stopping rule at 2 years.

5.2.6 The cost-effectiveness of relaxing the 2-year stopping rule

The EAG revised base case applies a two year stopping rule for all treatments. The company base case assumes no stopping rule for tirzepatide. The cost effectiveness of relaxing the two year stopping rule for the company base case is presented in Table 60.

Table 60: Cost-effectiveness of the 2-year stopping rule

	With stopping rule		Without rule		Net effect		
	Cost	QALY	Cost	QALY	Cost	QALY	ICER
SEMA	[redacted]	16.153	[redacted]	16.480	[redacted]	0.327	£9,425
TIRZ 5mg	[redacted]	16.191	[redacted]	16.680	[redacted]	0.489	£14,925

TIRZ 10mg	[redacted]	16.174	[redacted]	16.653	[redacted]	0.479	£14,298
TIRZ 15mg	[redacted]	16.211	[redacted]	16.767	[redacted]	0.556	£15,805

The company model estimates that relaxing the 2-year stopping rule is cost effective at conventional willingness to pay thresholds, though this needs to be read in conjunction with section 4.7 on model validation above. But the main message from the above is that for the company base case the model estimates that relaxing the 2-year stopping rule for semaglutide has a superior ICER to relaxing it for tirzepatide. If the 2-year stopping rule for semaglutide was primarily economically driven the model suggests that applying it for semaglutide but not applying it for tirzepatide may be irrational.

EAG expert opinion also suggests that weight gain is quite rapid after withdrawal of treatment and that it may be unlikely that the 2-year stopping rule will be applied in practise for any of the GLP-1s. This is mirrored by the 52 week off-treatment extension of the STEP-1 trial to which around 16% of the original trial population, 228/1,306 for semaglutide and 99/655 for placebo, were recruited. Participants were required to have completed treatment with semaglutide or placebo at week 68. It appears that both active treatment, placebo and the lifestyle interventions were withdrawn, since Wilding et al [55] report that "*participation in lifestyle interventions that might impact weight were not recorded*". It is unclear to what extent weight gains during the extension phase were due to treatment being withdrawn and what were due to diet, counselling and exercise not being actively promoted, but weight loss and weight regain in the placebo arm was limited.

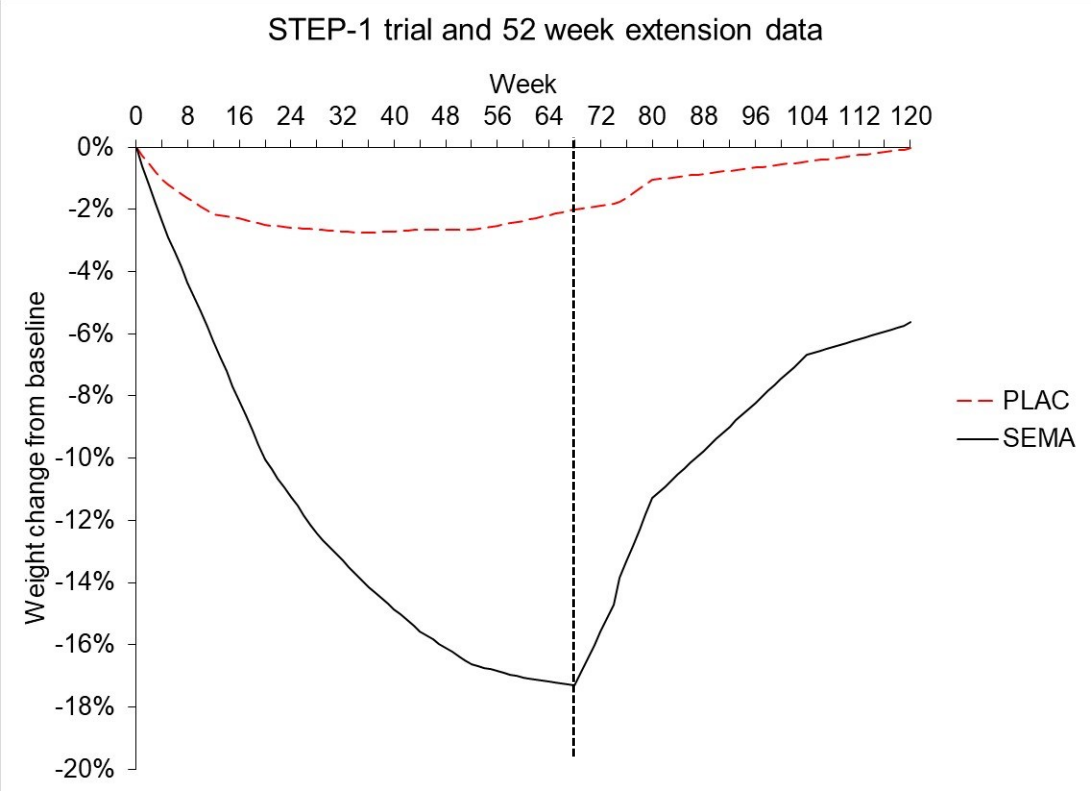


Figure 14: STEP-1 weight loss from baseline and 52 week treatment withdrawal

EAG expert opinion suggests that despite the NICE recommendation, for those doing well on semaglutide it is unlikely that the 2-year stopping rule will be applied. The EAG thinks that this argues for a full set of analyses that do not apply the 2-year stopping rule for any of the active treatments.

The above also suggests that the duration of loss of effect after treatment cessation may be closer to 2 years than the 3 years assumed by the company. The EAG will perform scenario analyses of durations of loss of effect after treatment cessation of 2 years and 4 years.

5.2.7 Extrapolation and treatment waning

The modelling assumes that up to age 68 the treatment effect upon weight increases over time for those on treatment due to a constant weight being assumed while those off treatment are assumed to have an annual BMI 0.145 kgm^{-2} worsening if female and 0.175 kgm^{-2} if male.

The only medium term data for ongoing treatment with a GLP-1 for obesity that the EAG is aware of is the extension phase of the SCALE trial population with

prediabetes at baseline to 160 weeks as presented during TA664[***]. This presents the percentage change from baseline in the mean fasting body weight among those remaining followed up, these numbers being presented in Table 61.

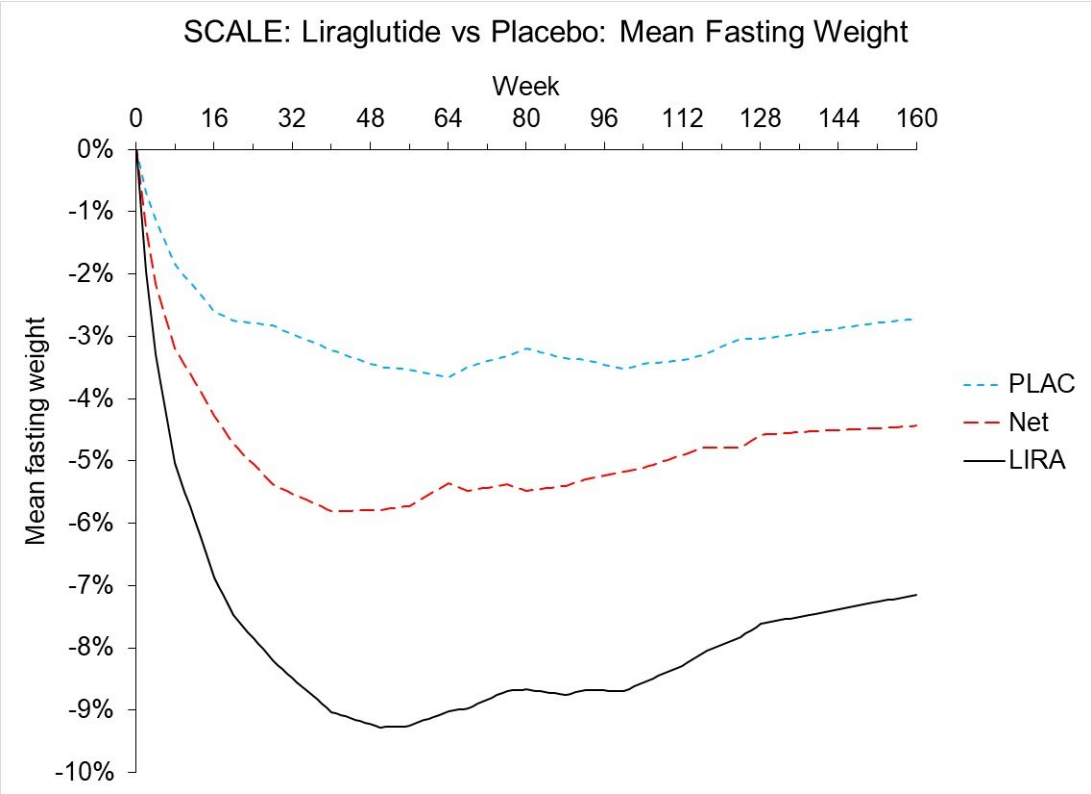


Figure 15: SCALE weight loss from baseline to 160 weeks: Prediabetes population

Table 61: SCALE prediabetes patient numbers to 160 weeks

Week	0	28	56	80	104	124	160
LIRA	1,467	1,223	1,100	971	885	833	747
PLAC	734	576	508	436	375	355	322

It can also be noted that there was a rapid regain of weight during a 12 week off treatment phase after week 160, the regain being faster in the liraglutide arm than in

[***] TA664 Company submission Figure 7

the placebo arm. Interestingly, this maintained the dietary restrictions and physical exercise elements.

Figure 15 suggests that there may be a waning of both the absolute treatment effect and the net treatment effect for liraglutide over time. The NICE 2022 methods guide states "*When the effect of technologies is estimated beyond the results of the clinical studies … alternative scenarios reflecting different assumptions … are desirable. These should include assuming the technology does not provide further benefit beyond the technologies' use, as well as more optimistic assumptions*". The EAG is unclear whether this suggests that for a treatment with continual ongoing use a waning of the treatment effect after the trial period should be modelled.

The EAG thinks that an increase in the net treatment effect should not be modelled. Since it cannot revise the rate of change of BMI for those on treatment, it sets the rate of change for those off treatment to zero.

The EAG thinks that a waning of the treatment effect should be explored in the light of the SCALE trial extension data. Unfortunately, the EAG cannot amend the current model to apply this.

5.2.8 Mutually exclusive treatment arms and optimal sequencing of treatments

SURMOUNT-1 was composed of four arms, tirzepatide 5mg, 10mg and 15mg doses and placebo, all in conjunction with a diet and exercise regime. As a consequence, within the current model structure the tirzepatide 5mg, 10mg, 15mg doses and placebo must be treated as mutually exclusive alternatives. This is the reason that the EAG presents a fully incremental analysis in Table 51 rather than pairwise comparisons.

It seems possible that in practice tirzepatide 5mg may be tried first in patients. This could be for clinical reasons to minimise side effects, but it also relates to cost effectiveness. Within the company pricing structure tirzepatide 5mg is less costly than tirzepatide 10mg, with tirzepatide 15mg being the most costly dose. It may be most cost effective to try tirzepatide 5mg first and only to use the more costly tirzepatide doses among those who do not respond or have a poor response to tirzepatide 5mg.

In a similar vein, tirzepatide 5mg is assumed within the company submission to be more costly than semaglutide. It may be more cost effective to try semaglutide first and only to use the more costly tirzepatide 5mg among those who do not respond or have a poor response to semaglutide.

The model cannot currently address or inform the likely optimal sequencing of treatments. It would require extensive reworking. Assumptions would also have to be made about 2nd line effectiveness among 1st line non-responders. The obvious upper bound would to assume the same effectiveness for 2nd line effectiveness among 1st line non-responders as was observed across all patients. This effectiveness estimate could be reduced as guided by expert opinion; e.g. to only 75% of 1st line effectiveness, or to only 50% of 1st line effectiveness, etc. and the effect upon optimal sequencing examined.

EAG expert opinion is that the goal of treatment will be the maximum tolerated dose in order to maximise weight loss rather than a treatment goal such as losing 5% of body weight. This may mean that the 15mg treatment arm of SURMOUNT-1 is the most relevant to the NHS. For this reason the EAG retains a presentation of pairwise results for the tirzepatide arms, relative to both semaglutide and placebo for the position sought in the base case.

5.2.9 Baseline prevalence of modelled complications

It appears that the model assumes that at baseline patients have none of the modelled complications. At clarification the company supplied SURMOUNT-1 data for the target group of those with a BMI ≥ 30 kgm^{-2} and at least one comorbidity showing a baseline prevalence of 4.2% ASCVD, 11% OSA and 1.5% NAFLD. It is possible that this group had also experienced other modelled events such as MI or knee replacement. At a minimum the general population age specific prevalences should be applied.

Not applying the baseline prevalence data is likely to bias the analysis in favour of the more effective treatments. The EAG cannot revise the model to address this.

5.2.10 Clinical effectiveness among responders remaining on treatment

The clinical effectiveness estimates for tirzepatide 5mg, 10mg and 15mg are based upon an EAS analysis of SURMOUNT-1; i.e. it relates to all those remaining on treatment during the trial.

The model applies the same weight loss percentage, and other clinical effectiveness estimates, across all patients within the cohort; i.e. equally for responders and non-responders. The model then assumes that those responding to and continuing with treatment beyond 6 months have the mean trial EAS weight loss and other clinical effects. This underestimates the weight loss among the responders who remain on treatment. This is also likely to underestimate the other treatment effects among responders.

Data supplied at clarification for SURMOUNT-1 for the target group of those with a BMI 30 kgm^{-2} and at least one comorbidity shows the differences in the 72 week effect estimates between all patients and those with a minimum weight loss of 5% at 36, 48 and 48 weeks for tirzepatide 5mg, 10mg and 15mg respectively. These timepoints were chosen as the SURMOUNT-1 monitoring timepoints which best correspond with the 30, 38 and 46 weeks for titration and 6 months maintenance dose for tirzepatide 5mg, 10mg and 15mg, though it can be argued that the SURMOUNT-1 data points of 36 weeks would have been more appropriate for 10mg tirzepatide.

The above data may need to be treated with some caution due to the patient numbers it relates to suggesting proportions of responders of only [redacted] for tirzepatide 5mg, 10mg and 15mg compared to 90%, 96% and 96% within the modelling and Document B table 74.

Table 62: Target group effects: restricted to those with minimum 5% weight loss

	Target group				Target group 5% responders			
		TIRZ				TIRZ		
	PLAC	5mg	10mg	15mg	PLAC	5mg	10mg	15mg
N[†††]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HDL (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prediab reversal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
incl. unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
excl. unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given the relatively high responder rate for tirzepatide restricting the effect estimates to 5% responders does not have a dramatic effect upon weight loss, SBP or prediabetes reversal though all the estimates improve. The main differences within SURMOUNT-1 appear to be in the HDL and total cholesterol which given baseline values of 48.7 mg/dL and 194 mg/dL may be non-trivial.

The EAG has not been able to source any corresponding responder analysis within TA875. TA664 provides some responder analyses but the EAG has not been able to source corresponding non-responder analyses to compare these to.

The degree of bias this introduces seems likely to increase with the modelled rate of non-response and treatment cessation at 6 months though the actual bias will depend upon the weight loss distribution within the various trials. As per Table 38 above, liraglutide is modelled as having the highest non-responder rate, followed by semaglutide, tirzepatide 5mg and tirzepatide 10mg with tirzepatide 15mg having the lowest non-responder rate. This seems likely to bias the analysis in favour of the higher doses of tirzepatide, to have little effect upon the comparison of tirzepatide 5mg with semaglutide, and to bias the analysis against liraglutide other things being equal.

[†††] Based upon clarification response Table 31 and Document B Table 22

5.2.11 Rates of 5% weight loss responders: Tirzepatide

The responder rates for tirzepatide are based upon week 72 data, this being assumed to apply at around week 26 and lead to treatment withdrawal. As shown in Document B Figure 10 within the SURMOUNT-1 EAS analysis there were reasonably substantial additional gains between week 24, the timepoint nearest to 26 weeks, and week 72.

The EAG thinks that the company should provide the SURMOUNT-1 proportions of patients achieving a 5% weight loss by weeks 24, 36 and 48 and should explore applying these estimates within the model. The availability of corresponding data for semaglutide and liraglutide may be problematic, but this may illustrate the effect for the comparison with placebo. The EAG did not explicitly request this data at clarification but the patient numbers supplied at clarification as outlined above can be used for a scenario analysis that assumes responder rates of [redacted] for tirzepatide 5mg, 10mg and 15mg respectively. This should be read in conjunction with the section below.

5.2.12 Rate of 5% weight loss responders: Semaglutide

The 10% estimate of non-responders for semaglutide is based upon expert opinion due to it being redacted from TA875 for the target population. This compares to response rates of [redacted] for tirzepatide 5mg, 10mg and 15mg.

For STEP-1 across all patients, those with a BMI ≥ 27 kg^{-2} and at least one comorbidity or with a BMI ≥ 30 kgm^{-2} so reasonably aligned with SURMOUNT-1 in terms of inclusion criteria, Wilding et al [11] report that by 68 weeks 31.5% in the placebo arm and 86.4% of those in the semaglutide arm had lost at least 5%, assessing "*effects regardless of treatment discontinuations*", a crude net effect estimate of 54.9%. This compares to [redacted] as reported in the SURMOUNT-1 CSR for the 72 week treatment regimen estimand for placebo and tirzepatide 5mg, 10mg and 15mg respectively and crude net effects relative to placebo of [redacted]. Bearing in mind the slightly different time points this may suggest that the response rate of semaglutide on a treatment regimen estimand basis is more akin to tirzepatide 10mg and 15mg and less akin to tirzepatide 5mg.

Within the company NMA the weight reduction estimates are [redacted] for tirzepatide 5mg, 10mg and 15mg compared to [redacted] for semaglutide. This pulls the other way and suggests semaglutide may be more akin to tirzepatide 5mg.

The EAG will provide a scenario analysis that applies the EAG NMA estimates, and also a scenario that equalises the response rate for semaglutide with that of tirzepatide 15mg.

5.2.13 Reversal of prediabetes

Due to the EAG mainly considering applying the 2-year stopping rule for all active treatments or not applying the 2-year stopping rule for all active treatments the handling of the loss of prediabetes reversal is broadly the same across the active treatments.

This does not apply to placebo. The model is structured to so that all prediabetes reversal for placebo is lost between year 2 and year 3. The EAG thinks that this seriously biases the analysis in favour of the active treatments. The EAG cannot reliably revise the model to retain the placebo prediabetes reversal so that its handling is aligned with the active treatments. The best that the EAG can do is to apply the net effect estimates for all parameters, with placebo having no effect upon weight, SBP, HDL, total cholesterol or prediabetes.

The EAG also provides a scenario analysis that applies the EAG NMA estimates, due to the large differences in the placebo arm response rates of SURMOUNT-1, SCALE and STEP-1: [redacted], 35% and 46% respectively.

5.2.14 Discontinuations due to adverse events

The company applies ongoing annual discontinuation due to adverse events probabilities of 3.1%, 5.2% and 4.5% for tirzepatide 5mg, 10mg and 15mg and of 5.5% and 9.2% for semaglutide and liraglutide respectively.

At clarification the company supplied SURMOUNT-1 discontinuation data for any reason and discontinuation data due AEs.

The Kaplan Meier data for those remaining on treatment is presented in Figure 16 below.

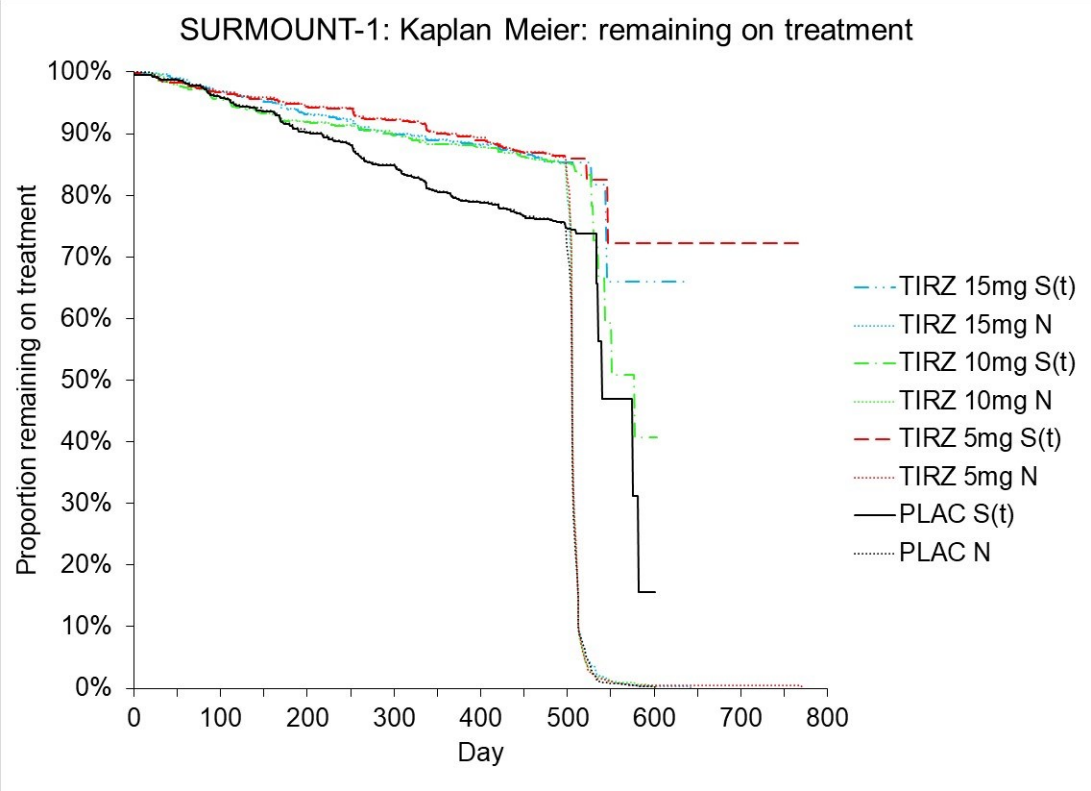


Figure 16: SURMOUNT-1: Kaplan Meier: Proportion remaining on treatment

There is minimal censoring prior to around day 500, or week 72. The proportions discontinuing due to any event from the above can be presented alongside those for discontinuation due to AEs, calculated in a like manner.

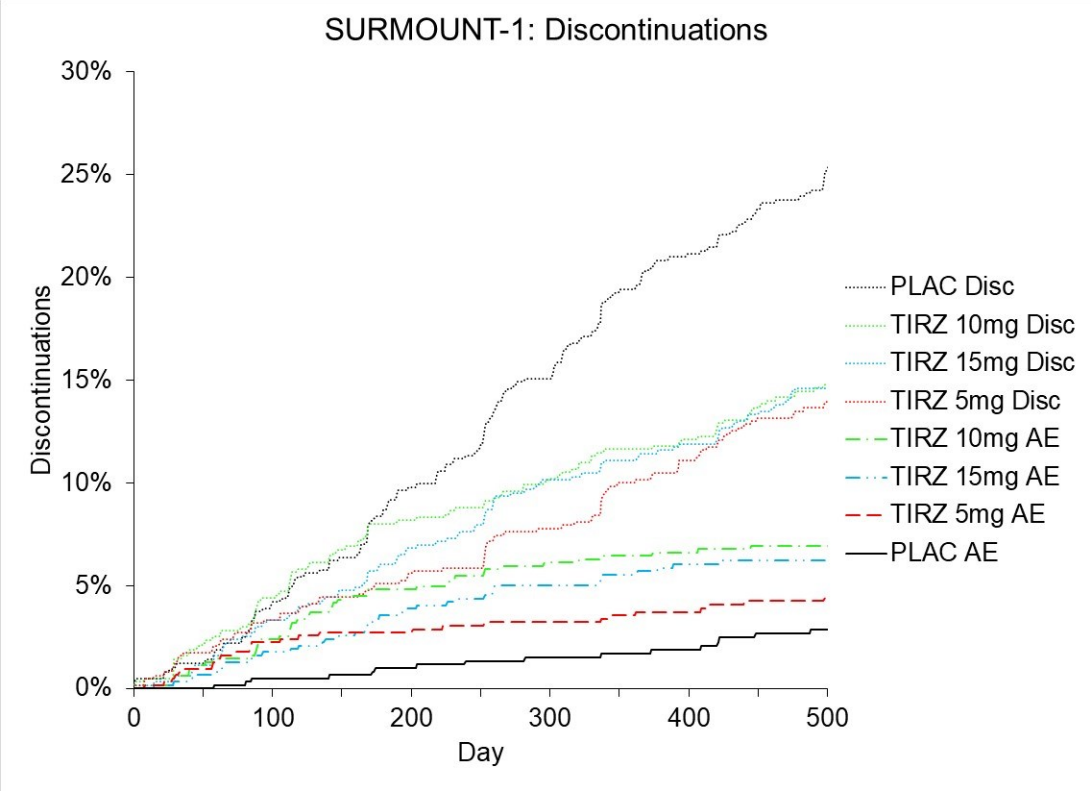


Figure 17: SURMOUNT-1: Kaplan Meier: Proportion discontinuing treatment

What is immediately striking about Figure 17 is that despite the differences in the proportions with, say, a minimum 5% weight loss the total discontinuations during SURMOUNT-1 are not noticeably different between the tirzepatide arms. There is more differentiation between the tirzepatide arms in terms of discontinuations due to AEs, but this appears to occur relatively early in the trial with the curves for all the tirzepatide arms flattening out thereafter.

Table 63: SURMOUNT-1: KM discontinuations due to AEs

Year	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
0.25	0.5%	2.2%	2.2%	1.6%
0.50	1.0%	2.7%	4.8%	3.6%
0.75	1.3%	3.2%	6.0%	5.0%
1.00	1.7%	3.7%	6.5%	5.7%
1.37	2.9%	4.4%	7.0%	6.2%

It seems likely that there is some random variation within the data due to tirzepatide 10mg having a higher rate of discontinuations due to AEs than tirzepatide 15mg. Also apparent from the above is that annualising the year 1.37, around 72 weeks, to annual figures of 3.1%, 5.2% and 4.5% for tirzepatide 5mg, 10mg and 15mg respectively does not tally with the year 1 values due to the discontinuations due to GI events curves flattening out.

The proportion of new discontinuations each quarter can be calculated and annualised as in Table 64, the annualization of the last period being on the basis of 0.37 years.

Table 64: SURMOUNT-1: Annualised quarterly discontinuations due to AEs

Year	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
0.25	1.9%	8.7%	8.7%	6.3%
0.50	2.0%	1.9%	9.9%	7.5%
0.75	1.4%	2.0%	4.5%	5.8%
1.00	1.5%	2.0%	2.0%	2.7%
1.37	3.1%	1.9%	1.3%	1.4%

For the tirzepatide arms the annualised quarterly discontinuation rates due to adverse events fall as time progresses as might be expected, being only around 1-2% towards the end of the trial. It seems reasonable to expect these latter rates to be the upper bounds of the ongoing discontinuation rates due to adverse events, it being possible that they will continue to fall as time progresses.

The rates of discontinuations due to AEs tending to flatten out over time has implications for the comparison with semaglutide and liraglutide. These are evaluated at 56 weeks and 68 weeks respectively with total discontinuations due to AEs of 7.04% and 9.89%.

The 7.04% 56 week value for semaglutide is not particularly different from the 6.6% and 6.0% rates for tirzepatide 10mg and 15 mg respectively. It is questionable whether these should be differentiated, particularly for modelling that assumes that treatment is ongoing beyond year 2.

For the EAG base case that applies a 2-year stopping rule for all treatments these issues are largely moot. But the scenarios that do not apply a 2-year stopping rule for any treatment are affected. Unfortunately, given the model structure the EAG cannot apply 1 year discontinuation rates followed by annual 1% discontinuation rates for all treatments. The closest to this that the EAG can perform is to add the 1 year discontinuation rates for tirzepatide 5mg, 10mg and 15mg to the primary treatment failure rates, assume semaglutide has the same discontinuation rate as tirzepatide 15mg, add a 9% discontinuation rate to the primary treatment failure for liraglutide and assume a common 1% annual discontinuation rate for all treatments thereafter.

5.2.15 Hazard ratios and incidence of NAFLD

The company derived hazard ratio functions for the development of NAFLD appear to be based upon Loomis et al [36] figure 4(D) as derived an analysis of the 2007-2013 UK THIN database.

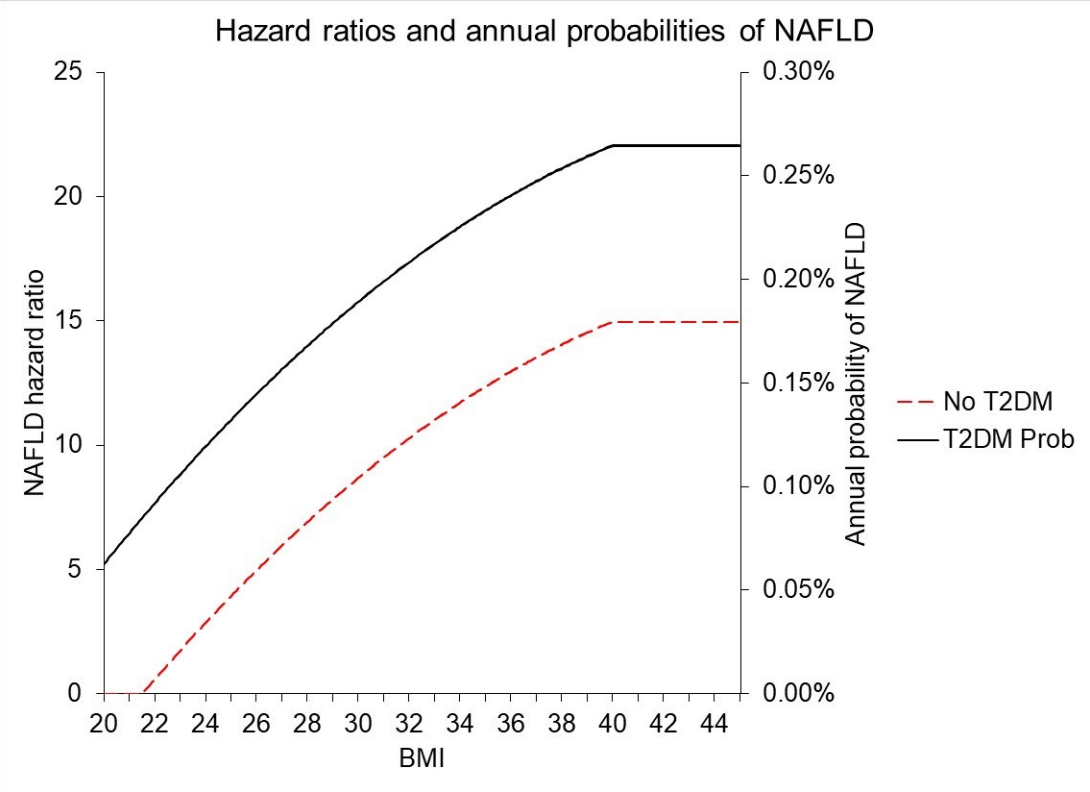


Figure 18: Hazard ratios and annual probabilities of developing NAFLD

Figure 18 broadly mirrors Figure 4(D) of Loomis et al though there are some differences. The company function somewhat overestimates the impact of diabetes for lower BMI values while underestimating it for higher BMI values. It may have been better to estimate separate functions for those with and without diabetes rather than have diabetes as a variable within the pooled analysis, or rather more simply to have used the values of Loomis et al much as the company has used the BMI SMRs of Bhaskaran et al.[42] The company function is also linear from a BMI of 40 kgm^{-2} whereas the values of Loomis et al appear lower for those with a BMI of 40 to 60 kgm^{-2} compared to those with a BMI of 37.5 to 40 kgm^{-2}.

Given the apparent use of Figure 4(D) of Loomis et al the reference probability that the hazard rates are applied to should be the annual incidence among the non-T2DM population with a BMI of 20.0 to 22.5. This is taken from an analysis of the 1995-2017 UK THIN database by Vusirikala et al [37] which provides an annual incidence risk for those of a normal weight of 18.5 to 25.0 kgm^{-2} without T2DM of 0.12 per 1,000 patient years.

Vusirikala et al also estimated hazard ratios by BMI and the presence of none, one or more than one metabolic disorder. These can be compared with those of the company function at rough midpoints of the bands used by Vusirikala et al.

Table 65: NAFLD hazard ratios

Vusirikala et al					Company from Loomis		
BMI		Metabolic disorders			BMI		
Low	High	0	1	2	Value	No T2DM	T2DM
..	18.5	0.50	0.77	..	18.5	-3.8	3.3
18.5	25	1.00	2.27	2.39	21.8	0.3	7.4
25	30	3.32	7.33	9.62	27.5	6.4	13.5
30	..	6.92	12.16	17.88	35.0	12.4	19.4

The company values are somewhat in excess of those of Vusirikala et al and suggest a somewhat stronger BMI effect. For instance for the overweight with no T2DM Vurisikala et al suggest a hazard ratio of 3.32 while the company function estimates a hazard ratio of 6.4.

The company states that it uses Loomis et al to estimate its function due to its finer BMI gradation, but Vurisikala et al for the incidence rate due to it being the more

recent study. The EAG is uncomfortable with this pairing given the apparently very different hazard ratios involved. The EAG has not been able to source a baseline risk from Loomis et al‡‡‡. Given that the hazard ratios of the company are roughly double those of Vusirikala for its base case the EAG halves the incidence rate to 0.06/1,000 patient years, presenting a scenario analysis that retains the 0.12/1,000 patient years. This is less than ideal and it would be better to amend the company hazard ratio function. But time constraints mean that the EAG has not undertaken this.

5.2.16 Incidence of OSA

The odds ratios of Erridge et al [38] for BMI are being applied with a BMI of 30 to 35 kgm^{-2} as the reference group, i.e. this group has an odds ratio of 1.000. It can be noted that those in the Cleveland Family Study of Tishler et al [39] were not necessarily obese and so the 7.5% five year risk of sleep disturbed breathing may be an underestimate of the OSA five year risk.

However, the overall prevalence of OSA within the UK CRPD obese patients data of Erridge et al was only 5.4%. The two data sources appear to be misaligned. Given that roughly a third of patients were in each of the three BMI category patient and that the BMI univariate odds ratios were 1.000, 1.563 and 3.235 respectively, this suggests OSA prevalences by BMI category of 2.85%, 4.38% and 8.67%. These are prevalences and not 5 year risks, so may overestimate the 5 year risk of OSA.

The EAG will apply the UK CPRD OSA prevalence of 2.85% BMI of 30 to 35 kgm^{-2} as a proxy for the five year risk for those with a BMI of 30 to 35 kgm^{-2}.

5.2.17 Event risk functions overestimation of events

It appears that e.g. the 10 year risk of T2DM is annualised within the model with the annualised risk being applied that cycle. It seems likely that the incidence of events is not linear. It may tend to be back ended due to patients health tending to worsen over time. The model may estimate that events occur too early. This will bias the model due both to patients being modelled as having events for too long a period and due to the effects of discounting.

‡‡‡ Unfortunately the Endocrine Society website was undergoing maintenance and the EAG could not source the supplementary material which might contain it.

Related to the above, it appears that the model updates the annualised probabilities based upon the patients' worsening health. For instance, in a given year the 10 year risk of an event may be 20%, with this being annualised to 2.2%. But the model then updated this annualised probability for the next cycle. Suppose that there is a 10% worsening in the 10 year risk to 22%, this then being annualised to 2.5%. Continuing this process over the 10 years of the model the modelled 10 year risk is 32% rather than the correct 20%.

To the extent that this applies the model will overestimate the incidence of events. But it is not possible to quantify the extent of this.

5.2.18 Modelling GLP-1 use among those with T2DM

Patients who have developed T2DM may in time be eligible for treatment with GLP-1 therapy. Current NICE guidance, NG28 which is in the process of being updated, is that GLP-1 can be used at triple therapy if they have a BMI ≥ 35 kgm-2 and psychological problems with obesity or a BMI < 35 kgm-2 and either occupational problems that make insulin undesirable or when weight loss would benefit other significant obesity related comorbidities.

The current modelling assumes that GLP-1 is only initiated at baseline, whereas in practice if not initiated at baseline it may be initiated among those developing T2DM. This may bias the analysis against placebo.

5.2.19 Modelling of the progression of diabetes: ESRD

The model does not estimate the incidence of end stage kidney disease and the possibility of dialysis, with the associated effects upon cost and mortality. This will tend to bias the analysis against the treatment that is more effective in reversing prediabetes, and in reducing the risk factors for the development of diabetes.

5.2.20 Cost-effectiveness for the subgroup between 30kgm-2 and 35kgm-2

The company cost-effectiveness estimates suggest that tirzepatide is more cost effective among those with a BMI ≥ 35kgm^{-2} than among those with a BMI ≥ 30kgm^{-2}. This raises the possibility that it may be somewhat less cost effective among those with a BMI between 30kgm^{-2} and 35kgm^{-2}.

Cost-effectiveness estimates for this subgroup can be derived from the estimates for those with a BMI ≥ 30kgm^{-2} and for those with a BMI ≥ 35kgm^{-2}, coupled with the

numbers of these patients in SURMOUNT-1 being N=[redacted] and N=1,523 (63%) respectively. This suggests the following cost-effectiveness estimates for those with a BMI between 30kgm^{-2} and 35kgm^{-2}.

Table 66: BMI between 30kgm^{-2} and 35kgm^{-2}: Deterministic

			ICER	
	Cost	QALY	Incr.	vs PLAC
PLAC	[redacted]	17.158		
TIRZ 10mg	[redacted]	17.702	Ext. Dom	£18,999
TIRZ 5mg	[redacted]	17.820	£15,795	£15,795
TIRZ 15mg	[redacted]	17.724	Dominated	£22,671

The above suggests that tirzepatide has a worse cost-effectiveness among those with a BMI between 30kgm^{-2} and 35kgm^{-2} compared to the results for those with a BMI ≥ 35kgm^{-2} as reported in Table 56 on page 125 above, the ICERs being 25%, 62% and 75% higher for tirzepatide 5mg, 10mg and 15mg respectively. Depending upon the willingness to pay threshold it is possible that tirzepatide 15mg may be deemed not to be cost effective, even when viewed outside the incremental analysis and only within a pairwise comparison with placebo.

The cost and QALY estimates of Table 66 are based upon the values that when coupled with the cost and QALY estimates for those with a BMI ≥ 35kgm^{-2} of Table 56 in a [redacted] weighted average result in the cost and QALY estimates for those with a BMI ≥ 30kgm^{-2} of Table 55.

5.3 *EAG critique of the handling of quality of life within the model*

5.3.1 SURMOUNT-1 baseline QoL vs modelled baseline QoL

The company submission Document B section B.3.4.1 on page 180 states that "*SURMOUNT-1 assessed HRQoL via 2 distinct measures*", the SF-36 and the IWQOL-Lite-CT, going on to state that "*given the misalignment with the NICE reference case to derive utility values, data from the literature were used instead*". The SURMOUNT-1 CSR outlines that EQ-5D-5L was administered, the company submission appendix M Table 126 providing a mean baseline value of 0.85, valued using the NICE recommended methods.

The mean patient baseline characteristics can be inputted to the Soltøft et al [48] quality of life function as applied by the company[§§§], including 7.8% with OSA but assuming none of the other comorbidities that Soltøft control for. This results in baseline quality of life values of 0.929 for men and 0.848 for women, which if pooled 34:66 results in a mean of 0.875 which is reasonably close to the 0.85 SURMOUNT-1 mean value.

Given the mean baseline BMI of 42.6kgm^{-2} the function the company applies for those with a BMI ≥ 35kgm^{-2} which is in part derived from Soltøft et al can also be applied with this resulting in estimates of 0.920 for men, 0.877 for women and a mean of 0.888.

Some of the reason for the discrepancies between SURMOUNT-1 and the quality of life functions of the model may be that the quality of life function of Soltøft et al as applied by the company only uses a subset of the coefficients. The full Soltøft function also includes coefficients for the general health questionnaire score, the age when education ended and whether in non-manual work. It can also be noted that Soltøft et al estimated their function from general population data rather than among those who were seeking treatment to reduce their BMI.

The EAG thinks that due to the company function not applying many of the coefficients of Soltøft et al the intercept of the quality of life functions should be reduced by 0.025 for the function for those with a BMI < 35kgm^{-2} and by 0.038 for the function for those with a BMI ≥ 35kgm^{-2}. But this needs to be read in conjunction with section 5.3.2 below.

5.3.2 Alignment of BMI ≤ 35kgm^{-2} and BMI > 35kgm^{-2} QoL functions

The company uses two quality of life functions, that of Soltøft et al [48] for those with a BMI < 35kgm^{-2} and an amended version of this for those with a BMI ≥ 35 kgm^{-2}. Ignoring the modelled comorbidities, the effect of which is to move both quality of life functions down by the same amount, the base case quality of life functions are presented in Figure 19 below, the Soltøft et al function being taken beyond a BMI ≥ 35kgm^{-2} for illustrative purposes.

[§§§] Note that within the company modelling the quality of life for those with a BMI of more than 35 is based upon a difference function. But as reviewed later this also causes problems and suggests that it may be better to rely upon a single quality of life function.

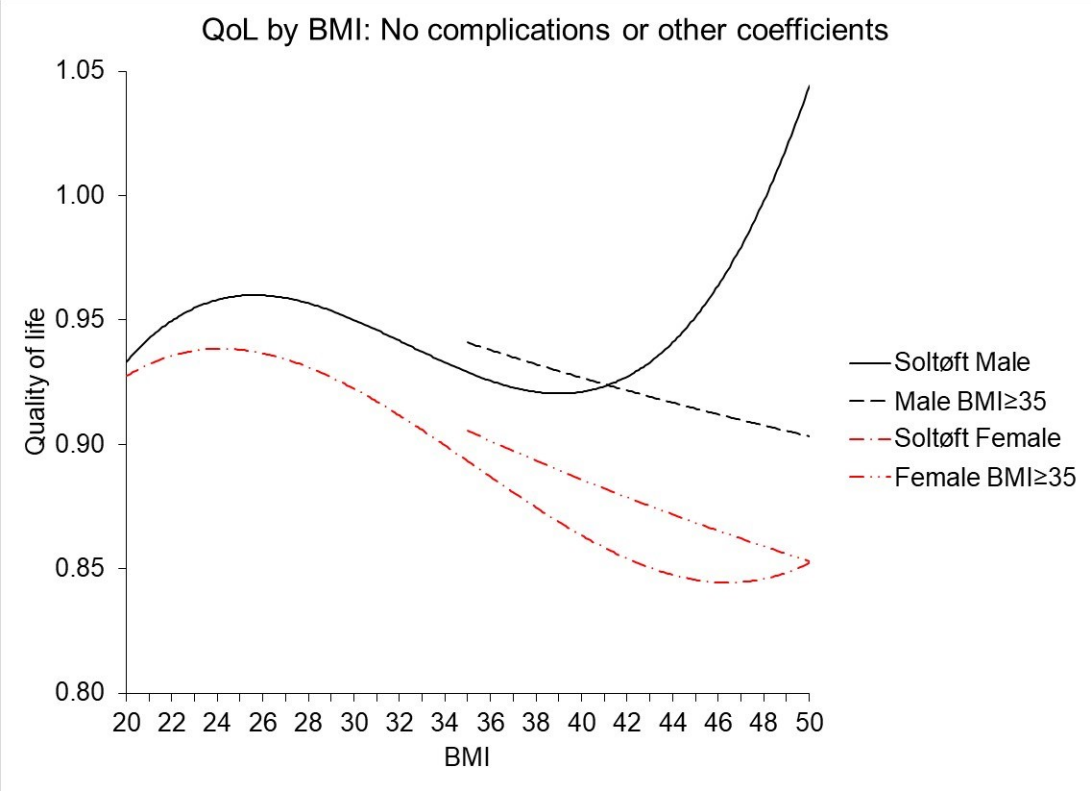


Figure 19: Quality of life functions

An initial objection to pushing the Soltøft et al function much above a BMI of 35kgm^{-2} might appear to be that it causes the quality of life to increase above one. It would be relatively easy to cap quality of life at one, but as outlined in section 5.3.1 above there are other coefficient within Soltøft et al which if applied would tend to pull the quality of life functions downwards.

The main objection is that due to the positive coefficients for BMI^3 the functions suggest a better quality of life as BMI increases beyond 39.0kgm^{-2} for men and 46.5kgm^{-2} for women.

There is also a discontinuity between the two functions at a BMI of 35 kgm^{-2}. This means that patients whose BMI is modelled as falling below 35 kgm^{-2} see their quality of life fall, this loss remaining until their BMI falls further to below 32.2 kgm^{-2} for men and 33.0 kgm^{-2} for women. This will tend to bias the analysis against the more effective treatment, effectiveness being in terms of both size and assumed duration of effect. Within the company quality of life functions this argues for reducing the intercept for the BMI ≥ 35 kgm^{-2} by 0.012 for both men and women.

The above also illustrates the arbitrariness of the company cutoff of a BMI of 35 kgm^{-2} for the switch between quality of life functions, the function for a BMI ≥ 35 kgm^{-2} being taken from TA664. Soltøft et al report the BMI distribution among the N=14,416 adults who contributed EQ-5D data, though for estimating the function there were apparently only 11,920 observations. Assuming that the distribution of observations is the same as the distribution of adults, the number of observations in different BMI categories is reported in Table 67 below.

Table 67: Soltøft et al distribution of observations

BMI	Men		Women	
< 18.5	55	(1%)	103	(2%)
18.5 - 24.9	1,653	(30%)	2,623	(41%)
25.0 - 29.9	2,486	(45%)	2,178	(34%)
30.0-39.9	1,226	(22%)	1,353	(21%)
≥ 40	55	(1%)	187	(3%)

The number of observations with a BMI of less than 18.5kgm^{-2} or more than 40kgm^{-2} is small and the EAG thinks that it is sensible not to push the Soltøft et al functions beyond these values. This also implies that the number of observations close to these boundaries will also be small. But it is not obvious that this applies for all BMI values between 35kgm^{-2} and 40kgm^{-2} given that there are 1,226 observations for men and 1,353 observations for women between 30 kgm^{-2} and 40 kgm^{-2}. A 37.5 kgm^{-2} cutoff for the switch between functions may be reasonable. This would require the intercept for the BMI ≥ 35 kgm^{-2} function be reduced by 0.012 for men and by 0.018 for women to avoid stepped functions.

In the light of this and section 5.3.1 above the EAG will reduce the intercepts by 0.025 for men and women within the Soltøft et al functions and by 0.037 for men and women for the BMI ≥ 35.0 kgm^{-2} functions.

There is an argument for exploring different cutoffs for men and women given the behaviour of the functions in Figure 19, with a higher cutoff for women, perhaps 37kgm^{-2}. The EAG does not explore this due to time constraints.

5.3.3 Double counting the QoL effects of BMI

The quality of life effects of BMI driven events that are not explicitly included within Søltoft et al [48] seem likely to be accounted for within the BMI coefficients, and possibly also in part within the coefficients for the events that are included within Søltoft et al due to multicollinearity. As a consequence, for its revised base case the EAG will only apply the coefficients of Søltoft et al, together with the adverse event disutilities. Given the infrequency of bariatric surgery, the EAG will retain the disutility for this despite it not being within Søltoft et al. The EAG will supply a scenario analysis that also applies the quality of life event coefficients that the company sources from references other than Søltoft et al.

A critique of the above is that comorbidities might also be picked up in the general health questionnaire aspect of Soltøft et al, this also potentially applying more generally.

5.3.4 Validation of quality of life functions

Due to the mean baseline BMI of SURMOUNT-1 being greater than the values at which the Soltøft et al quality of life functions turn positive the EAG thinks it may be useful for the company to provide two scatter plots of SURMOUNT baseline EQ-5D values against baseline BMI, one for men and one for women together with simple OLS lines of best fit together with their goodness of fit parameters. The EAG did not ask for this at clarification. More sophisticated analyses controlling for patient characteristics and not imposing linearity could also be provided as the company sees fit.

5.4 *EAG critique of the handling of costs within the model*

5.4.1 On treatment and off treatment resource use

Other than the initial £24 cost for the first administration ongoing treatment costs for those on treatment and those off treatment are the same: £234 for quarterly GP visits, twice quarterly nurse visits and annual blood tests. The modelling assumes that active treatments incur no additional ongoing cost, implying that they are managed in primary care and not within an SWMS.

While difficult to be precise given the varied nature of patients EAG expert opinion suggests that within an SWMS during the first year a patient on active treatment

would see a consultant 3 time, a dietician 8 times and a psychologist 3 times. Thereafter annual consultant visits and dietician visits might be 2 and 4 visits annually. The EAG costs consultant and psychologist visits at the consultant led Dietetics Service non-admitted face to face OP cost of £152.14 and the dietician visits at non-consultant led Dietetics Service non-admitted face to face OP cost of £98.43. This results in a first year cost of £1,645 and an ongoing annual cost of £698.

The EAG base case will apply these costs, also presenting a scenario that does not apply them.

5.4.2 Annual cost of diabetes

The annual cost of T2DM is stated as being the average NHS reference cost for those with diabetes with hypoglycaemic disorders, currency codes KB01C through to KB02K. This includes all elective, non-elective long stay, non-elective short stay, day case and regular day or night admissions. It does not include the costs of dialysis.

The company has inadvertently not included KB02K, the inclusion of which reduces the average cost from £1,770 to £1,612.

These reference costs cover 74,041 hospital attendances at a total cost of a little under £120 million. Given the UK prevalence of T2DM of perhaps around 4 million this would suggest an average annual T2DM cost of £30. But most of the costs of T2DM are not incurred within the NHS costs of the company costings.

The EAG thinks that the obvious source for the costs of T2DM are the reasonably recently updated UKPDS 84 cost estimates,[53] applying those for a patient with no additional complications due to the model separately estimating the various complications. This will not take into account the more expensive items of care for end stage renal disease, dialysis and transplant, but since the patients under consideration are newly developing T2DM this may be an acceptable approximation. The resulting annual inpatient and non-hospital costs of T2DM for the baseline age of 48 years and weighted 66% female and 33% male is £933 in 2012 prices, which when uprated by 14% for inflation to 2021 prices suggests an annual cost of £1,064. This does not take into account direct drug treatment costs for T2DM which involve some additional costs once the patient has progressed to multiple oral anti-diabetic medicines or to insulin use.

The £1,064 annual inpatient and non-hospital cost for a patient with T2DM and no other comorbidities is a total cost, not a net cost compared to an obese patient. Given the lack of comorbidities in may be more reasonable to only apply the UKPDS non-hospital costs, £674, inpatient costs perhaps tending to be incurred for general health reasons and so likely to be similar for the obese and those with T2DM without any comorbidities.

The EAG will revise the annual cost of T2DM to £674. It will also provide scenarios that set it to £1,064 and £1,612. The possible avoidance or delay of dialysis costs for some patients should be borne in mind, these typically being around an annual £30,000.

5.5 *Minor Issues*

5.5.1 Minor Issue: NAFLD mortality hazard ratio

The 1.93 hazard ratio for NAFLD sourced from the Simon et al [44] analysis of Swedish liver biopsy data illustrates the possible double counting of mortality effects through sourcing multiple mortality multipliers from different sources. Compared to control those with histologically confirmed NAFLD had more CVD, 20% vs 12%, diabetes, 11% vs 3%, hypertension, 10% vs 5%, and obesity, 4% vs 0.4%. But it can be noted that the 1.93 hazard ratio was controlled for cardiovascular disease and metabolic syndrome defined as a variable from 0 to 4 with 1 point for each of diabetes, obesity, hypertension and dyslipidaemia, though the EAG is unclear whether this was for matching with the control or a multivariate adjustment of the hazard ratio.

Simon et al also analysed their data by stage of NAFLD, the 67%, 12%, 16% and 6% with simple steatosis, NASH without fibrosis, fibrosis without cirrhosis and cirrhosis being estimated to have hazard ratios of 1.71, 2.14, 2.44 and 3.79 respectively.

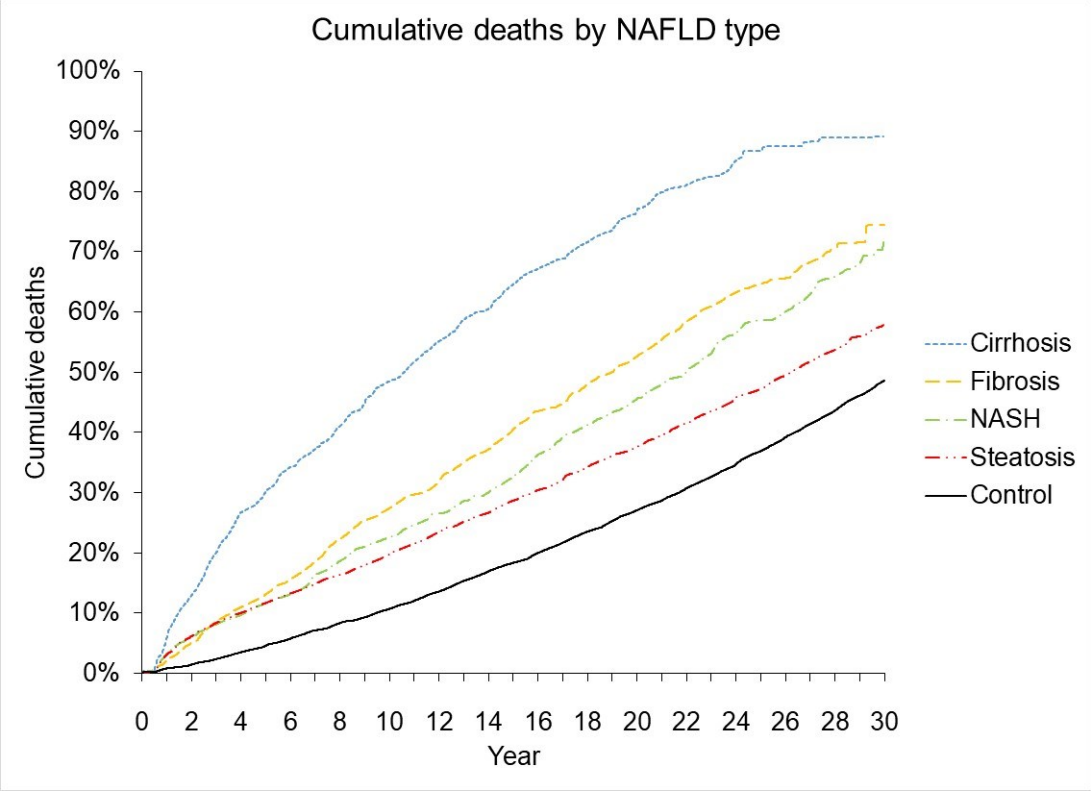


Figure 20: Cumulative deaths by NAFLD type vs control group

The EAG thinks that the above curves relate to patients' NAFLD status at baseline. There is no mention within Simon et al of biopsies subsequent to baseline. As a consequence, it appears that the hazard ratio for those with simple steatosis will include the effects of the proportion of patients who progress to more serious forms of NAFLD during their lifetime. What is also striking is that after the initial 5 years or so the distance between the steatosis curve and the control curve shows no sign of widening, whatever increased hazard applies for steatosis appearing to mainly apply during the first five years since biopsy confirmed diagnosis.

Since the model simulates the incidence of new NAFLD which would generally be expected to be steatosis the EAG thinks this argues for only applying the 1.71 hazard ratio within the analyses that require an NAFLD mortality hazard ratio.

5.5.2 Minor Issue: Down titration and treatment costs

The model assumes that those on treatment are treated with tirzepatide 5mg, 10mg or 15mg weekly, semaglutide 2.4mg weekly or liraglutide 3.0mg daily. Within the relevant trials there was some down titration due to issues with tolerance. This could

bias the analysis due to the cost implications of down titrating for tirzepatide compared to semaglutide and liraglutide, the liraglutide pre-filled pens permitting more doses for those who down titrate from the 3.0mg maximum dose.

Within SURMOUNT-1 down titration occurred in [redacted] of 5mg, 10mg and 15mg patients respectively. The EAG has reviewed the literature and notes that down titration from 2.4mg to 1.7mg was permitted in the semaglutide trial but that down titration of liraglutide was not permitted. Unfortunately, the number of patients down titrating from 2.4mg to 1.7mg was not stated. Given the similarity in the proportions of adverse events leading to treatment discontinuation for semaglutide and tirzepatide 15mg, an EAG scenario analysis will apply the down titration [redacted] proportion of tirzepatide 15mg to semaglutide 2.4mg. This can be criticised as being too pessimistic for analyses which also contain discontinuations due to adverse events as the two elements may be linked: patients with GI events may have down titrated but if this did not work may then have discontinued treatment.

5.5.3 Minor Issue: incidence of severe or serious GI events

Wilding et al [11] only report the serious GI event rates, 1.4% for semaglutide and 0.0% for placebo. Severe rates for gastrointestinal events are graphed in the supplementary appendix for nausea, diarrhoea, vomiting and constipation, severe being sufficiently serious to prevent everyday activities. The severe are such small portions of the bar charts it is difficult to have confidence in the values that could be digitized from them. It is also unclear quite what events are included and what the data definitions are for the SURMOUNT-1 data. If the company can supply more detail of the estimates for semaglutide it may be reasonable to apply them. The EAG will equalise severe and serious GI events for semaglutide with tirzepatide 15mg.

5.5.4 Minor Issue: Ongoing incidence of severe or serious GI events

The company model assumes that the rates of severe or serious GI events applies for the duration of treatment. The EAG thinks that if GI events occur they tend to occur relatively early during treatment and that repeat GI events are unlikely due to those experiencing them discontinuing from treatment as reviewed in the section above.

The EAG thinks that the most reasonable approach is to only apply the estimates for severe and serious GI events once within the modelling.

5.5.5 Minor Issue: NAFLD annual costs

The annual cost of NAFLD is subject to the same criticism as the costs of T2DM. It is largely based upon the mean inpatient cost for those admitted with liver failure disorders[****].

- 240 elective admissions with an average cost of £3,350
- 3,996 short stay admissions with an average cost of £870
- 9,708 non-elective long stay admissions with an average cost of £4,097

But rates of NAFLD only differ between the arms in terms of newly incidence NAFLD. It is not obvious that these costs should be applied to these patients. Patients with simple steatosis are unlikely to require inpatient treatment. The model in effect assumes that all patients with NAFLD of whatever severity are hospitalised once each year.

NICE reports[††††] a prevalence of 23% for Europe though whether this is diagnosed NAFLD or population NAFLD is not made clear. If the £3,108 average cost of the 13,944 liver failure disorder admissions applied to the population of England and Wales it would suggest a prevalence of diagnosed NAFLD of 0.02%, and this assumes that all the admissions for liver failure disorders were for NAFLD. If the NHS reference costs for liver failure disorder admissions are to be applied, their cost should be averaged over a much large population than 13,944.

The EAG thinks that it is unreasonable to apply the average inpatient cost for liver failure disorders as the ongoing annual cost of NAFLD. These costs seem likely to be too high.

The only reference providing annual costs the EAG has been able to source is the Allen et al study of US insurance claims.[56] It notes that insurance claims for NAFLD among those with private insurance were an annual US$2,298 higher than a matched cohort without NAFLD. Converting with the 2018 exchange rate of around US$1.30 to the pound and increasing by 7.7% for inflation results in an annual cost

[****] Thre are minor day case and other costs but the numbers of these is very small compared to the number of IP admissions.
[††††] https://cks.nice.org.uk/topics/non-alcoholic-fatty-liver-disease-nafld/background-information/prevalence/

of £1,904. But this is in the context of US private insurance claims, and again may tend to relate to when NAFLD progresses rather than its early incidence.

The EAG will arbitrarily halve the £1,904 to £952 for its base case, applying the full £1,904 in a scenario analysis.

5.5.6 Minor Issue: Costs of other events

The knee replacement costs are an average of the NHS reference costs that are suitable to apply. These apply to fully completed episodes which the EAG thinks means that they include hospital based rehabilitation services.

Time constraints mean that the EAG has not reviewed the costs of the other events. Their effect upon net costs is relatively muted.

5.5.7 Model revisions for minor Issues

The EAG makes the following minor changes to the model.

- Correcting the T2DM disutility during the initial 4 weekly cycles
- Correcting the model error identified by the company at clarification
- Revising the NAFLD mortality hazard ratio to 1.71
- Equalising the semaglutide rate of severe and serious GI events with that of tirzepatide 15mg
- Only apply the severe and serious GI rates once
- Revising the annual NAFLD cost to £952
- Semaglutide response assessment at 42 weeks

5.6 *Exploratory and sensitivity analyses undertaken by the EAG*

5.6.1 EAG modelling caveat

The company model is programmed almost exclusively in visual basic for applications (VBA) with only a very limited amount of functionality in Excel. This somewhat reduces the transparency of the model structure. The EAG has not rebuilt the model and cannot warrant that it is correctly implemented.

The EAG has amended some of the VBA. Given the complexity of the VBA model the EAG urges the company to check the EAG changes for errors.

5.6.2 EAG model revisions

The EAG makes the following changes to the company base case.

- EAG01: No 2-year stopping rule
- EAG02: Only applies the BMI mortality multipliers
- EAG03: No annual worsening of BMI for those off treatment
- EAG04: Mainly applying the adverse event discontinuation rates in the first year, with a common 1% annual rate thereafter
- EAG05: An annual NAFLD rate of 0.06/1,000 patient years
- EAG06: A 5 year OSA risk of 2.85%
- EAG07: Revising the quality of life function intercepts to align with SURMOUNT-1 quality of life data and align the two quality of life functions at 35 kgm^{-2}
- EAG08: Only applying the QoL coefficients of Søltoft et al
- EAG09: Adding first year SWMS costs of £1,645 and annual costs of £698 for those remaining on treatment thereafter
- EAG10: An annual cost for T2DM of £674
- EAG11: The minor issues revisions outlined in section 5.5.7 above‡‡‡‡.

As outlined previously, the EAG presents two full sets of analyses:

- EAG BC01: A 2-year stopping rule for all active treatments: EAG01 to EAG11
- EAG BC02: No 2-year stopping rule: EAG02 to EAG11

‡‡‡‡ The EAG has tried to amend the company VBA as per the revised model sent at clarification but this has no apparent effect upon results. The company notes that the error had minimal effects upon overall results.

Table 68: EAG changes: pairwise cost-effectiveness estimates vs placebo

		ICER vs PLAC		
	Section	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
Company base case	4.2	£11,510	£11,777	£12,792
EAG01a: All 2-year stopping	5.2.6	£3,372	£5,372	£5,343
EAG01b: No 2-year stopping	5.2.6	£11,510	£11,777	£12,792
EAG02: Only BMI SMRs	5.2.3	£11,181	£11,050	£12,598
EAG03: No BMI worsening	5.2.7	£14,683	£14,150	£15,102
EAG04: AE Disc. Year 1	5.2.14	£12,114	£12,898	£13,825
EAG05: NAFLD 0.06/1,000	5.2.15	£11,750	£11,760	£13,089
EAG06: OSA 5 year 2.85%	5.2.16	£11,727	£11,989	£13,035
EAG07: QoL intercepts	5.3.2	£10,726	£10,878	£11,884
EAG08: Only Søltoft QoL	5.3.3	£12,336	£12,002	£13,131
EAG09: EAG SWMS costs	5.4.1	£22,298	£21,646	£21,734
EAG10: T2DM cost £674	5.4.2	£15,550	£16,323	£16,970
EAG11: Minor issues	5.5	£11,633	£11,886	£13,015
EAG BC01: EAG01a to EAG11	..	£21,058	£19,690	£19,563
EAG BC02: EAG01b to EAG11	..	£33,473	£29,310	£30,570

Table 69: EAG changes: pairwise cost-effectiveness estimates vs semaglutide

		ICER vs SEMA		
	Section	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
Company base case	4.2	£14,910	£15,454	£16,062
EAG01a: All 2-year stopping	5.2.6	£14,716	£41,524	£18,534
EAG01b: No 2-year stopping	5.2.6	£23,858	£26,855	£23,622
EAG02: Only BMI SMRs	5.2.3	£13,774	£13,627	£15,220
EAG03: No BMI worsening	5.2.7	£18,709	£17,918	£18,365
EAG04: AE Disc. Year 1	5.2.14	£14,776	£15,154	£16,009
EAG05: NAFLD 0.06/1,000	5.2.15	£15,430	£15,509	£16,573
EAG06: OSA 5 year 2.85%	5.2.16	£15,228	£15,770	£16,403
EAG07: QoL intercepts	5.3.2	£13,916	£14,255	£14,929
EAG08: Only Søltoft QoL	5.3.3	£16,265	£15,767	£16,535
EAG09: EAG SWMS costs	5.4.1	£27,146	£26,544	£25,745

EAG10: T2DM cost £674 EAG11: Minor issues	5.4.2 5.5	£18,383 £14,922	£19,570 £15,408	£19,790 £16,191
EAG BC01: EAG01a to EAG11	..	Dom'ted	£33,022	£28,415
EAG BC02: EAG01b to EAG11	..	£284,719	£32,472	£36,136

5.6.3 EAG BC01: 2-year stopping rule for all active treatments

For the company target population of those with a BMI ≥ 30 kgm^{-2} and at least one comorbidity the cost-effectiveness estimates are presented in Table 70 below.

Table 70: ERG BC01: 2-year stopping rule for all treatments: Deterministic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	[redacted]	15.856	..	..	..
SEMA	[redacted]	15.992	£16,366	..	£16,366
TIRZ 5mg	[redacted]	15.990	Dominated	Dominated	£21,058
TIRZ 10mg	[redacted]	16.026	Ext. Dom	£33022	£19,690
TIRZ 15mg	[redacted]	16.041	£28,415	£28415	£19,563

Semaglutide is estimated to have a cost-effectiveness of £16,366 per QALY compared to placebo and to dominate tirzepatide 5mg, but it would be more accurate to describe them as having the same patient benefits but tirzepatide 5mg having higher total costs. Tirzepatide 10mg does confer additional patient benefits but is extendedly dominated by tirzepatide 15mg. Tirzepatide 15mg has a cost-effectiveness estimate of £28,415 compared to semaglutide and £19,563 compared to placebo.

The above shows that if all treatments are limited to only 2 years use there is very little difference in the modelled patient benefits. Results are driven by relative treatment costs, the company submission assumed prices for semaglutide resulting in a lower annual cost than all the tirzepatide formulations.

Compared to placebo the active treatments have a cost-effectiveness between £15,000 per QALY and around £20,000 per QALY.

Unfortunately, due to modelling difficulties and time constraints the EAG has not been able to produce a set of probabilistic results. The EAG notes that the central estimates for the probabilistic modelling of the company base case are little different from the deterministic estimates.

5.6.4 EAG BC02: No 2-year stopping rule for any active treatment

For the company target population of those with a BMI ≥ 30 kgm^{-2} and at least one comorbidity the cost-effectiveness estimates are presented in Table 71below.

Table 71: ERG BC02: No 2-year stopping rule for any treatment: Deterministic

			ICER		
	Cost	QALY	Incr.	vs SEMA	vs PLAC
PLAC	[redacted]	15.856	..	..	..
SEMA	[redacted]	16.558	£28,096	..	£28,096
TIRZ 5mg	[redacted]	16.573	Ext. Dom	£284,719	£33,473
TIRZ 10mg	[redacted]	16.828	£32,472	£32,472	£29,310
TIRZ 15mg	[redacted]	16.870	£59,326	£36,136	£30,570

With no stopping rule the modelled QALYs differ more between the active treatments. The cost-effectiveness of semaglutide worsens to around £30,000 per QALY. Tirzepatide 5mg is no longer dominated by semaglutide but is extendedly dominated by tirzepatide 10mg, which has a cost-effectiveness relative to semaglutide of £32,472 per QALY. The cost-effectiveness of tirzepatide 15mg compared to tirzepatide 10mg is poor at £59,326 per QALY.

Compared to placebo all the active treatments have an estimated cost-effectiveness at around or above £30,000 per QALY.

5.6.5 EAG scenario analyses

The EAG presents the following scenario analyses.

- SA01: Applying all the mortality effects of the company base case
- SA02: Applies the BMI SMRs of the systematic review of Aune et al

- SA03: Applies 2-year stopping rules for semaglutide and liraglutide
- SA04: Responder rates of [redacted] for tirzepatide 5mg, 10mg and 15mg
- SA05: Responder rates taken from the EAG NMA
- SA06: Equalising the responder rate of semaglutide with tirzepatide 15mg
- SA07: Prediabetes reversal percentages from the EAG NMA
- SA08: Only applying the net effects relative to placebo
- SA09: An annual NAFLD annual rate of 0.12/1,000 patient years
- SA10: Not applying the EAG SWMS costs, and not applying them for placebo and not applying them for placebo and tirzepatide
- SA11: T2DM annual costs of £1,064 and £1,612
- SA12: NAFLD annual costs of £1,904
- SA13: Semaglutide [redacted] down titration
- SA14: Both EAG NMAs
- SA15: Duration of loss of effect after treatment cessation of 2 years and 4 years.

For reasons of space the results of the scenario analyses are only presented as pairwise comparisons with placebo and semaglutide.

Table 72: EAG BC01: 2-year stopping rule throughout: Scenarios: vs PLAC

	ICER vs PLAC		
	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
EAG BC01	£21,058	£19,690	£19,563
SA01: Company mortality effects	£21,569	£20,424	£18,655
SA02: Aune et al BMI SMRs	£20,898	£18,034	£18,070
SA03: 2-year stopping rule SEMA and LIRA	..	..	..
SA04: Tirzepatide responder rates	£19,905	£18,976	£18,227
SA05: EAG NMA responder rates	£20,724	£19,586	£19,425
SA06: SEMA responders TIRZ 15mg	..	..	..
SA07: EAG NMA diabetes reversal	£21,478	£19,789	£19,565

SA08: Net effects vs placebo	£30,539	£22,804	£21,747
SA09: Annual NAFLD 0.12/1,000	£21,263	£19,877	£19,712
SA10a: No SWMS costs	£12,946	£12,766	£13,228
SA10b: No SWMS costs for PLAC	£30,321	£26,994	£26,267
SA10c: No SWMS costs for PLAC & TIRZ	£12,907	£12,735	£13,200
SA11a: T2DM cost £1,064	£18,391	£17,320	£17,280
SA11b: T2DM cost £1,612	£14,643	£13,991	£14,072
SA12: NAFLD cost £1,904	£20,853	£19,577	£19,415
SA13: SEMA [redacted] down titration	..	..	..
SA14: Both EAG NMAs	£21,143	£19,685	£19,426
SA15a: 2 year loss of effect	£26,656	£24,200	£24,056
SA15b: 4 year loss of effect	£16,830	£15,765	£16,129

Table 73: EAG BC01: 2-year stopping rule throughout: Scenarios: vs SEMA

	ICER vs SEMA		
	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
EAG BC01	Dom'ted	£33,022	£28,415
SA01: Company mortality effects	Dom'ted	£38,841	£23,475
SA02: Aune et al BMI SMRs	Dom'ted	£22,329	£21,451
SA03: 2-year stopping rule SEMA and LIRA	..	..	..
SA04: Tirzepatide responder rates	Dom'ted	£42,768	£26,186
SA05: EAG NMA responder rates	Dom'ted	£33,224	£28,551
SA06: SEMA responders TIRZ 15mg	£140k	£33,418	£29,391
SA07: EAG NMA diabetes reversal	Dom'ted	£44,194	£34,305
SA08: Net effects vs placebo	Dom'ted	£28,687	£23,321
SA09: Annual NAFLD 0.12/1,000	Dom'ted	£33,152	£28,415
SA10a: No SWMS costs	Dom'ted	£29,451	£26,025
SA10b: No SWMS costs for PLAC	..	..	..
SA10c: No SWMS costs for PLAC & TIRZ	£855k SW	Dom	Dom
SA11a: T2DM cost £1,064	Dom'ted	£31,582	£27,011
SA11b: T2DM cost £1,612	Dom'ted	£29,557	£25,039
SA12: NAFLD cost £1,904	Dom'ted	£33,269	£28,415
SA13: SEMA [redacted] down titration	..	..	..
SA14: Both EAG NMAs	Dom'ted	£43,914	£34,302

SA15a: 2 year loss of effect	Dom'ted	£41,073	£35,008
SA15b: 4 year loss of effect	Dom'ted	£25,566	£24,274
Dom: Dominant: Tirzepatide provides more benefits at lower cost than semaglutide			

Applying the company approach to mortality and applying the higher BMI mortality multipliers of Aune et al improves the cost-effectiveness of tirzepatide 15mg compared to semaglutide.

The EAG NMA results for responders has little effect upon the cost-effectiveness estimates, while the EAG NMA results for reversal of prediabetes somewhat worsens the cost-effectiveness of tirzepatide.

Results remain reasonably sensitive to the annual cost of T2DM.

The assumed duration of loss of effect has a reasonably large effect upon results.

Table 74: EAG BC02: No 2-year stopping rule throughout: Scenarios: vs PLAC

	ICER vs PLAC		
	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
EAG BC02	£33,473	£29,310	£30,570
SA01: Company mortality effects	£35,273	£30,538	£30,912
SA02: Aune et al BMI SMRs	£31,142	£25,123	£26,349
SA03: 2-year stopping rule SEMA and LIRA	..	..	..
SA04: Tirzepatide responder rates	£33,737	£28,688	£31,221
SA05: EAG NMA responder rates	£33,447	£29,292	£30,489
SA06: SEMA responders TIRZ 15mg	..	..	..
SA07: EAG NMA diabetes reversal	£33,930	£29,540	£30,903
SA08: Net effects vs placebo	£38,672	£31,621	£31,843
SA09: Annual NAFLD 0.12/1,000	£33,527	£29,370	£30,577
SA10a: No SWMS costs	£20,022	£18,599	£20,361
SA10b: No SWMS costs for PLAC	£35,196	£30,582	£31,788
SA10c: No SWMS costs for PLAC & TIRZ	£20,014	£18,593	£20,356
SA11a: T2DM cost £1,064	£31,841	£27,918	£29,179
SA11b: T2DM cost £1,612	£29,548	£25,963	£27,226
SA12: NAFLD cost £1,904	£33,365	£29,213	£30,456
SA13: SEMA [redacted] down titration	..	..	..

SA14: Both EAG NMAs	£33,913	£29,522	£30,822
SA15a: 2 year loss of effect	£33,798	£29,528	£30,823
SA15b: 4 year loss of effect	£33,257	£29,158	£30,440

Table 75: EAG BC02: No 2-year stopping rule throughout: Scenarios: vs SEMA

	ICER vs SEMA		
	TIRZ 5mg	TIRZ 10mg	TIRZ 15mg
EAG BC02	£285k	£32,472	£36,136
SA01: Company mortality effects	£83,929	£29,159	£30,421
SA02: Aune et al BMI SMRs	£687k	£23,712	£27,284
SA03: 2-year stopping rule SEMA and LIRA	£37,455	£31,406	£32,759
SA04: Tirzepatide responder rates	Dom'ted	£31,599	£46,141
SA05: EAG NMA responder rates	£128k	£30,495	£33,897
SA06: SEMA responders TIRZ 15mg	Dom'ted	£32,917	£36,863
SA07: EAG NMA diabetes reversal	£4.9mn	£34,954	£38,829
SA08: Net effects vs placebo	Dom'ted	£31,881	£32,476
SA09: Annual NAFLD 0.12/1,000	£284k	£32,520	£36,014
SA10a: No SWMS costs	£256k	£28,060	£32,496
SA10b: No SWMS costs for PLAC	..	..	..
SA10c: No SWMS costs for PLAC & TIRZ	Dom	Dom	Dom
SA11a: T2DM cost £1,064	£280k	£31,550	£35,153
SA11b: T2DM cost £1,612	£273987	£30,254	£33,772
SA12: NAFLD cost £1,904	£285k	£32,409	£36,014
SA13: SEMA [redacted] down titration	..	..	..
SA14: Both EAG NMAs	£237k	£32,620	£36,242
SA15a: 2 year loss of effect	£299k	£32,488	£36,302
SA15b: 4 year loss of effect	£31k	£32,587	£36,318

Due to treatment being ongoing, results are more sensitive to the EAG NMA of response rates, this improving the cost-effectiveness of tirzepatide. The effects of two EAG NMAs now largely cancels out.

If semaglutide is judged as effective as tirzepatide 15mg in terms of response rates the cost-effectiveness of tirzepatide worsens somewhat.

Removing the EAG SWMS costs improves the cost-effectiveness of tirzepatide. Removing the EAG SWMS costs for only tirzepatide causes it to be dominant.

5.6.6 EAG subgroup BMI ≥ 35 kgm^{-2}, prediabetes, high CVD risk

The deterministic estimates for those with a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk are presented in Table 76 and Table 77.

Table 76: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk: 2-year stopping

			ICER			
	Cost	QALY	Incr.	vs SEMA	vs LIRA	vs PLAC
PLAC	[redacted]	15.365	..	..	..	..
SEMA	[redacted]	15.469	Ext. Dom	..	Dominant	£18,669
TIRZ 5mg	[redacted]	15.468	Dom'ted	Dom'ted	Dominant	£23,826
TIRZ 10mg	[redacted]	15.528	Ext. Dom	£17,606	Dominant	£18,287
TIRZ 15mg	[redacted]	15.552	£17,546	£16,136	Dominant	£17,546
LIRA	[redacted]	15.410	Dom'ted	Dom'ted	..	£109,911

Tirzepatide 15mg dominates or extendedly dominates the other treatments, having a cost-effectiveness relative to placebo of 17,546 per QALY. Liraglutide is dominated by the other active treatments.

Compared to placebo semaglutide, tirzepatide 10mg and 15mg have similar cost-effectiveness estimates of around £20,000 per QALY, and tirzepatide 5mg perhaps more towards £25,000 per QALY.

Table 77: BMI ≥ 35kgm^{-2}, prediabetes and high CVD risk: No 2-year stopping

			ICER			
	Cost	QALY	Incr.	vs SEMA	vs LIRA	vs PLAC
PLAC	[redacted]	15.365	..	..	..	..
SEMA	[redacted]	16.134	Ext. Dom	..	Dominant	£23,818
TIRZ 5mg	[redacted]	16.147	Ext. Dom	£314k	Dominant	£28,797
TIRZ 10mg	[redacted]	16.500	£23,736	£23,565	Dominant	£23,736
TIRZ 15mg	[redacted]	16.572	£38,002	£25,941	Dominant	£24,589
LIRA	[redacted]	15.690	Dom'ted	Dom'ted	..	£107,127

Without a 2-year stopping rule tirzepatide 10mg is no longer extendedly dominated, having a cost-effectiveness relative to placebo of £23,736 per QALY. The cost-effectiveness of tirzepatide 15mg compared to tirzepatide 10mg is £38,002 per QALY. Liraglutide is dominated by the other active treatments.

Compared to semaglutide, tirzepatide 10mg and 15mg have a cost-effectiveness of around £25,000 per QALY.

Compared to placebo semaglutide and tirzepatide 10mg and 15mg have similar cost- effectiveness estimates of around £25,000 per QALY, while tirzepatide stands at a little under £30,000 per QALY.

5.7 *Conclusions of the cost-effectiveness section*

There are a number of issues that may affect results that have not been quantified. These increase the uncertainty around the cost-effectiveness estimates.

BMI mortality multipliers decline with age. Not taking this into account substantially increases the uncertainty around the cost-effectiveness estimates.

It may be most cost effective to start patients on the less costly treatment and only use the more expensive treatments among those with a poor response.

Elements that are likely to bias the analysis in favour of the more active treatments are:

- Assuming the treatment effect is maintained indefinitely. There is evidence that the GLP-1s' treatment effect may wane in the medium term, both their absolute effect and relative to placebo.
- Assuming a baseline prevalence of the modelled complications of zero.
- The modelling applies the subgroup specific treatment effectiveness estimates to the non-responders and responders alike. Those who respond are likely to have superior clinical effects than those who do not and who discontinue. The degree of bias is likely to be inversely related to the responder proportion.

- The multi-year event risk functions seem likely to unduly bring forward events. Due to updating the risk functions each cycle they are also likely to estimate too many events occurring.

Uncertainty around the quality of life functions that are applied could be reduced by the company presenting scatterplots of the SURMOUNT-1 baseline and post baseline EQ-5D quality of life values against contemporaneous BMI.

6 SEVERITY MODIFIERS

The model appears to contain quality of life values to enable severity modifiers to be applied. There is no obvious setting within the model that enables this to be explored but setting these to zero has does not affect the cost-effectiveness estimates. Document B Section B.3.6, page 192, states that no severity weights were used in the evaluation of quality adjusted life expectancy.

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For the Appendices

Appendix 1 Table ROB assessment SURMOUNT-1

Criteria	**Risk of bias** **Company assessment**	**Risk of bias** **EAG assessment**
Was randomisation carried out appropriately?	Yes	Yes
	Participants were randomly assigned 1:1:1:1 to the treatment groups. Assignment to treatment group was determined by a computer-generated random sequence using an IWRS.	Agree
Was the concealment of treatment allocated adequate?	Yes	Yes
	Treatment group assignment was determined by computer-generated random sequence using an IWRS.	Agree
	Yes	Yes

Were the groups similar at the outset of the study in terms of prognostic factors?	As stated in Jastreboff 2021 "The demographic and clinical baseline characteristics were generally similar across treatment groups"	Demographic and clinical baseline characteristics checked and appear similar.
Were the care providers, participants and outcomes assessors blind to treatment allocation?	Yes	Yes
	Double-blinding	Investigators, site staff, clinical monitors and participants were blinded. A limited number from the Sponsor were unblinded for interim analysis and week 72 database lock. Emergency unblinding performed through IWRS.
	No	Unclear

Were there any unexpected imbalanced in drop-outs between groups?	All dropouts accounted for	A higher proportion in the placebo arm discontinued treatment (most commonly due to protocol deviations and withdrawal by subject), and discontinued the study (most commonly due to withdrawal by subject). 13.5% of the placebo arm discontinued treatment due to protocol deviations, but there were no discontinuation for this reason in the tirzepatide arms. CSR Table GPHK.4.2 lists important protocol deviations, but these appear balanced across all arms and it is not clear which led to treatment discontinuation. Discontinuation due to adverse events was slightly higher in the tirzepatide arms compared with placebo.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
	All outcomes in method section were reported	All outcomes listed in the clinical trial record were reported in the CS or CSR.
	Yes	Yes

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Appropriate imputation methods were utilised	Modified ITT was used, including all randomly assigned participants who are exposed to at least 1 dose of study drug; participants were included in the treatment group they were randomized to. Methods used to account for missing data were described in the statistical analysis plan.

ROBIS assessment company SLR.

EAG assessment of risks of bias of the CS systematic review in relation to the scope of the appraisal (modified ROBIS).

ROBIS domain, and signalling questions	**EAG's rating**	**Reasoning**
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably no**	Eligibility criteria are outlined in CS Appendix D Table 7. Appendix D.1.1 states a protocol approval but it is not clear if the protocol was published or registered. Additional steps to assess studies for the NMA were subsequently taken, described in CS B.2.9.3.2 but these criteria do not appear to have been pre-defined.

1.2 Were the eligibility criteria appropriate for the review question?	**No**	The pre-specified criteria of the SLR (Adults ≥18 years of age with obesity or overweight and at least one weight-related comorbidity) were not aligned with the NICE scope in terms of the intervention, the CS decision problem is also narrower than the NICE scope as it focusses on adults with obesity (and at least one weight-related comorbidity), rather than obesity and overweight (and at least one weight-related comorbidity). The CS decision problem excludes the comparator drug orlistat but this was included in the eligibility criteria. Also, two outcome measures listed in the NICE scope are not included in the CS decision problem (cardiovascular events, mortality) but mortality was included in the eligibility criteria.
1.3 Were eligibility criteria unambiguous?	**Probably yes**	Eligibility criteria were sufficiently detailed in CS Appendix D but were not fully aligned with the decision problem. Additional steps regarding eligibility were undertaken as part of a feasibility for the NMA but it was defined apriori.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Probably yes**	Restrictions were applied to include only RCTs which the EAG considers appropriate. As part of the feasibility study for the NMA studies focused on three interventions, studies with similar populations, above a certain sample size and duration of follow-up (CS B.2.9.3.2). While these may be appropriate they were not specified in advance.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes**	Non-English language studies were excluded. Although no justification for this was provided this is common and is likely to be reasonable.

Concerns regarding specification of study eligibility criteria	**Unclear concern**	There is a chance that relevant studies could have been excluded from the review and not all eligibility criteria were specified a priori.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**	Searches were conducted in MEDLINE and MEDLINE In-process, Embase, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and WHO International Clinical Trials Registry Platform Search Portal
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**	CS Appendix D1.2 reports conference abstracts that were searched (for the four preceding years) and that the reference lists of published SLRs of relevance were searched. It was unclear how these SLRs were identified. The list of SLRs were provided in clarification response C7.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably Yes**	Suitable intervention and RCT terms were used and concepts combined appropriately. Population terms were reasonably sensitive, but the thesaurus term for obesity was not exploded. Lifestyle comparators were not included. Records with a term for child (or synonyms) or animal were removed even if it was also indexed with adult or human terms respectively. Furthermore, remaining results in MEDLINE and Embase are later limited to human, meaning that newer records that haven't been indexed yet will have been removed at this point
2.4 Were restrictions based on date, publication format, or language appropriate?	**Probably no**	There were no restrictions based on date or publication format (e.g full text). Language was restricted to English therefore there is a potential for publication bias.

2.5 Were efforts made to minimise errors in selection of studies?	**Probably no**	For the primary selection of studies titles and abstracts and full text articles were screened independently by two reviewers with discrepancies resolved by a third reviewer. No details were provided of the processes taken for the subsequent stage of selection. Clarification response A11 states the selection of studies was undertaken by via a repeated feasibility assessment by a number of colleagues.
Concerns regarding methods used to identify and/or select studies	**Unclear concern**	A variety of search methods were used to identify relevant studies, however, there were some limitations and restrictions in the searches. Appropriate steps were taken to minimise bias and errors in the selection of studies for the initial selection but no details were provided for the subsequent stages of assessing studies for the NMA.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Data from the included studies were extracted into standardised data extraction tables in Microsoft® Excel by two independent reviewers with differences resolved through consensus or a third reviewer if necessary
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Probably Yes**	Minimal study characteristics of the key tirzepatide study were presented in the CS. Data extractions and summary tables of the comparator trials used in the NMA were not presented. Data used in the NMA were provided in response to clarification A16 and A20.
3.3 Were all relevant study results collected for use in the synthesis?	**Probably Yes**	Results from the SURMOUNT-1 trial whole population were reported in tables and figures, results for the subgroup of relevance were provided in the clarification response.

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	The company states that risk of bias was assessed using the Cochrane risk of bias assessment tool, but in fact they used questions from CRD Report 2009, as referenced in CS Table 13. These are the minimum criteria recommended by NICE. The EAG has undertaken assessment using Cochrane ROB2 questions and report differences to the assessment of risk of bias in the EAG report.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes**	The assessment of risk of bias was undertaken by two reviewers and any discrepancies resolved by a third reviewer. It is unclear if the two reviewers were independent.
Concerns regarding methods used to collect data and appraise studies	**Low concern**	All responses are either rated Yes or Probably Yes with no obvious areas of bias identified.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	**Yes**	The SLR included all of the relevant studies for the decision problem
4.2 Were all predefined analyses followed or departures explained?	**No information**	The company refers to an approved protocol (appendix D) but no reference to a protocol for the SLR is given
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Probably yes**	The synthesis was appropriate given the lack of head-to-head trials. EAG assessment of similarity identified some potential differences across studies in their outcome definitions and geographic diversity which should be taken into account.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Probably yes**	There was observed statistical heterogeneity in the whole trial population but this was addressed in the synthesis.

4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**No information**	No funnel plots were presented, and results of sensitivity analyses were not presented in the submission.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	**No**	Bias was not explicitly incorporated into the findings/ conclusions of the SLR
Concerns regarding the synthesis and findings	**Unclear concern**	There is insufficient information reported to fully consider the risk of bias
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	Unclear concern	A number of domains were assessed as unclear concern

Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 15 November 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Major Issues (EAG report)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>In all analyses conducted by the EAG, the incorrect price for semaglutide is used. Specifically, the current analyses assumes that the price of semaglutide does not vary between the disclosed price of the initial titration doses (0.25 mg, 0.5 mg, 1 mg) and the higher titration dose (1.7 mg) and maintenance dose (2.4 mg). However, this assumption is invalid given that the list prices for semaglutide 1.7 mg and 2.4 mg were disclosed by NICE on 4th September 2023 in an update to TA875.[1]

As a result of this incorrect assumption on price, it is stated on Page 130 that “The company is seeking a price premium over the assumed</td>
<td>Re-run all analyses and update interpretation of the cost-effectiveness results (including those specifically noted in the left-hand column) using the following pack costs for semaglutide:

<table>
<tr><th>Semaglutide dose</th><th>Pack cost</th></tr>
<tr><td>Semaglutide (0.25 mg)</td><td>£73.25</td></tr>
<tr><td>Semaglutide (0.5 mg)</td><td>£73.25</td></tr>
<tr><td>Semaglutide (1.0 mg)</td><td>£73.25</td></tr>
<tr><td>Semaglutide (1.7 mg)</td><td>£124.53</td></tr>
<tr><td>Semaglutide (2.4 mg)</td><td>£175.80</td></tr>
</table>
Source: NICE, 2023 (TA875 TAG)[1]</td>
<td>Use of the incorrect list price for semaglutide has resulted in false conclusions regarding Lilly seeking a price premium, artificially high ICERs for tirzepatide compared with semaglutide and subsequent inaccurate interpretation of cost-effectiveness results throughout the report.</td>
<td>The costs of semaglutide used in the EAG report reflect those used in the company submission.

The EAG reviewed the prices quoted within this document with NICE and retained the company assumed values for consistency with the company submission The EAG report conforms to the price tracker provided by NICE for this assessment.

The correct semaglutide cPAS prices have been applied in the cPAS appendix. Since this is the information that the Committee will base its decision upon the EAG will not revise either the company Document B results or the EAG results.

The EAG will replace:</td>
</tr>
</table>

prices of semaglutide and liraglutide." Similarly, page 144 states that *"..tirzepatide 5mg is more costly than semaglutide"* On Page 169 it is further stated that "*Semaglutide is estimated to have a cost effectiveness of £25,524 per QALY and to dominate tirzepatide 5mg, but it would be more accurate to describe them as having the same patient benefits but tirzepatide 5mg* ***having higher total costs***" Later on Page 169, it is also stated that "*Results are driven by relative treatment costs, the assumed prices for semaglutide resulting in a lower annual cost than all the tirzepatide formulations."*	Any mention of Lilly seeking a price premium over semaglutide and liraglutide **must** also be removed. The prices quoted for semaglutide in Table 45 (Page 116) should also be updated.		Page 130 Replace: "The company is seeking a price premium over the assumed prices of semaglutide and liraglutide. It may consequently be more cost effective to trial semaglutide or liraglutide first and to reserve the more costly tirzepatide for non or poor responders to semaglutide or liraglutide." With: "The company is seeking a price premium over the prices it assumed apply to semaglutide and liraglutide. It may consequently be more cost effective to trial semaglutide or liraglutide first and to reserve the more costly tirzepatide for non or poor responders to semaglutide or liraglutide." Page 144: Replace:

			"tirzepatide 5mg is more costly than semaglutide" With: *"tirzepatide 5mg is assumed within the company submission to be more costly than semaglutide"* Page 169: Replace: "*Results are driven by relative treatment costs, the assumed prices for semaglutide resulting in a lower annual cost than all the tirzepatide formulations."* With: "*Results are driven by relative treatment costs, the company submission assumed prices for semaglutide resulting in a lower annual cost than all the tirzepatide formulations."*
Page 139 states *"It can be further noted that SURMOUNT-1 appears to have been mainly if not*	Please remove this paragraph, or amend in line with the	It is factually inaccurate that the SURMOUNT-1 setting was more akin to SWMS referral	The EAG will append to the end of:

exclusively conducted in secondary care rather than primary care. All arms included a diet and exercise programme. Patients were also required to have a history of "at least one self-reported unsuccessful dietary effort to lose body weight" which may accord to some extent with the CG189 referral to SWMS criterion of when "conventional treatment has been unsuccessful". As a consequence, this may mean that the SURMOUNT-1 setting was more akin to an SWMS referral than to treatment in primary care, with its clinical effectiveness estimates being most directly relevant to treatment within an SWMS."	justification provided in the right-hand column.	than to treatment in primary care. As per the PH53 guidelines (which provide recommendations for Tier 2 services in primary care), it is recommended that weight management programmes should "last at least 3 months, and that sessions are **offered at least weekly or fortnightly and include a 'weigh-in' at each session**." The guideline further states that Tier 2 weight management programmes should be delivered by "a **multidisciplinary team**". In SURMOUNT-1, lifestyle program visits were provided four-weekly for the first 3 months (between Week 0 to Week 12) and then once every 12 weeks thereafter (from Week 12 to Week 72). The lifestyle program provided at these visits comprised advice on healthy food choice and focus on calorie restriction	*As a consequence, this may mean that the SURMOUNT-1 setting was more akin to an SWMS referral than to treatment in primary care, with its clinical effectiveness estimates being most directly relevant to treatment within an SWMS."* *The following:* *"However, at error check the company noted that the frequency of weight management advice in SURMOUNT-1 was foru weekly for the first quarter, and quarterly thereafter which is less frequent than the at least fortnightly visits during the first quarter for tier 2 weight management services. It also noted that SURMOUNT-1 did not include support from a multi-disiplinary team as require for Tier 2 and Tier 3/4 weight management services.*

		provided by a dietician/nutritionist, or equivalent qualified delegate, as well as advice on increasing their physical activity to at least 150 minutes per week. In other words, the lifestyle program provided in SURMOUNT-1 was **less frequent** than the recommendations for weight management programs provided **in primary care** in NHSE, and also did not include support from MDT team, as is characteristic of Tier 2 programmes and Tier 3/4 SWMS services. The Company would also like to point out that it is inaccurate to relate the requirement for "at least self-reported unsuccessful dietary effort to lose body weight" to the requirements for Tier 3 eligibility. Firstly, the Company would point out that if a patient had successfully lost weight, they would not be a candidate	*The EAG will include a scenario analyses that remove the SWMS costs from diet and exercise, from diet and exercise and tirzepatide and from all arms."*

		for a drug for weight management and therefore would not be eligible for inclusion in the SURMOUNT-1 trial. Secondly, this assertion is not accurate when considering the current treatment pathway in NHSE clinical practice. This is because the initial management for obesity is typically a visit with a GP, in which diet and exercise advice would be provided to reduce body weight (as per CG189). In addition, as part of the Tier 1 population health initiatives, patients would have already received advice to eat less and move more. Following a self-reported unsuccessful dietary effort, the next step for referral for those with a comorbidity (similar to those present within the target population for this submission) **is not to SWMS but to the NHS Digital Weight Management Programme or other similar community**	

		support programmes. As detailed above, these support programmes are more intensive than the support provided in SURMOUNT-1, thus further demonstrating that the SURMOUNT-1 setting is more aligned with primary not secondary care in NHSE.	
Page 16 states *"The whole trial population of SURMOUNT-1 included people with BMI ≥27 to <30, but limited to those with at least one of hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. People with other weight-related comorbidities such as chronic kidney disease or heart failure were excluded, and people with prediabetes were only eligible if they also had one of the four specified comorbidities."* Page 16 also states *"Evidence of the effectiveness of*	Please update Page 16 to: The whole trial population of SURMOUNT-1 included people with BMI ≥27 to <30, but limited to those with at least one of hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. People with **a BMI ≥27 to <30 with** other weight-related comorbidities such as chronic kidney disease ~~or heart failure~~ were excluded, and people with **a BMI ≥27 to <30 and** prediabetes were only eligible if they also had one of the ~~four~~ specified comorbidities.	The Company wishes to clarify that contrary to the EAG's interpretation in several places throughout their report, the comorbidities listed in the SURMOUNT-1 protocol (hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease) were required **only in participants with a BMI ≥27 to <30 kg/m^2**. In contrast, participants with a BMI >30 (i.e. the focus of the Company submission) were not subject to this requirement, and as such had a much wider range of comorbid conditions at baseline (as shown in the baseline characteristics tables	The EAG clarified the text around BMI (BMI ≥27 to <30) and removed heart failure text. We aligned the text throughout the report. The additional text added by the company is not a factual error.

tirzepatide in the people with different weight-related comorbidities and in different ethnic backgrounds with lower BMI thresholds would improve the generalisability of the evidence base." Re-iteration of this point is made on Page 69, which states: *"People with BMI ≥27 to <30 and other weight-related comorbidities, such as chronic kidney disease or heart failure, would also not have been eligible for SURMOUNT-1, and people with T2DM were excluded from the trial."* Finally, Page 93 states *"The SUMOUNT-1 eligibility criteria were more strict, specifying that the weight-related comorbidity had to be one of hypertension, dyslipidaemia, OSA or cardiovascular disease."*	Please update the second instance of this error on Page 16 to "Evidence of the effectiveness of tirzepatide in ~~the people with a different weight-related comorbidities and in~~ different ethnic backgrounds with lower BMI thresholds would improve the generalisability of the evidence base **For the economic analyses of the full indication, evidence of the effectiveness of tirzepatide in people with a BMI ≥27 to <30 kg/m^2 with different weight-related comorbidities would also improve the generalisability of the evidence base**." Please update Page 69 to: "People with BMI ≥27 to <30 and other weight-related comorbidities, such as chronic kidney disease ~~or heart failure~~, would also not have been eligible for SURMOUNT-1, and people with T2DM were excluded from the trial."	on Page 535 of the SURMOUNT-1 CSR).[2] In this respect, the data informing the base case economic analysis are in fact likely to be highly generalisable with regards to the presence of weight-related comorbidities. On a related note, the Company would like to clarify that contrary to the EAG's interpretation, heart failure was included as one of the eligible weight-related comorbidities in participants with a BMI ≥27 to <30 kg/m^2, given that the SURMOUNT-1 protocol specifically states as one of the inclusion criteria: "cardiovascular disease (for example ischemic cardiovascular disease, New York Heart Association (NYHA) Functional Class I-III **heart failure**".	

	Please update Page 93 to "The SUMOUNT-1 eligibility criteria were more strict **for people with a BMI ≥27 to <30**, specifying that the weight-related comorbidity had to be one of hypertension, dyslipidaemia, OSA or cardiovascular disease, **although this did not apply to the Company's target population**."		
Page 23 states under Issue 7 that "***There is some evidence from the liraglutide trial that in the medium term patient weight loss reverses, and also that the net effect compared to placebo falls***" This is expanded on in Page 142 which states "*The only medium term data for ongoing treatment with a GLP-1 for obesity that the EAG is aware of is the extension phase of the SCALE trial population with prediabetes at baseline to 160 weeks as presented*	Page 23 "~~There is some evidence from the liraglutide trial that in the medium term patient weight loss reverses, and also that the net effect compared to placebo falls~~" – this change would suggest to remove Issue 7 entirely, as it no longer has a rationale Page 142 "This presents the percentage change from baseline in the mean fasting body weight ~~with last observation carried forward (LOCF)~~ **as the observed mean relative change in**	The EAG have misread the source data from the prediabetes extension of the SCALE trial[4] – the mention of LOCF in their original source refers only to a single separate data point for each treatment arm at week 160 which is LOCF (being −1.9% and −6.1%, respectively), whereas all of the week-by-week data which form their Figure 15 are not LOCF but rather the observed mean relative change in bodyweight for individuals in the full-analysis set who completed	The EAG accepts that EAG Report Figure 15 is not LOCF but is the data from the N remaining followed up as presented in Table 61. The EAG will correct the heading of Figure 15 and will amend page 142 from: "This presents the percentage change from baseline in the mean fasting body weight with last observation carried forward (LOCF)." To "This presents the percentage change from baseline in the

during TA664. ***This presents the percentage change from baseline in the mean fasting body weight with last observation carried forward (LOCF)****."* Figure 15 states that the data are LOCF. Page 143 then states "***Figure 15 suggests that there may be a waning of both the absolute treatment effect and the net treatment effect for liraglutide over time****." and "The EAG thinks that a waning of the treatment effect should be explored* ***in the light of the SCALE trial extension data****."*	**bodyweight for individuals in the full-analysis set who completed each scheduled visit**." Figure 15 – remove ~~LOCF~~ Page 143 "~~Figure 15 suggests that there may be a waning of both the absolute treatment effect and the net treatment effect for liraglutide over time~~" Page 143 "The EAG thinks that a waning of the treatment effect should be explored ~~in the light of the SCALE trial extension data~~."	each scheduled visit, the number of which has roughly halved over the 160 weeks due to withdrawals from the trial. Furthermore, these observed data are not specified to have been taken only from patients remaining on treatment and may therefore reflect patients who stopped treatment but did not withdraw from the trial – the SCALE trial reports that "The prespecified efficacy analyses used data from the full-analysis set of all randomised individuals who received at least one treatment dose and had at least one post-baseline assessment".[4] This statement implies that the observed data may include patients who were no longer taking liraglutide. As such, Issue 7 should be removed from the report as it is based on a misreading of the SCALE trial, while several parts of the	mean fasting body weight among those remaining followed up, these numbers being presented in Table 61." The EAG will also amend Figure 15 to present the loss of effect during weeks 160 to 172, also presenting the patient numbers for this in Table 61. Issue 7 on page 23 has no factual error and does not require revision.

		report should be amended accordingly.	
Page 47 states *"The company clarified that results were presented using the efficacy analysis set (EAS) which is different to the modified ITT (mITT) group. Participants in the mITT group were analysed according to the treatment they were randomised to. EAS includes the selection of* ***data*** *from relevant participants, aligned with the estimand definitions used. The EAS relates to the efficacy estimand and uses 'data obtained during the treatment period from the mITT population, excluding data after discontinuation of study drug (last dose + 7 days)"*	Please update to "The company clarified that results were presented using the efficacy analysis set (EAS)**, and that the mITT pertains to the selection of participants, whereas the efficacy analysis set (EAS) pertains to the selection of data from relevant participants,** ~~which is different to the modified ITT (mITT) group. Participants in the mITT group were analysed according to the treatment they were randomised to. EAS includes the selection of data from relevant participants,~~ aligned with the estimand definitions used. The EAS relates to the efficacy estimand and uses 'data obtained during the treatment period from the mITT population, excluding data	The Company are dissatisfied with the description of the mITT versus the EAS, and has corrected the definition to be more closely aligned with the Company response to clarification question A6.	Amended.

	after discontinuation of study drug (last dose + 7 days)"		
Page 83 states "*Change from baseline in HDL (%): tirzepatide 15 mg achieved statistical superiority over semaglutide* and placebo, but only numerical superiority over the other tirzepatide doses"	Please update to: "Change from baseline in HDL (%): **all** tirzepatide **doses** ~~15 mg~~ achieved statistical superiority over semaglutide and placebo~~,~~ ~~but only numerical superiority over the other tirzepatide doses~~"	Incorrect reporting of key NMA results.	Not a factual error. Tirzepatide 15 mg achieved numerical superiority over the 10 mg and 5 mg tirzepatide doses, when comparing the tirzepatide doses only, as can be seen by the overlapping credible intervals.
Page 91, Table 29 (Data inputs for the prediabetes and weight loss NMA)	Remove liraglutide from NMA1 NMA2 and NMA3 – which will then require the NMAs to be re-run. (Note also this table is affected by missing confidentiality highlighting addressed in the relevant section of comments below, as well as an apparent typo separately addressed).	Remove liraglutide from NMA1 as the data given are for the subpopulation in NMA4, not the whole trial. Remove liraglutide from NMA2 because the values given are stated in TA664 to be "the parameter is sourced from week 56 glycaemic status results in SCALE 1839 and is calculated as one minus the proportion of patients with prediabetes at week 56 divided by the total population at risk" – this is not therefore	For the target group the inclusion or exclusion of liraglutide trial data in the EAG NMA has minimal verging upon no effects upon the clinical effect estimates for tirzepatide and semaglutide.

		data for patients with prediabetes at baseline who had reverted to normoglycaemia at Week 56, it is the proportion without prediabetes at Week 56, divided by the proportion with prediabetes at baseline; these are not equivalent. Remove liraglutide from NMA3 entirely as it is not recommended by NICE for use in this population.	
Page 121 states "*The company presents results separately for 5mg, 10mg and 15mg tirzepatide. Due to these being mutually exclusive alternatives, the EAG groups these into an incremental analysis in Table 49 as required by the NICE methods guide, also presenting the pairwise cost effectiveness estimates for the individual treatments with semaglutide and with placebo.*"	Please remove these statements and update all results tables and interpretation in the EAG report such that each tirzepatide dose is compared individually to the relevant comparators (semaglutide and diet and exercise in the base case) only.	In line with the EAG expert opinion (see page 144 of EAG report) in clinical practice the maximum tolerated dose of tirzepatide will be used, as the treatment goal is to maximise weight loss. As such, it is incorrect to compare tirzepatide doses to each other. Contrary to the EAG's analyses and interpretation, tirzepatide 5 mg will not, for example, be used in place of tirzepatide 10/15 mg where	No factual error, no revision required. The separate arms of SURMOUNT-1 remain mutually exclusive and require a fully incremental presentation. The EAG has also presented pairwise ICERs. This provides Committee with the most information possible. If the company position is that tirzepatide can only be

Page 122 goes on to state that "*Both the deterministic estimates and probabilistic central estimates suggest that the most cost effective use of tirzepatide may be to limit its use to tirzepatide 5mg due to tirzepatide 10mg being extendedly dominated and tirzepatide 15mg having a cost effectiveness estimate greater than £20,000 per QALY.*"		the 10/15 mg doses are well-tolerated. Further, there is no specific guidance in the NICE manual which pertains to the inclusion of all treatment doses of an intervention designed to be used at maximum tolerated dose in a fully incremental analysis. Specifically, the NICE manual states that "Economic evaluation results should be presented in a fully incremental analysis",[5] which the Company have adhered to.	approved or not approved in total the EAG thinks it would have to present an analysis pooled across tirzepatide doses that estimates the proporortions of patients who would receive 5mg, 10mg and 15mg coupled with the reasons why and what the clinical effects would be for each of these subgroups.
Page 97 states "*No*" in response to the question on whether the Company has aligned with the reference case for the type of economic analysis. The EAG then go on to say that *"A fully incremental analysis is not presented in the company submission."*	Please update this to" "Yes" and "A fully incremental analysis is ~~not~~ presented in the Company submission **for each tirzepatide dose individually**"	As above, the NICE manual does not provide any specific guidance on the requirements of a fully incremental analysis when a Company is seeking reimbursement for multiple treatment doses, particularly when it is clinically unsound to be comparing doses to each other. The Company therefore consider it factually inaccurate to state that the Company has	No factual error, no revision required. See above.

		not adhered to the reference case given that a fully incremental analysis has in fact been presented for each tirzepatide dose individually.	
Page 103, Table 34.	Please remove the liraglutide row from the table.	As detailed in the CS, liraglutide is not a relevant comparator in the base case population (BMI ≥30 with at least one weight-related comorbidity) due to the NICE recommendation for this treatment being restricted to a narrow subgroup.	The EAG accepts the proposed amendment.
Page 103 states "*Within the position sought of BMI ≥ 30kgm-2 due to a lack of data for liraglutide the company assumes that the all patient EAS NMA data applies"*	Please update to: "Within the position sought of BMI ≥ 30kgm-2, **liraglutide is not considered a relevant comparator** ~~due toa lack of data for liraglutide the company assumes that the all patient EAS NMA data applies~~"	As above, liraglutide is not a relevant comparator in the base case population (BMI ≥30 with at least one weight-related comorbidity).	The EAG accepts the proposed amendment.
Page 104, Table 36.	Please update the 84% figure quoted for liraglutide in the 'target pop' with "N/A"	As above, liraglutide is not a relevant comparator in the base case population (BMI	The EAG accepts the proposed amendment.

		≥30 with at least one weight-related comorbidity).	
Page 105 states "*The 10% estimate for semaglutide is based upon expert opinion, while the 7% estimate for liraglutide is taken from that reported in TA875.*"	Please update to: The 10% estimate for semaglutide is based upon expert opinion, while the **1**7% estimate for liraglutide is taken from that reported in TA875."	Incorrect reporting of data for the proportion of patients discontinuing liraglutide in the model.	The EAG accepts the proposed amendment.
Page 105 states *"The draft SmPC states that "[redacted]". There is some ambiguity as to whether this relates to 6 months on treatment or 6 months on the maintenance dose."*	Please update to: "if patients have been unable to lose at least 5% of their initial body weight ~~after~~ 6 months **after titrating to the highest tolerated dose**~~, on treatment~~ a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient". Please then remove the second sentence, as it is clear from the license wording that primary treatment failure assessment should be performed 6 months after the maintenance dose is reached.	Misquoting of the license wording given in the Company submission, leading to unfair conclusions regarding the clarity of the recommendations. Please also note the license wording is no longer confidential, since the MHRA license has now been granted.	The EAG accepts the proposed amendment.

Page 106 states "*NICE has not yet stipulated whether tirzepatide should be provided within an SWMS or not. The company assumes it will not …*"	Please amend to "~~*NICE has not yet stipulated whether tirzepatide should be provided within an SWMS or not*~~ ***In TA875 and TA664 the relevant manufacturer sought a restricted position within SWMS as part of their ingoing submissions, and consequently the NICE guidance contains this stipulation. In the present appraisal,*** ~~*T*~~***t****he company* ~~*assumes it will*~~ ***has*** *not* ***sought this restriction****…*"	The EAG misunderstand the place of NICE in the decision-making process: it is not for NICE to stipulate whether tirzepatide is restricted to an SWMS or not other than if this were to be a necessary consequence of their decisions on the generalisability of the evidence base provided or the final committee-preferred cost-effectiveness estimates. Decisions on which setting services are commissioned in is the remit of NHS England, and, as described in CS Section B.1, HM Government are seeking to increase access to weight management outside of SWMS. Furthermore, the restriction to SWMS in TA875 and TA664 were the restricted position **requested by the relevant manufacturer in their ingoing appraisal submissions** – they were not "stipulations" imposed by	The EAG will amend the wording from: *"NICE has not yet stipulated whether tirzepatide should be provided within an SWMS or not. The company assumes it will not…"* To *"It has not yet been stipulated whether tirzepatide should be provided within an SWMS or not. The company assumes it will not be, and so does not apply a stopping rule for tirzepatide at 2 years"*

		NICE during the appraisal process. As such, the EAG report is factually inaccurate in its description of the restrictions to SWMS.	
When discussing the application of monitoring visits in the ingoing Company submission, Page 117 states "*This presupposes that the active treatments are administered in primary care rather than in an SWMS. It appears that these costs may be applied to all patients, regardless of treatment status."*	Please update to: "**These costs are applied regardless of pharmacological treatment given that the support provided in the diet and exercise arm is equivalent to the support provided in conjunction with pharmacological treatments** ~~This presupposes that the active treatments are administered in primary care rather than in an SWMS. It appears that these costs may be applied to all patients, regardless of treatment status.~~"	As detailed further below (see Model Errors), assumptions on the treatment setting (and subsequently the costs) for the diet and exercise support provided alongside tirzepatide should also apply to the diet and exercise arm, aligning with the comparators defined in the final scope and the efficacy inputs used for the diet and exercise arm.	No factual error, no revision required. But the EAG will revise: *"It appears that these costs may be applied to all patients, regardless of treatment status."* To: *"At error check the company confirmed that these costs are applied to all patients, regardless of treatment status."*

Model errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Facility to implement PAS discounts for semaglutide and liraglutide in the model incorrectly implemented	Amend the EAG implementation of the PAS discounts to specify per-pack discounts, rather than applying a fixed percentage to all packs. This may also require the EAG to consider the fact that liraglutide has two differing packs available (3-pen [initiation and titration pack] and 5-pen [30-day maintenance pack]), which may also be relevant to the details of their commercial arrangement.	The EAG amendments to the model have added the facility to apply a simple discount PAS to each pharmacological therapy, however this has been incorrectly implemented because it applies a single fixed percentage for each therapy to **all** packs, both titration and maintenance doses. Given that the list prices of each of the therapies considered are dose-dependent, rather than flat priced, and that during TA875 the first three titrations doses of semaglutide had their price disclosed publicly throughout while the final titration dose and the maintenance dose had their price redacted until 4th September 2023 when dose-specific list prices were disclosed alongside the existence of a commercial arrangement, it seems highly unlikely the discount applies a fixed percentage to all packs.	The cPAS revised model was submitted to NICE at the same time as the model sent to the company. Given the prices assumed by the company for semaglutide as discussed in the points above the model sent to the company was not structured to apply different cPAS discounts for the different doses of semaglutide and liraglutide. The cPAS revised model supplied to NICE does have this facility. Where required additional cPAS discounts are applied for each dose, implemented in the same fashion as those in the model supplied to the company only to the specific doses.

Implementation of SWMS costs: • The EAG have added an option to allow the user to add SWMS costs for liraglutide and semaglutide (EAG row 36) and an option to allow the user to add SWMS costs for tirzepatide (EAG row 37). • The EAG has calculated a cost which is assumed to apply for the first year in SWMS (Data Store AC182), and a cost for every year thereafter (Data Store AC183) • The 2 year + cost is converted to a 4-week cycle (Data Store AC185) • The incremental difference between the first-year and 2 year + costs is calculated, and for each treatment, this is adjusted to account for discontinuation due to	**Error 1:** Apply adjustment (in which SWMS cost is removed from the calculated monitoring costs) to the total costs in the Primary Deterministic Results sheet and the calculation of probabilistic results so that the first-year increment is not applied to the total costs even when the user has not chosen to apply the SWMS cost for tirzepatide **Error 2:** Remove SWMS costs from all treatment arms, or apply SWMS costs to the diet and exercise arm alongside the pharmacological treatment arms when performing EAG scenarios EAG BC01.	**Error 1:** Implementation error. **Error 2:** The application of SWMS costs in the pharmacological treatment arms only in EAG scenario EAG BC01 is incorrect when considering the final scope for this appraisal and the efficacy estimates applied to the diet and exercise arm. Specifically, the draft scope for this appraisal states that the comparator is "Standard management without tirzepatide (**including a reduced calorie diet and increased physical activity**)". Given this comparator definition, the ingoing Company submission applied efficacy estimates for diet and exercise support (derived from the NMA) in the model base case. Importantly, whilst the EAG have retained the efficacy estimates for diet and exercise support in their EAG BC01	Issue 1: When in the EAG Tab B37 is set to TRUE and B38 to FALSE the first year SWMS costs are retained in Data Store U183 but are removed from tirzepatide in Primary Deterministic Results N55:N57 due to Primary Deterministic Results T37 now being non-zero and equal to £860.35, the same value as in Data Store U183. The total costs in Primary Deterministic Results O55:O57 are the summation of the values to the left of this including the adjusted values in N55:N57. The EAG Total Costs for Tirzepatide in K105:K108 are taken from N55:N57. It is not

primary treatment failure in the first year of treatment, with half-cycle correction (Data Store AA182:AA186) • This incremental difference for the first year is then averaged over treatments (Data Store AA187) • If the SWMS cost is applied for liraglutide and semaglutide, the training cost for the first SQ administration is replaced by the incremental difference for first year SWMS (Treatment Costs I61) • If SWMS is not applied to tirzepatide, this cost is subsequently removed from the calculated monitoring costs in the Primary Deterministic Results sheet, and replaced with the original SQ initial admin cost (T37) • **Error 1:** this adjustment is not applied to the total		scenario, they have applied SWMS costs to the pharmacological treatment arms (which provide diet and exercise support) but have not applied the same costs to the diet and exercise arm. This effectively assumes that either provision of diet and exercise support incurs no cost (in which case it would be incorrect to apply SWMS costs to the active treatment arms only) or 2) that the comparator is no intervention at all (which is incorrect vs the final scope). Application of SWMS costs in this way also results in undue consideration of the cost-effectiveness of SWMS itself, rather than of the cost-effectiveness of the interventions defined in the final scope. To circumvent this issue, SWMS cost should either be applied to all arms, or to no arms (as in the ingoing Company submission).	clear to the EAG why this is incorrect. The EAG has not used its revised model to estimate probabilistic results as outlined in the EAG report. Issue 2: The EAG SWMS costs are applied to active treatments while on treatment. The model cannot easily be revised by the EAG to apply SWMS costs to diet and exercise given that this is assumed to cease from year 2: e.g. see EAG report figure 4. The bias that would result from applying SWMS costs to diet and exercise throughout would be substantially greater than the bias that results from not applying them. The EAG will provide a scenario that applies 1 and 2 years worth of SWMS costs to

costs in the Primary Deterministic Results sheet (which is used to calculate the ICER), and is not applied to the probabilistic results at all – i.e. the first year increment is applied to the total costs even if the user has not chosen to apply the SWMS cost for tirzepatide • The 2 year + per-cycle cost is added to the per-cycle cost (Treatment Costs P41:P56) • **Error 2:** This cost is not applied to the diet and exercise arm at all, and is applied for the pharmacological treatments for precisely as long as the patient remains on that treatment			diet and exercise, though the latter will be too pessimistic for diet and exercise.
Change of Intercept for the Soltoft et al. utility mapping:	Apply correct reduction in the model.	Data error.	The EAG accepts the proposed amendment.

In the EAG report, it is stated that the EAG prefers to reduce the intercept term in the utility mapping by 0.038 for patients with a BMI of over 35 (Page 157). However, the reduction implemented in the model (cells Y23 and AA23 in the Data Store, and cells M25 and O25 in the Utilities sheet) is 0.037.			
Alternative Semaglutide AE Incidence The EAG have implemented a scenario in which the annual rate of severe or serious GI AEs for semaglutide is set equal to the rate for tirzepatide 15mg. The formulae implementing this scenario (cell I114 in the Data Store and cell I19 in the Adverse Events sheet) are currently incorrect.	The formula should be updated as follows: =IF(EAG.GI.Events.Once,0,IF(EAG.SEMA.GI.Same.TIRZ.15,**I17**,4.9%))	Implementation error.	The EAG accepts the proposed amendment and will revise the scenario analysis accordingly.
Applying AE costs and disutilities only in year 1: • The EAG have implemented a scenario in	Correctly apply AE costs and disutilities.	Implementation error.	The EAG thinks that the costs of AEs for Tirzpeatide are correctly implemented in this

which the annual AE rates are set to zero in the Adverse Events sheet, and instead costs and disutilities for adverse events over one year are applied in the Primary Deterministic Results sheet • Similarly to the SWMS first-year incremental cost (see above), the one-year AE costs and disutilities in this scenario are not applied to the total deterministic or probabilistic costs, leading to effectively 0 disutility or costs applied due to AEs			scenario: see EAG comment on Error 1 on SWMS as the same considerations apply. The EAG accepts that the costs of AEs for the other comparators have been omitted from this scenario, and that the QoL effects have been omitted for all comparators.
Alternative semaglutide primary treatment failure: The EAG have implemented a scenario in which the primary treatment failure rate for semaglutide is set equal to the rate for tirzepatide 15mg. The formulae implementing this scenario (cell L38 in the Data Store and cell I61 in the	The formula should be updated as follows: =IF(EAG.Apply.Primary.Disc,IF(EAG.SEMA.Same.Response.TIRZ.15,I59,IF(EAG.NMA.responders,12.7%,10%)),0)+EAG.AE.Disc.SEMA	Implementation error.	The EAG accepts the proposed amendment and will revise the scenario analysis accordingly.

Efficacy sheet) are currently incorrect			

Minor comments (EAG report)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 states *"An annual cost of £674 based upon the UKPDS."*	Please update to include the year that the UKPDS data are from.	Lack of clarity in current reporting.	The EAG will amend Page 161 from: "The resulting annual inpatient and non-hospital costs of T2DM for the baseline age of 48 years and weighted 66% female and 33% male is £933 in 2012 prices, which when uprated by 14% for inflation suggests an annual cost of £1,064." To:

			"The resulting annual inpatient and non-hospital costs of T2DM for the baseline age of 48 years and weighted 66% female and 33% male is £933 in 2012 prices, which when uprated by 14% for inflation to 2021 prices suggests an annual cost of £1,064." The inflation upgrade applies equally to both £1,064 and £674.
Page 47 states *"Most participants were female (67.1% to 67.9%, lowest to highest percentage arms) capped in the SURMOUNT-1 recruitment at 65%) "*	Please update to "Most participants were female (67.1% to 67.9%, lowest to highest percentage arms) **as per the SURMOUNT-1 protocol, which capped enrolment for females at 70%.** ~~in the SURMOUNT-1 recruitment at 65%~~	Incorrect reporting of SURMOUNT-1 protocol.	Text clarified and amended.
Page 47 states "*Most participants were female (67.1% to 67.9%, lowest to highest percentage arms)"* in reference to the SURMOUNT-1 trial.	Please update this to "Most participants were female (67.1% to ~~67.9%~~ **67.8%**, lowest to highest percentage arms)"	Incorrect data.	Text amended.

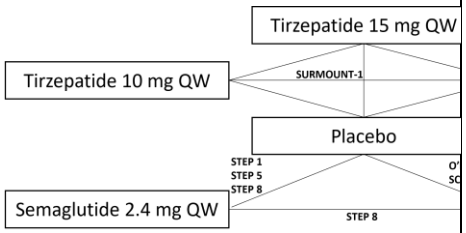
Page 49 states "*The company states that risk of bias was assessed using the Cochrane risk of bias assessment tool, but in fact they used questions from CRD Report 2009, as referenced in CS Table 13.*"	Please update to "The company ~~states that~~ **includes a** risk of bias was assess**ment** using the Cochrane risk of bias assessment tool **in Appendix D.2.2 as part of the NMA feasibility assessment, and they also** ~~but in fact they~~ used questions from CRD Report 2009, as referenced in CS Table 13 **(although they inaccurately referenced the Cochrane risk of bias assessment tool in the accompanying table text)**."	The Company performed a risk of bias assessment using the Cochrane risk of bias assessment in the appendix as part of the NMA feasibility assessment, so the statement made by the EAG is incorrect in its current form.	Not a factual error. The same set of questions were used in Appendix D2.2 as to was used in Table 13 CS. Table 13 clearly references the CRD (reference 103, Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Last accessed: February 2023).
Page 50 states "*A higher proportion in the placebo arm discontinued treatment due to protocol deviations and from participant withdrawal and more in the placebo arm also discontinued the study, most commonly due to withdrawal.*"	Please update to "A higher proportion in the placebo arm discontinued treatment due to protocol deviations, **although the proportion was low (0.3%),** and from participant withdrawal and more in the placebo arm also discontinued the study,	Omission of key detail, leading to inaccurate representation of participant disposition.	Error in the company submission. Figure 5 in the company submission (Doc B) states that 13.5% discontinued because of protocol deviation. However, the *n* for this figure is only 2. Please confirm the

	most commonly due to withdrawal.		correct values for figure 5.
Page 50 states *"The portion of participants achieving ≥5% body weight reduction (co-primary endpoint) was 89.4%, 96.2% and 93.6%, respectively,…"*	Please update to "The portion of participants achieving ≥5% body weight reduction (co-primary endpoint) was 89.4%, 96.2% and **96.3**%, respectively,…"	Incorrect reporting of data.	Number corrected.
Page 51 states "*The portion of participants with a change in glycaemic states from prediabetes to normoglycaemia was 89.4%, 94.7%, 94.3% and 96.8% respectively, compared with 61.9% of the placebo group."*	Please update to "The portion of participants with a change in glycaemic states from prediabetes to normoglycaemia was ~~89.4%~~, 94.7%, 94.3% and 96.8% respectively, compared with 61.9% of the placebo group."	Incorrect or superfluous data without context.	Text updated.
Page 52 states "*The CS use the surrogate outcomes of SBP, HDL cholesterol and total cholesterol in their economic model* ***Error! Reference source not found.****."*	Please update to "The CS use the surrogate outcomes of **CfB weight (%),** SBP, HDL cholesterol and total cholesterol in their economic model 3.1.2."	The EAG has omitted a surrogate endpoint used in the economic model.	Text amended.
Page 54 states "*However, this may be a reflection of the dose*	Please update to "However, this may be a reflection of the dose escalation which was performed	Lack of clarity in current reporting, given that the 5 and 10	Text added.

escalation which was performed up to 20 weeks."	up to 20 weeks **for the 15 mg tirzepatide dose**."	mg doses have different titration periods.	
Page 64, Table 18 states the number of patients with Asthma or COPD at baseline for the placebo arm to be "*69 (15.9)"*	Please update to "69 (~~15.9~~**15.8**)"	Incorrect data.	Amended.
Page 65, Table 19 states the number of patients in the tirzepatide 5 mg arm with baseline and post-baseline value at Week 72 to be "*N=369*"	Please update to "N=~~369~~**368**"	Data misquoted from Clarification Response A1.	Amended.
Page 70 states "*The original SLR identified 6,345 records. After duplicates were removed, 3,873 remained. After title and abstract and full-text screening, 205 publications remain (figure 1 of D.1.3). The updated search in March 2023 identified a further seven publications (figure 2 of D.1.3).*"	Please update to "The original SLR identified ~~6,345~~ **6,355** records. After title and abstract and full-text screening, 205 publications remain (figure 1 of ~~D.1.3~~ **D.1.5**). The updated search in March 2023 identified a further seven publications (figure 2 of ~~D.1.3~~ **D.1.5**)."	Data calculated incorrectly from Figure 1 and section number incorrect.	Amended.

Page 71 states *"Mean BMI was around 37-39 kg/m^2"*	Please update to "Mean BMI was around ~~37-39~~ **37.5–39.5** kg/m^2"	Incorrect data quoted from CS Table 28.	Amended.
Page 72 states *"O'Neil 2018 and STEP 5 analysed data at 52 weeks, SCALE at 56 weeks, STEP 1 and STEP 8 at 68 weeks."*	Please update to "O'Neil 2018 and STEP 5 analysed data at 52 weeks, SCALE **Obesity and Prediabetes** at 56 weeks, STEP 1 and STEP 8 at 68 weeks."	Incomplete study name.	Amended.
Page 74 states *"...with confidence intervals for each study demonstrating non-overlapping ranges."*	Please update to "…with confidence intervals for each study demonstrating ~~non-~~ overlapping ranges."	Incorrect description of NMA interpretation.	Amended.
Page 80 states *"If the posterior distribution of tau, usually representing between-study heterogeneity or variance, was uniform , informative priors were used, based on the approach by Turner et al."*	Please update to "If the posterior distribution of tau, usually representing between-study heterogeneity or variance, **demonstrated a lack of convergence** ~~was uniform,~~ informative priors were used, based on the approach by Turner et al."	Inaccurate description of Company NMA methodology.	Amended.
Page 80 states *"If these criteria were similar, the fixed effects model was chosen over the random effects model for ease*	Please update to: "If these criteria were similar, the fixed effects model was chosen over the random effects model for	The Company are dissatisfied with the explanation provided for the selection of models in the NMA.	Not a factual error.

of interpretation, the baseline risk model over the standard model, and the inconsistency model if an inconsistency was possible in the network (existence of at least one closed loop).”	ease of interpretation. The baseline risk model **was chosen if an interaction existed between the baseline risk and treatment effect, as indicated by the CrI for the interaction effect** ~~over the standard model.~~ **Finally,** the inconsistency model **was selected** if **there was evidence of inconsistency by assessing the DIC, total residual deviance and between-study SD** ~~an inconsistency was possible in the network (existence of at least one closed loop).~~		
Page 84 states *“The company’s NMA feasibility assessment was presented in CS appendix D.”*	Please update to: “The company’s NMA feasibility assessment was presented in CS**, Section B.2.9.3**.”	Incorrect cross-reference to the CS.	Amended.

Page 85 presents this diagram:  	Please update the diagram to include Step 8 alongside O'Neil and SCALE obesity and prediabetes, since Step 8 also included a comparison between placebo and liraglutide 3.0mg.	Incorrect network plot.	Amended.
Page 87 states "However, an I-squared of 50% , 67% and 72% indicate substantial heterogeneity"	Please update to: "However, an I-squared of **45%** , 67% and 72% indicate substantial heterogeneity"	Misquoting of data.	Amended.
Page 89 states *"There were four NMAs for prediabetes reversal and one for 5% weight loss. The inputs used in the NMA."*	Please update with the rest of the sentence.	Incomplete sentence.	Amended.
Page 91, Table 29.	Please update "97.7" quoted for the placebo response for NMA4 for tirzepatide 15 mg to "63.1%". (Note also this table is affected by a major error with regards to the inclusion of liraglutide addressed above, as well as various issues with	Incorrect data reported.	Amended.

	confidentiality highlighting, as detailed further below).		
Page 94 states "Discontinuations from the study due to AEs in the tirzepatide arms ranged from 4.8-7.2%."	Please update to "Discontinuations from the study **treatment** due to AEs in the tirzepatide arms ranged from 4.8–7.2%."	Incorrect reporting of data.	Amended.
Page 97 states "*But the EQ-5D data of SURMOUNT-1 is ignored."*	Please update to: "But the EQ-5D data of SURMOUNT-1 ~~is ignored~~ **was considered less appropriate that literature-sourced inputs**".	Inaccurate representation of Company rationale.	No factual error, no revision required. The company submission Document B explicitly ignores the EQ-5D data.

Page 101 states • *"A population without T2DM and a BMI ≥ 30kgm-2 for a comparison with placebo,* • *A population without T2DM and a BMI ≥ 30kgm-2 for a comparison with placebo, and"*	Please update to: • "A population without T2DM and a BMI ≥ 30kgm^{-2} for a comparison with placebo, • A population without T2DM and a BMI ≥ 3**5**kgm^{-2} for a comparison with placebo, and"	Repetition of one of the subgroups and omission of another.	The EAG accepts the proposed revision.
Page 101 states "*For the scenario analyses:* • *The TA664 based analysis compares tirzepatide 5mg, 10mg and 15mg with liraglutide and placebo, all in conjunction with diet and exercise."*	Please update to: "For the scenario analyses: • The TA664 based analysis compares tirzepatide 5mg, 10mg and 15mg with liraglutide, **semaglutide** and placebo, all in conjunction with diet and exercise."	Omission of one of the modelled comparators.	The EAG accepts the proposed revision.
Page 105 states "*Despite 28% of the EAS placebo arm patients of SURMOUNT-1 achieving a weight reduction of at least 5% the model assumes that all those in the placebo arm in effect discontinue at week 72 and see their weight loss reversed."*	Please update to: "Despite 28% of the EAS placebo arm patients of SURMOUNT-1 achieving a weight reduction of at least 5% the model assumes **that there is no maintained efficacy, as there were no data to inform the efficacy estimates for diet and exercise in the model beyond 72 weeks** ~~all those in~~	Inaccurate representation of the model inputs, driven by the EAG mistakenly assuming that patients may discontinue from diet and exercise.	No factual error, no revision required. The EAG thinks this is the most reasonable representation. It can equally well be noted that there were no data to inform estimates for

	~~the placebo arm in effect discontinue at week 72 and see their weight loss reversed~~."		the active treatment arms beyond week 72.
Page 105, Table 38.	Please remove the placebo row.	As above, patients may not discontinue from diet and exercise in the model. Therefore it is inaccurate to include this intervention in this table.	No factual error. See above point.
Page 106, Table 39.	<table><tr><th></th><th>AE Disc</th><th>Weeks</th><th>Annual</th></tr><tr><td>TIRZ 5mg</td><td>4.29%</td><td>72</td><td>3.11%</td></tr><tr><td>TIRZ 10mg</td><td>7.08%</td><td>72</td><td>5.16%</td></tr><tr><td>TIRZ 15mg</td><td>6.19%</td><td>72</td><td>4.51%</td></tr><tr><td>SEMA</td><td>7.04%</td><td>56</td><td>6.56%</td></tr><tr><td>LIRA</td><td>9.89%</td><td>68</td><td>7.**59**%</td></tr></table>	Incorrect data reported for discontinuations due to adverse events in the liraglutide arm.	The EAG accepts the proposed revision.
Page 108 states *"For liraglutide, because no stopping rule is applied the initial treatment effect at 72 weeks…"*	"For ~~liraglutide~~ **tirzepatide,** because no stopping rule is applied the initial treatment effect at 72 weeks…"	Incorrect intervention has been noted.	The EAG accepts the proposed revision.
Page 109 states "*The CVD events of myocardial infarction, stroke and angina 1st events and recurrent events using the"*	Please complete the rest of the sentence.	Incomplete sentence.	The EAG will revise the first bullet from: • "The CVD events of myocardial

			infarction, stroke and angina 1st events and recurrent events using the “ To • “The CVD events of myocardial infarction, stroke and angina 1st events and recurrent events“
Page 110 states “…*under 65 years of age, 53 per 100,000 patient years, and over 65 years of age, 120.22 per 100,000 patient years”*	Please update to “…under 65 years of age, 53**.52** per 100,000 patient years, and over 65 years of age, 120.22 per 100,000 patient years”	Inconsistency in number of decimal points to which data is reported.	The EAG accepts the proposed revision.
Page 111 states “*Bariatric surgery is associated with an*	Please update to “Bariatric surgery is associated with an	Misleading information as RYGB, sleeve gastrectomy and OAGB	The EAG will revise the text to:

<table>
<tr>
<td>average weight loss of around 30% and rates of prediabetes reversal and OSA remission of around 50-60%”</td>
<td>average weight loss of around 30% (for RYGB, sleeve gastrectomy and OAGB) and rates of prediabetes reversal and OSA remission of around <s>50-60%</s>31—68%”</td>
<td>have around 30% weight loss, but gastric band has 16.3%, as can be seen in Table 71 of CS Document B. Rates of prediabetes reversal and OSA remission are 31—68%.</td>
<td>“Bariatric surgery is associated with an average weight loss of around 30% for RYGB, sleeve gastrectomy and OAGB and 16% for gastric band and rates of prediabetes reversal and OSA remission of around 31—68%”</td>
</tr>
<tr>
<td>Page 116, Table 45.</td>
<td>Please update the liraglutide column as follow:
<table>
<tr><th colspan="2">Liraglutide</th></tr>
<tr><td>3 x 18mg</td><td>£117.72</td></tr>
<tr><td>5 x 18mg</td><td>£196.20</td></tr>
</table>
</td>
<td>To reflect the two pack sizes and costs for liraglutide (noting the price per dose is unaffected).</td>
<td>The EAG accepts the proposed revision.</td>
</tr>
<tr>
<td>Page 117 states “Quarterly GP visits and twice quarterly nurse visits are assumed together with one prescription, yielding an annual cost of £234.”</td>
<td>Please update to “Quarterly GP visits, blood tests and twice quarterly nurse visits are assumed together with one prescription, yielding an annual cost of £234.”</td>
<td>Inaccurate reporting of model inputs.</td>
<td>The EAG accepts the proposed revision.</td>
</tr>
<tr>
<td>Page 121 states “…gain from tirzepatide 5mg relative to placebo increases from 0.695 QALYs to 0.703 QALYs..”</td>
<td>Please update to: “…gain from tirzepatide 5mg relative to placebo increases from 0.695 QALYs to 0.730 QALYs..”</td>
<td>Incorrect data.</td>
<td>The EAG accepts the proposed revision.</td>
</tr>
</table>

Page 130 states *"The model does not provide any guide to the likely cost effectiveness of liraglutide for the treatment of T2DM patients."*	Please update to: "The model does not provide any guide to the likely cost effectiveness of **tirzepatide** for the treatment of T2DM patients."	Incorrect intervention has been noted.	The EAG accepts the proposed revision.
Page 139 states "*This needs to be read in conjunction with Document B Section B.1.3 page 20, which states that due to increasing criticism of the tiered obesity management system HM government is piloting a two year study of the use of incretin based therapies within primary care. It also notes that it is anticipated that there will be substantial changes to the NICE guidelines for the management of obesity.* *The use of incretin-based therapies is not obviously directly addressed by any of the September 2023 review questions, though it could be interpreted to be within some of them. The economic plan is limited to examining "partial*	Page 139 "*This needs to be read in conjunction with Document B Section B.1.3 page 20, which states that due to increasing criticism of the tiered obesity management system HM government is piloting a two year study of the use of incretin based therapies within primary care. It also notes that it is anticipated that there will be substantial changes to the NICE guidelines for the management of obesity.* ***Furthermore, it noted forthcoming guidance from NICE on using digital technologies to provide treatment with pharmacological therapies without requiring face-to-face appointments in SWMS (which has subsequently***	This section of the report does not clearly distinguish between three related but separate items cited in B.1.3: 1. Ongoing update to the NICE guideline 2. NICE HTE14 recommending apps through which incretin-based therapies can be prescribed alongside lifestyle support, without requiring face-to-face SWMS 3. HM Government pilot of incretin-based therapies for weight loss in primary care setting	No factual error, no revision required. But the EAG will append to the end of: "*The current anticipated publication date of the guidelines is the same as that of this assessment: 27 March 2024*" The following paragraph. "At error check the company highlighted the publication of NICE HTE14 on 26 October 2023. This provides guidance on digital technologies that may be able to deliver SWMS services to manage weight-management

diet replacements, intermittent fasting, plant-based and low carbohydrate diets". The current anticipated publication date of the guidelines is the same as that of this assessment: 27 March 2024"	***been published as NICE HTE14).*** *The use of incretin-based therapies is not obviously directly addressed by ~~any of the September 2023 review questions, though it could be interpreted to be within some of them. The economic plan is limited to examining "partial diet replacements, intermittent fasting, plant-based and low carbohydrate diets".~~* ***The update to the NICE guideline, but is covered in NICE HTE14 (published 26th October 2023).*** *The current anticipated publication date of the* ***updated NICE*** *guidelines is the same as that of this assessment: 27 March 2024"*		medicine, instead of requiring face to face SWMS services. HTE14 recognises the potential for the digital technologies to meet unmet need in areas where SWMS are not available. HTE14 allows 5 out of 8 digital weight management technologies to be used for 4 years in order to generate more evidence. HTE14 also recognises that cost effectiveness will also be driven by the costs of face to face SMWS, which are also poorly enumerated and require further research. NICE will review results and make a recommendation on their routine adoption at the end of the 4 year evidence generation period."

Page 140, Table 60.	Please specify clearly what comparison the ICER is based on – it is not immediately clear to the reader that the ICER in each row refers to a comparison of the given treatment without a 2yr stopping rule compared to having a 2yr stopping rule	To improve clarity of a comparison that is not immediately clear to the reader	No factual error. No revision required. The EAG cannot think how to make the table any clearer. The subsequent text hopefullu alleviates any misunderstanding.
Page 147 states *"The 10% estimate of non-responders for semaglutide is based upon expert opinion due to it being redacted from TA875 for the target population. This compares to 90.3%, 96.2% and 96.3% for tirzepatide 5mg, 10mg and 15mg."*	Please update to: "The 10% estimate of non-responders for semaglutide is based upon expert opinion due to it being redacted from TA875 for the target population. This compares to **response rates of 89.4**%, 96.2% and 96.3% for tirzepatide 5mg, 10mg and 15mg."	The way this is currently written implied that the data cited are discontinuation rates (equivalent to the 10% for semaglutide) whereas in fact these data are response rates. Additionally, there is a misquoting of data.	The EAG accepts the proposed amendment.
Page 171, Table 71.	Please update the header row to: "ICER vs PLAC"	Incorrect table header.	No factual error. No revision necessary. The EAG does not understand what error the company is identifying. It may wish to provide an alternative table to make this clear.

Page 172, Table 73.	Please could the EAG clarify whether “Dom” in the tirzepatide 10 mg column means “dominant” or “dominated”.	Lack of clarity in current reporting.	The EAG will amend the table with a footer “* Dom = dominant”
Page 185 states *“A higher proportion in the placebo arm discontinued treatment (most commonly due to protocol deviations and withdrawal by subject), and discontinued the study (most commonly due to withdrawal by subject)”*	Please update to “A higher proportion in the placebo arm discontinued treatment (most commonly due to ~~protocol deviations and~~ withdrawal by subject), and discontinued the study (most commonly due to withdrawal by subject).”	Protocol deviations in the placebo arm represented on 0.3% of discontinuations from the study treatment, which was not one of the most common reasons.	Please see earlier comment (Figure 5, CS, Doc B).
Page 185 states *“13.5% of the placebo arm discontinued treatment due to protocol deviations, but there were no discontinuation for this reason in the tirzepatide arms.”*	Please update to “13.5% of the placebo arm discontinued treatment due to **withdrawal by subject**~~, but there were no discontinuation for this reason in the tirzepatide arms~~.”	Misquoting of data.	Please see earlier comment (Figure 5, CS, Doc B). Figure 5 does not present values for protocol deviation in the tirzepatide arms.

Confidentiality highlighting amendments (EAG report)

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>ERG Response</th></tr>
<tr><td>Page 52, Table 11.</td><td>Data in Table 11 pertaining to glycaemic status should be marked as confidential..</td><td>Please amend to:<table><tr><th colspan="5">Glycaemic status</th></tr><tr><td>Proportion with prediabetes at baseline to normoglycaemia at 72-weeks, n (%) (exploratory endpoint)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Amended.</td></tr>
<tr><td>Page 66, footnotes of Table 19</td><td>Footnotes are marked as confidential and do not need to be marked as confidential.</td><td>Please amend to:
“[a] p<0.001 versus placebo for superiority.
[b] p<0.001 versus baseline.”</td><td>Amended.</td></tr>
<tr><td>Page 66, footnotes of Table 20</td><td>Footnotes are marked as confidential</td><td>Please amend to:
“[a] p<0.001 versus placebo for superiority.
[b] p<0.001 versus baseline.”</td><td>Amended.</td></tr>
</table>

<table>
<tr><td></td><td>and do not need to be marked as confidential.</td><td></td><td></td></tr>
<tr><td>Page 82, Table 25.</td><td>All data in Table 25 should be marked as confidential.</td><td>Data in Table 25 not highlighted as confidential, please amend to:<table><tr><th>Outcome</th><th>Model</th><th>N trials</th><th>Tirzepatide 5 mg</th><th>Tirzepatide 10 mg</th><th>Tirzepatide 15 mg</th><th>Semaglutide 2.4 mg</th></tr><tr><td>CfB in weight (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>CfB in HDL (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>CfB in total cholesterol (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>CfB in SBP (mmHg)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td colspan="7">Reference treatment = placebo, CfB Change from baseline, FE: fixed effect.</td></tr></table></td><td>Amended.</td></tr>
<tr><td>Page 83, Table 26.</td><td>All data in Table 26 should be marked as confidential.</td><td>Data in Table 26 not highlighted as confidential, please amend to:<table><tr><th>Outcome</th><th>Model</th><th>N trials</th><th>Tirzepatide 5 mg</th><th>Tirzepatide 10 mg</th><th>Tirzepatide 15 mg</th><th>Liraglutide 3 mg</th><th>Semaglutide 2.4 mg</th></tr></table></td><td>Amended.</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>CfB in weight (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>CfB in HDL (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>CfB in total cholesterol (%)</td><td>FE unadjusted</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>CfB in SBP (mmHg)</td><td>FE baseline risk</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Reference treatment = placebo, CfB: FE: fixed effect.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Page 87, Table 27.</td>
<td>All data in Table 27 should be marked as confidential.</td>
<td>Data in Table 27 not highlighted as confidential, please amend to:
<table>
<tr><th>Outcome</th><th>Efficacy Estimand</th><th>Treatment Regimen Estimand</th></tr>
<tr><td>Cfb in weight (%)</td><td></td><td></td></tr>
<tr><td>Cfb in HDL (%)</td><td></td><td></td></tr>
<tr><td>Cfb in total cholesterol (%)</td><td></td><td></td></tr>
<tr><td>Cfb in SBP (45mHg)</td><td></td><td></td></tr>
</table>
</td>
<td>Amended.</td>
</tr>
</table>

<table>
<tr>
<td>Page 91, Table 29.</td>
<td>Data in Table 29 table taken from CS Doc B should be marked as confidential, except for “Primary responders: Minimum 5% weight loss in full trial population”</td>
<td>Data in Table 29 table taken from CS Doc B not highlighted as confidential. Please correct to:
<table>
<tr><th>Intervention</th><th>Placebo</th><th>Intervention rates</th><th>Placebo rates</th><th>Intervention N</th><th>Placebo N</th><th>Source</th></tr>
<tr><td colspan="7">NMA1: Prediabetes in the whole trial population</td></tr>
<tr><td>TIRZ 5mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>TIRZ 10mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>TIRZ 15mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>LIRA</td><td>Placebo</td><td>75.5%</td><td>35.2%</td><td>400</td><td>95</td><td>TA664</td></tr>
<tr><td>SEMA</td><td>Placebo</td><td>90.4%</td><td>45.8%</td><td>1306</td><td>655</td><td>STEP 1</td></tr>
<tr><td colspan="7">NMA2: Prediabetes in the whole trial population scenario analysis using results of liraglutide early responders</td></tr>
<tr><td>TIRZ 5mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>TIRZ 10mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>TIRZ 15mg</td><td>Placebo</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>CS Doc B</td></tr>
<tr><td>LIRA</td><td>Placebo</td><td>82.8%</td><td>40.7%</td><td>314</td><td>55</td><td>TA664</td></tr>
<tr><td>SEMA</td><td>Placebo</td><td>90.4%</td><td>45.8%</td><td>1306</td><td>655</td><td>STEP 1</td></tr>
<tr><td colspan="7">NMA3: Prediabetes in the BMI ≥30 kg/m^2 with at least one weight-related comorbidity subgroup</td></tr>
</table>
</td>
<td>Amended.</td>
</tr>
</table>

		TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		LIRA	Placebo	75.5%	35.2%	400	95	TA664		
		SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1		
		NMA4: Prediabetes in the BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD subgroup								
		TIRZ 5mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		TIRZ 10mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		TIRZ 15mg	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	CS Doc B		
		LIRA	Placebo	75.5%	35.2%	400	95	TA664		
		SEMA	Placebo	90.4%	45.8%	1306	655	STEP 1		
		NMA5: Primary responders: Minimum 5% weight loss in full trial population								
		TIRZ 5mg	Placebo	89.4%	27.9%	630	643	CS Doc B		
		TIRZ 10mg	Placebo	96.2%	27.9%	636	643	CS Doc B		
		TIRZ 15mg	Placebo	96.3%	27.9%	630	643	CS Doc B		
		LIRA	Placebo	59.9%	20.3%	531	271	TA664		
		SEMA	Placebo	92.4%	33.1%	1059	499	STEP 1		

<table>
<tr><td></td><td></td><td>(Note also this table is affected by a major error with regards to the inclusion of liraglutide addressed and an apparent misquoting of data separately addressed in the relevant section of comments above).</td><td></td></tr>
<tr><td>Page 101, Table 32.</td><td>Data in this table does not need to be highlighted as confidential.</td><td>Data in Table 32 does not require confidentiality highlighting. Please correct to:
<table><tr><th></th><th>All patients</th><th>Target pop</th><th>TA664 pop</th></tr><tr><td>Age</td><td>45</td><td>47</td><td>47</td></tr><tr><td>Female</td><td>68%</td><td>66%</td><td>66%</td></tr><tr><td>BMI</td><td>38.0</td><td>38.8</td><td>42.6</td></tr><tr><td>SBP</td><td>123.3</td><td>124.8</td><td>126.5</td></tr><tr><td>TC</td><td>187.9</td><td>194.0</td><td>158.8</td></tr><tr><td>HDL</td><td>47.3</td><td>48.7</td><td>45.3</td></tr><tr><td>Pre-diabetes</td><td>41%</td><td>58%</td><td>100%</td></tr></table></td><td>Amended.</td></tr>
<tr><td>Page 102, Table 33</td><td>Data in this table should all be highlighted as confidential.</td><td>Data in Table 33 requires confidentiality highlighting. Please correct to:
<table><tr><th></th><th>Weight</th><th>SBP</th><th>HDL</th><th>TC</th></tr><tr><td>PLAC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>LIRA</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>SEMA</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>TIRZ 5mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>TIRZ 10mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Amended.</td></tr>
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<tr><td>Page 103, Table 34.</td><td>Data pertaining to semaglutide in this table should be highlighted as confidential.</td><td>Data in Table 34 requires confidentiality highlighting. Please correct to:
<table>
<tr><th></th><th>Weight</th><th>SBP</th><th>HDL</th><th>TC</th></tr>
<tr><td>PLAC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>LIRA</td><td>-7.8%</td><td>-5.3</td><td>1.8%</td><td>-2.7%</td></tr>
<tr><td>SEMA</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>TIRZ 15mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Page 103, Table 35.</td><td>Data pertaining to liraglutide and semaglutide in this table should be highlighted as confidential.</td><td>Data in Table 35 requires confidentiality highlighting. Please correct to:
<table>
<tr><th></th><th>Weight</th><th>SBP</th><th>HDL</th><th>TC</th></tr>
<tr><td>PLAC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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Page 155.	Unnecessary confidentiality marking	Please remove confidentiality marking and update to “N=1,523 (63%) respectively”	Proposed amendment accepted.
Multiple instances, primarily in Section 3	The list price for tirzepatide is no longer confidential following the publication of TA924.[6]	Please remove all confidentiality highlighting related to the list price of tirzepatide.	Proposed amendment accepted. The EAG would like to ask whether this means that all total costs can also have their CIC marking removed.

Minor typographical and grammatical errors (EAG report)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
The Company have summarised some of the more noticeable grammatical, typographical and punctuation errors below. However, the Company would also urge the EAG to conduct a thorough proofread of their report before it is published, as numerous additional errors are present. Please also ensure all table and figure cross-references are correct.			
Page 10 states "*Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition 1, technology and evidence and information on non-key issues are in the main EAG report 2, and 3."*	Please update to: "Sections 1.3 to 1.6 **of the Executive Summary** explain the key issues in more detail. Background information on the condition, ~~1, technology and~~ **clinical effectiveness and cost-effectiveness** evidence and information on non-key issues are **provided** in the main EAG report **in Sections 1, 2, and 3, respectively**."	Grammatical error.	Cross-referencing clarified.
Page 13 states *"…2 year stopping rule"*	Please update to: "2-year stopping rule"	Grammatical error.	Amended.
Page 14 states *"…2 year stopping rule"*	Please update to: "2-year stopping rule"	Grammatical error.	Amended.
Page 16 states *"…ongoing studies of tirzapatide"*	Please update to "ongoing studies of **tirzepatide"**	Typographical error.	Amended.

Page 18 states "*The economics models each arm of the SURMOUNT-1 trial…"*	Please update to: "The economics models each arm of the SURMOUNT-1 trial"	Typographical error.	Amended.
Page 24 states *"MUBARAK SECTION"*	Please update with the appropriate cross-reference (Section 2.3.5)	Typographical error.	Amended.
Page 28 states "*Table 1: ERG BC01: 2 year stopping rule"*	Please update to: "Table 5: E**A**G BC01: 2 year stopping rule"	Typographical error.	Amended.
Page 30 states *"The resulting abnormal or excessive body fat accumulation (BMI ≥30 kg/m2) presents a risk to health.[1-4] which may…"*	Please update to: "The resulting abnormal or excessive body fat accumulation (BMI ≥30 kg/m2) presents a risk to health**,**[1-4] which may…"	Typographical error.	Amended.
Page 32 states *"The EAG clinical advisor confirmed that trizepatide will be offered in tier 3 services."*	Please update to: "The EAG clinical advisor confirmed that **tirzepatide** will be offered in tier 3 services."	Typographical error.	Amended.
Page 33 states: *"…criteria or referral to SWMS"*	Please update to: "…criteria **for** referral to SWMS"	Typographical error.	Amended.
Page 35 states *"SURMOUNT-1 is wider than the population considered in the company decision problem (adults who have a BMI of ≥30 kg/m^2 and at least one weight-related comorbidity. The company's…"*	Please update to: *"*SURMOUNT-1 is wider than the population considered in the company decision problem (adults who have a BMI of ≥30 kg/m^2 and at least one weight-related comorbidity**)**. The company's…"	Typographical error (punctuation).	Amended.
Page 46 states *"Unlike the draft SmPC posology, The SURMOUNT-1 trial provides…."*	Please update to: Unlike the draft SmPC posology, **t**he SURMOUNT-1 trial provides	Typographical error.	Amended.

Page 46 states *"scheme was used for each of the tirzepatide arm as described in CS B.2.3.1.1 and Figure 4"*	Please update to: "scheme was used for each of the tirzepatide arm**s** as described in CS B.2.3.1.1 and Figure 4"	Typographical error.	Amended.
Page 49 states "*The ERG notes there is higher drop out"*	Please update to: "The **EAG** notes there is higher drop out"	Typographical error.	Amended.
Page 50 states "…*each dose of trizepatide compared with placebo"*	Please update to: "…each dose of **tirzepatide** compared with placebo	Typographical error.	Amended.
Page 52 states *"…company regarding the justification for this, see Section CC."*	Please update with the correct Section cross-reference.	Typographical error.	Amended.
Page 53 states *"…was found with each dose of tirzepatide (Table xx)."*	Please update with the correct Table cross-reference (Table 12).	Typographical error.	Amended.
Page 55 states "…*safety population of the intergrated SURMOUNT-1 and SURMOUNT-2 trials"*	Please update to: "…safety population of the **integrated** SURMOUNT-1 and SURMOUNT-2 trials"	Typographical error.	Amended.
Page 57 states *"Dose-descalations"*	Please update to "**Dose De-escalations**"	Typographical error.	Amended.
Page 57 states *"…de-escalatation"*	Please update to "…**de-escalation**"	Typographical error.	Amended.
Page 59 states "*The SUMOUNT-1 trial…"*	Please update to: "The SU**R**MOUNT-1 trial…"	Typographical error.	Amended.

Page 59 states "…*similar between arms* ([redacted]). *"*	Please update to "… similar between arms ([redacted])."	Typographical error.	Amended.
Page 59 states *"…on the significant interactions are summarised in Table xx."*	Please update with the correct Table cross-reference (Table 16).	Typographical error.	Amended.
Page 61 states *"…in the company's NMA and economic analysis is presented in Table xx below."*	Please update with the correct Table cross-reference (Table 17).	Typographical error.	Amended.
Page 61 states *"The ERG has summarised"*	Please update to: "The **EAG** has summarised"	Typographical error.	Amended.
Page 64 states "*Jostreboff et. al 2022, the company submission, clinical study report"*	Please update to: "**Jastreboff** *et. al***.** 2022, the company submission, clinical study report"	Typographical error.	Amended.
Page 67 states "…*metabolic health in latinos with obesity"*	Please update to: "…metabolic health in **Latinos** with obesity"	Typographical error.	Amended.
Page 70 states "*The EAG considers that the eligible populationswere comparable"*	Please update to: "The EAG considers that the eligible **populations were** comparable"	Typographical error.	Amended.
Page 73 states "It was assumed that the analysis of change from baseline (cfb) in weight (5) more"	Please update to: "It was assumed that the analysis of change from baseline (cfb) in weight (**%**) more"	Typographical error.	Amended.

Page 83 states *"Change in SBP (mmHG): tirzepatide…"*	Please update to: "Change in SBP (mmH**g**): tirzepatide…"	Typographical error.	Amended.
Page 86 states "…suggesting no evidence of loop inconsistency,"	Please update to: "…suggesting no evidence of loop inconsistency**.**"	Typographical error (punctuation).	Amended.
Page 87 includes erroneous green highlighting	Please remove highlighting	Formatting error.	Amended.
Page 109 states *"…mortality being address in section **Error! Reference source not found.**"*	Please update to: "…mortality being address**ed** in section **Error! Reference source not found.**"	Typographical error.	Amended.
Page 110 states *"The onset of OSA applies the odds ratio function that Erridge et al [7] derive from"*	Please update to: "The onset of OSA applies the odds ratio function that Erridge et al[7] derive**d** from"	Typographical error.	Amended.
Page 114 states "*SURMOUNT-1 collected EQ-5D data but this is not used in the economics."*	Please update to: "SURMOUNT-1 collected EQ-5D data but this is not used in the **health economic model**."	Incorrect grammar.	Amended.
Page 117 states "*The ongoing cost of OSA is taken an undocumented…"*	Please update to: "The ongoing cost of OSA is taken **from** an undocumented…"	Incorrect grammar.	Amended.
Page 127 states *"…model uncertainty can in part be addressed by comparison the current…"*	Please update to: "…model uncertainty can in part be addressed by compar**ing** the current…"	Typographical error.	Amended.

Page 135 states "…*it is debateable whether the model needs to incorporate these*"	Please update to: "…it is **debatable** whether the model needs to incorporate these"	Typographical error.	Amended.
Page 139 states "*Given the cost effectiveness estimates…"*	Please update to "Given the cost-effectiveness estimates…". This needs to be hyphenated throughout the document.	Typographical error.	Amended.
Page 140 states "*The cost effectiveness of relaxing the two year stopping rule for the company base case is presented in Table 58*"	Please update the Table cross reference, currently this is Table 60	Cross-referencing error.	Cross refrencing updated throughout the report.
Page 144 states "*As per Table 36 above, liraglutide is modelled …*"	Please update the Table cross reference, currently this is Table 38	Cross-referencing error.	Cross referencing updated throughout the report.
Page 156 states *"The cost and QALY estimates of* ***Error! Reference source not found.****"*	Please update to "The cost and QALY estimates of Table **66**" and check cross-references are correct throughout the document.	Cross-referencing error.	Cross referencing updated throughout the report.

1. National Institute for Health and Care Excellence (NICE). Semaglutide for managing overweight and obesity [TA875]. Available at: https://www.nice.org.uk/guidance/TA875/. Last accessed: March 2023.
2. Eli Lilly. Data on File. SURMOUNT-1 Clinical Study Report. 2022.
3. National Health Service (NHS). Diagnosis: Chronic kidney disease. Available at: https://www.nhs.uk/conditions/kidney-disease/diagnosis/#:~:text=Tests%20for%20CKD&text=This%20calculation%20is%20known%20as,rate%20is%20lower%20than%20this. Last accessed: November 2023. 2023.
4. Le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. The Lancet 2017;389:1399-1409.
5. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. January 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Last accessed: April 2022.
6. National Institute for Health and Care Excellence (NICE). Tirzepatide for treating type 2 diabetes [TA924]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10835. Last accessed: August 2023.
7. Erridge S, Moussa O, McIntyre C, et al. Obstructive Sleep Apnea in Obese Patients: a UK Population Analysis. Obes Surg 2021;31:1986-1993.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tirzepatide for managing overview and obesity

[ID6179]

EAG-requested data post-factual accuracy check

December 2023

Analysis pooled across tirzepatide doses

In the EAG's responses to the Company's factual accuracy check (File name: ID6179 Factual accuracy check & ACIC check form v0.2_23rdNov2023 ERG [CON]), the EAG stated that "*if the Company's position is that tirzepatide can only be approved or not approved in total the EAG thinks it would have to present an analysis pooled across tirzepatide doses that estimates the proportion of patients who would receive 5mg, 10mg and 15mg*". The Company have therefore presented below a pooled analysis, in which ICERs for tirzepatide have been calculated versus semaglutide and diet and exercise (based on their base case analysis), with the weighting for each dose being informed by the proportion of patients whose maximum tolerated dose was that observed for tirzepatide in the SURMOUNT-4 trial. As detailed further in the EAR response (File name: ID6179 EAR Response_8thDecember2023), the SURMOUNT-4 provides evidence for the clinical effectiveness of tirzepatide when used in a maximum tolerated dose regimen (where patients were titrated to either 10 mg or 15 mg), which is expected to reflect the use of tirzepatide in clinical practice. Specifically, in SURMOUNT-4, in the double-blind period of the study (Weeks 36 to 88, i.e. after 36 weeks of open-label tirzepatide for both arms), the highest dose of tirzepatide was:

- 10 mg for 7.5% of participants, and
- 15 mg for 92.5% of participants

Based on these data, the weighted ICERs presented in Table 1 were calculated using the following methodology:

- Incremental costs/QALYs for the combination of 10 mg and 15 mg doses were calculated by taking a weighted average of the calculated incremental costs/QALYs for the 10 mg and 15 mg doses, weighted by the proportion of patients who reached a maximum 10 mg or 15 mg dosage level respectively in SURMOUNT-4
- The overall ICER for the combination of 10 mg and 15 mg doses was then calculated by dividing the weighted incremental costs by the weighted incremental QALYs

Table 1. ICER for tirzepatide maximum tolerated dose regimen, based on proportions of patients receiving tirzepatide 10 mg and 15 mg in SURMOUNT-4

Comparator	Incremental Cost	Incremental QALYs	ICER
Semaglutide	£7,364.62	0.60	£12,201.58
D&E	£9,832.81	0.77	£12,846.54

Abbreviations: ICER; incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Clarification on Figure 5 in the Company Submission

In response to the EAG's query (on Page 28) surrounding the correct value for the proportion of patients discontinuing the study drug in the placebo arm due to a protocol deviation, the Company wishes to clarify that the value included in Figure 5 in the Company Submission was incorrect. The correct value for the proportion of patients who discontinued the study drug in the placebo arm due to a protocol deviation was 0.3% (n=2), as per the CSR.

1. **Patient Global Impressions of Status (PGIS) for Physical Activity (requested by committee)**

A summary of pre and post-baseline PGIS is presented in the SURMOUNT-1 CSR in section 5.1.5.6 and Table GPHK.5.25. Table 1 summarises the number of people in each PGIS response category for each of the different treatment arms. Pre-baseline, participants were broadly similar between groups, but post-baseline the tirzepatide arms saw the greatest improvements in ability to do physical activity.

Table 1. Summary of PGIS score pre- and post-baseline for SURMOUNT-1 participants; data from CSR section 5.1.5.6.

	Placebo		Tirzepatide 5 mg		Tirzepatide 10 mg		Tirzepatide 15 mg	
PGIS	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Not at all limited	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A little limited	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately limited	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very much limited	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely limited	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]The company notes, in the CSR, that of the [redacted] participants with moderately, very much, and extremely limited physical activity, [redacted] reported improvement to either not at all limited or a little limited categories. This is summarised in Table 2. [redacted]

Table 2. Improvements in PGIS (not including those missing post-baseline)

	PGIS post-baseline	
PGIS pre-baseline	**Not at all limited**	**A little limited**
Placebo	[redacted]	[redacted]
Moderately limited	[redacted]	[redacted]
Very much limited	[redacted]	[redacted]
Extremely limited	[redacted]	[redacted]
Tirzepatide 5 mg	[redacted]	[redacted]
Moderately limited	[redacted]	[redacted]
Very much limited	[redacted]	[redacted]
Extremely limited	[redacted]	[redacted]
Tirzepatide 10 mg	[redacted]	[redacted]
Moderately limited	[redacted]	[redacted]
Very much limited	[redacted]	[redacted]
Extremely limited	[redacted]	[redacted]
Tirzepatide 15 mg	[redacted]	[redacted]
Moderately limited	[redacted]	[redacted]
Very much limited	[redacted]	[redacted]
Extremely limited	[redacted]	[redacted]

2. Diet and exercise:

From the CSR page 27

[redacted]

3. Pre-Diabetes NMA

Weight loss NMA

Tirzepatide for managing overweight and obesity [ID6179]

Questions for NHS England

Question 1. How the multidisciplinary team (MDT) approach for obesity management is delivered in the NHS at present. Consider the services as they are today, indicating if the services described are covered by the weight management pilot.

- Which professionals are included in the MDT?

  Please enter your answer here

- In which settings it is currently available and delivered (for example, primary and secondary care or secondary care only)?

  Please enter your answer here

- What are the eligibility criteria for access to MDT?

  Please enter your answer here

- How long does MDT last? Is there a limit?

  Please enter your answer here

- Is assessment needed for the eligibility of multidisciplinary services? If so, who is doing the assessment?

  Please enter your answer here

- What main components of the current multidisciplinary approach and service for obesity in the NHS are being adapted or updated? Please highlight the most relevant for the delivery of anti-obesity drugs.

  Please enter your answer here

Question 2. How the multidisciplinary team approach for obesity management is being adapted and updated, both with and

without anti-obesity medication included. Please refer to the tables at the end of this section to complete relevant answers.

- What will the updated MDT service delivery model consist of:
    - Which professionals will be included?
    - How often will an individual accessing this service be seen by each professional in a year (specifying first and subsequent years, if different)?

      Please use tables 1 and 2 to give your answer

- In which settings will it be available:
    - In which settings will the services be available and delivered?

      Please enter your answer here

    - Will this service be entirely run outside hospital settings or across settings including hospitals depending on which setting the individuals access and start the service?

      Please enter your answer here

    - If run in a mixture of community and hospital settings, are different costs associated with these services in each setting?

      Please enter your answer here

    - Will specialist weight management services still exist and be an appropriate setting for tirzepatide treatment for people accessing these services?

      Please enter your answer here and provide further information in table 3 if applicable

- What are the eligibility criteria?

- Is an assessment for eligibility going to be needed before the initiation of multidisciplinary service?

  Please enter your answer here

- Are the eligibility criteria going to be the same or differ across settings where the multidisciplinary service will be available?

  Please enter your answer here

- Will the multidisciplinary service be the same for all regardless of the use of pharmacological products, or will additional support be needed if tirzepatide is recommended?

  Please use tables 1 and 2 to give your answer

- Will any of the components of the multidisciplinary services not be not needed because of the use of tirzepatide?

  Please use tables 1 and 2 to give your answer

- How long will this service be accessible for?

  - Does the length of time the service is accessible depend on whether the individual is taking pharmacological treatment?

    Please use tables 1 and 2 to give your answer

  - If time limited, would the service be used as long as an individual is on pharmacological treatment or would tirzepatide continue to be prescribed without the MDT support in the long-term?

    Please enter your answer here

- Is there any further information on the design and costs of the services needed for delivering tirzepatide that NHSE would like the committee to be aware of?

Please enter your answer here

Please complete the following tables with estimated resource use and associated costs for the updated obesity management service delivery model. Specify a range of values where appropriate.

Table 1 – MDT delivered in the community with anti-obesity medication

Category	No. per year, year 1	No. per year, year 2 & subsequent	Anticipated duration of support	Costs per visit	Comments
GP visit					
Nurse visit					
Psychologist visit					
Dietician visit					
Other resource – please specify (add rows if needed)					

Table 2 – MDT delivered in the community without anti-obesity medication

Category	No. per year, year 1	No. per year, 2nd & subsequent years	Anticipated duration of support	Costs per visit	Comments
GP visit					
Nurse visit					
Psychologist visit					
Dietician visit					
Other resource – please					

specify (add rows if needed)					

Table 3 – Specialist weight management services

Eligibility criteria – please specify anticipated eligibility criteria in the context of community-based MDT	
Anticipated proportion of people needing referral in the context of community-based MDT	
Anticipated duration of SWMS	

Background information:

Lifestyle interventions included in SURMOUNT-1 for all participants (SURMOUNT-1 trial protocol):

Participants will consult with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counselling at Weeks 0, 4, 8 and 12 during dose escalation and then at Week 24 and every 12 weeks thereafter through 72 weeks.

Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact by study staff.

At Visit 3 and subsequent visits, study participants will receive diet counselling by a dietician/nutritionist, or equivalent qualified delegate, according to local standard. Dietary counselling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of:

• maximum 30% of energy from fat

• approximately 20% of energy from protein • approximately 50% of energy from carbohydrates

• an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure (TEE).

To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counselling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

At Visit 3 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week.

Schedule of activities: details of how weight management support was provided for all participants:

Activity	Timing of activity (study treatment weeks)	Additional detail
Providing diary to participant and instructing use	Weeks 0, 12, 24, 36, 48, 60 and 72	Training should be repeated as needed to ensure compliance
Review study diary, including drug compliance	Started week 4, continued every 4 weeks	NA
Lifestyle programme instructions	Weeks 0, 4, 8, 12, 24, 36, 48, 60 and 72	Counselling on diet and exercise to be performed by a dietician or equivalent qualified delegate, according to local standards; to include calculation of individualised energy requirement and methods to change dietary composition and amount of physical activity. Dietary counselling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of: • maximum 30% of energy from fat • approximately 20% of energy from protein • approximately 50% of energy from carbohydrates • an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure (TEE) To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counselling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed. Beginning at week 8, the lifestyle program instruction may be delivered by phone.
Review of diet and exercise goals	Started week 0, continued every 4 weeks	Training should be repeated as needed to ensure compliance

*provisions for changes in study conduct during exceptional circumstances, including pandemics included (relevant due to study period during COVID-19;

start date December 2019; primary completion date April 2022): remote visits, and diaries acquired alternatively, for example by delivery.

Current company and EAG modelling assumptions around weight management support:

Company:

- Background disease-related resource use in the model encompasses general practitioner visits, nurse visits and blood tests. Frequency of resource in each category are based on Ara et al. 2012. Resource use is applied irrespective of treatment for the full time horizon of the model.

- No other costs which imply treatment setting are included in the company's model.

Table 2: company's estimated background resource cost

Category	Quantity per year	Unit cost	Annual cost	Source
GP visits*	4	£232/hour	£154.67	Quantity per year: Ara *et al.* 2012 Cost of GP visit: GP - Unit costs (including direct care). PSSRU 2022 Cost of nurse visit: Band 6 Nurse. PSSRU 2022 Cost of blood tests : DAPS05, NHS Reference Costs 2021/2022
Nurse visits*	8	£57/hour	£76.00	
Blood tests	1	£2.96	£2.96	
Total annual cost			£233.63	

Section B3.5.2.1, company submission

EAG:

- Estimated specialist weight management service (SWMS) costs from clinical expert opinion, which were applied to all arms in the model for the entire time horizon (see table 2). EAG also presented the following scenarios for comparisons with diet and exercise and semaglutide, either with or without 2-year stopping rules for all active treatments:

a) Removing all SWMS costs from all arms

b) Removing SMWS costs for diet and exercise arm

c) Removing SWMS costs for diet and exercise arm and tirzepatide arm

No alternative background costs were included when SWMS costs were removed.

Table 3: EAG's estimated background resource cost (specialist weight management service costs)

Category	Quantity per year, year 1	Quantity per year, second and subsequent years	Unit cost	Source
Consultant visit	3	2	£152.14	Consultant led dietetics Service non-admitted face to face OP cost
Psychologist visit	3	0	£152.14	
Dietician visit	8	4	£98.43	Non-consultant led dietetics Service non-admitted face to face OP cost
Total annual cost, year 1	**-**	**-**	**£1,645**	**-**
Total annual cost, year 2 and subsequent years	**-**	**-**	**£698**	**-**

Section 5.4.1, EAG report

Costs for digital technologies for weight management support:

No costs associated with the emerging digital technologies for delivering specialist weight management services to manage weight-management medicine were included in the model, by either the company or the EAG.

Details for the indicative costs used in the NICE Early Value Assessments for digital technologies for providing specialist weight management services can be found in table 25 of the assessment report for HTE14 (covering digital technologies with a prescribing function) and table 8.4 of the assessment report for Guideline in Development-HTE10023 (covering digital technologies without prescribing).

Tirzepatide for managing overweight and obesity [ID6179]

Questions for NHS England

The response to the questions below is based on the following output from the first committee meeting:

- The target population proposed by the company, which is people with a BMI of 30kg/m2 or more with at least 1 weight-related comorbidity, is appropriate.
- The primary comparator for tirzepatide is likely to be diet and exercise support delivered via multidisciplinary team (MDT) services in primary care.

The proposed clinical service and associated costs are mapped to the SURMOUNT-1 trial which is the main evidence source in the company submission. NHSE has no specific recommendations as to setting of care, although it is likely that the majority of care would be by community led services in primary care with a minority in secondary care.

Currently no MDT approach to obesity management routinely delivered in the NHS, at present, in primary care. However, weight management pilots are being designed to evaluate Specialist Weight Management Service (SWMS) delivery outside of a secondary care setting. The nature of these pilots is still being defined and, whilst it has not been included in the response, the pilots could potentially provide a mechanism for firming up assumptions about the model of care delivery required to support treatment with tirzepatide, or other weight loss drugs.

Question 1. **How the multidisciplinary team (MDT) approach for obesity management is delivered in the NHS at present. Consider the services as they are today, indicating if the services described are covered by the weight management pilot.**

- Which professionals are included in the MDT?

There is no MDT approach to obesity management delivered in the NHS, at present, in primary care.

Within specialist services, the MDT approach, via SWMS aligned per NICE Clinical Guidance [CG 189] requirements for MDT support with pharmacotherapy and, whilst precise local service configurations will vary, it is generally understood by NHSE to include:

- Clinical Lead – Consultant Endocrinologist/Bariatric Surgeon
- Consultant / GP with special interest
- Specialist Dieticians
- nurses,
- psychologists and psychiatrists, and,
- exercise/physical activity professionals (E.g. physiotherapists).

- In which settings it is currently available and delivered (for example, primary and secondary care or secondary care only)?

An MDT approach is available, via SWMS, is delivered in specialist services only. There are several 'community-based SMWS' which are affiliated as satellite services of existing secondary care-based SWMS, which allow for access to and clinical governance from the SMWS clinical lead/consultant and the prescribing rights to be extended for the current available GLP-1's into a community setting.

We are aware that NICE has recently published an Early Value Assessment of remote and digital delivery of SWMS, some of which are being deployed locally in the NHS. However, there appears to be little evidence to date relating to the clinical effectiveness of these models of delivery, hence the EVA approach to build the evidence base.

- What are the eligibility criteria for access to MDT?

The eligibility criteria for SWMS and subsequent MDT varies by ICB. Also, to note, there are ICB's without SWMS and where SWMS do exist referrals can be restricted once services are at capacity.

However, typical eligibility criteria can include the following (all BMIs should be adjusted for ethnicity):

- GP referral
- >30 BMI ≥30 with Type 2 Diabetes or BMI ≥ 35 plus comorbidities or BMI ≥ 40 (we would emphasise that this is highly variable across ICBs)
- Insufficient change from weight management intervention (achieving/maintaining weight loss)
- Exclusion criteria are often used. This can include pregnancy, cardiac conditions and mental health or substance abuse issues that are not stable or sub-optimally controlled.
- How long does MDT last? Is there a limit?

NHSE cannot provide insight on this point as this will vary based on locally commissioned services. However, the understanding is they can often last for a year or more – but commonly two years. However, this is subject to clinical judgement and criteria set by the local commissioners.

- Is assessment needed for the eligibility of multidisciplinary services? If so, who is doing the assessment?

Initial review of current Clinical Pathway into the tiers of weight management is predominantly conducted by General Practice in line with the assessment guidance of overweight, obesity and central adiposity as per NICE CG189.

Generally, as part of the clinical management of weight associated comorbidities and increased risk, and not an opportunistic review.

Referral for assessment is made by General Practice based on NICE CG189 and the local ICB referral pathway.
Once referred; SWMS will generally undertake an initial assessment of the patient, and this assessment would usually include assessment/identification of weight-related and other relevant comorbidities, across physical and mental health, and functional wellbeing.

- What main components of the current multidisciplinary approach and service for obesity in the NHS are being adapted or updated? Please highlight the most relevant for the delivery of anti-obesity drugs.

There is no planned adaptation of SWMS.
A pilot of weight management drugs is currently being developed by DHSC/NHSE to assess how and what components of a typical SWMS and an MDT approach in specialist care can be delivered outside of a specialist setting. The pilots were being designed in line with the NICE recommendation for semaglutide in specialist weight management services.

NHSE are awaiting the committee's findings to shape the pilots going forward, should tirzepatide access be supported via multidisciplinary team (MDT) services in primary care.

Question 2. How the multidisciplinary team approach for obesity management is being adapted and updated, both with and without anti-obesity medication included. Please refer to the tables at the end of this section to complete relevant answers.

This submission is what NHSE propose would be required to deliver weight management services related to the treatment with anti-obesity medication. NHSE has no specific recommendations as to setting of care, although it is likely that the majority of care will be by community led services in primary care with a minority in secondary care. There is currently no MDT approach to obesity management delivered in primary care in the NHS at present.

- What will the updated MDT service delivery model consist of:

- Which professionals will be included?
- How often will an individual accessing this service be seen by each professional in a year (specifying first and subsequent years, if different)?

  Please use tables 1 and 2 to give your answer

The pilot programme will adapt the multidisciplinary team approach stated by NICE [CG189] for the purpose of evaluating access and acceptability (through NIHR evaluation) through a General Practitioner (not with special interest) led process for assessment for patient eligibility and appropriateness to be managed/prescribed the associated weight loss drugs and either:

- Assume all associated prescribing of the weight loss drug from initiation through to titration and maintenance and continued medical patient management.
- Referral to an existing SWMS to prescribe the weight loss drug from initiation through to titration and then, through a shared care model of patient management, General Practitioner to resume prescribing from the maintenance phase and all medical patient management
- Referrer to a digital provider of SWMS and Prescribing for GLP-1RA* (appropriateness of remote prescribing of 1st in class GLP-1 RA/GIP therapy to be considered in line with digital clinical safety models, DCB0129, and the management of patients with regards to no previous availability or BAU prescribing of specific drug and patient management in a standard care setting)

Wrap around MDT care speciality service provision outside of prescribing of the drug will be provided by either:

a) Locally (ICB) procured wrap around MDT services specifically for the pilot patients only

b) A Nationally procured digital delivery of wrap around MDT care specifically for the pilot patients only

- In which settings will it be available:
  - In which settings will the services be available and delivered?

NHSE has no specific recommendations as to setting of care, although it is likely that the majority of care will be by community led services in primary care with a minority in secondary care.

- Will this service be entirely run outside hospital settings or across settings including hospitals depending on which setting the individuals access and start the service?

NHSE has no specific recommendations as to setting of care, although it is likely that the majority of care will be by community led services in primary care with a minority in secondary care. As part of planned pilots of weight management drugs, it remains our intention to evaluate the feasibility of delivery of services across a range of settings, including remote and digital delivery and delivery through a hybrid model where management would be shared between specialist care and community.

- If run in a mixture of community and hospital settings, are different costs associated with these services in each setting?

NHSE has costed for a service with GP costs and a specialist care service with consultant costings where relevant. All other costs are assumed to be the same for the purposes of this submission.

Note that the proposed pilots are intended to gather further information on the relative cost-effectiveness of delivery models in different settings.

- Will specialist weight management services still exist and be an appropriate setting for tirzepatide treatment for people accessing these services?

Existing SWMS commissioned by local NHS commissioners are expected to continue in the current format. They were established to assess patient's suitability and readiness for bariatric surgery and that need is not expected to change.

- What are the eligibility criteria?
    - Is an assessment for eligibility going to be needed before the initiation of multidisciplinary service?

Yes, there will need to be an assessment for eligibility that includes inclusion and exclusion criteria and in particular psychological assessment informed by the relevant NICE recommendations but will also need to take account of system capacity.

- Are the eligibility criteria going to be the same or differ across settings where the multidisciplinary service will be available?

Eligibility criteria would be set by the ICB but informed by relevant NICE recommendations.

Will the multidisciplinary service be the same for all regardless of the use of pharmacological products, or will additional support be needed if tirzepatide is recommended?

The proposed clinical service and costs are specifically for tirzepatide and mapped to the SURMOUNT-1 trial and the proposed obesity prescribing pilots.

Please use tables 1 and 2 to give your answer

- Will any of the components of the multidisciplinary services not be not needed because of the use of tirzepatide?

No. There is currently no MDT approach to obesity management delivered in the NHS at present that maps to the SURMOUNT-1 trial. It is too early to say if any changes to the MDT approach to management in secondary care would be needed.

Please use tables 1 and 2 to give your answer

- How long will this service be accessible for?
  - Does the length of time the service is accessible depend on whether the individual is taking pharmacological treatment?

Please use tables 1 and 2 to give your answer

- If time limited, would the service be used as long as an individual is on pharmacological treatment or would tirzepatide continue to be prescribed without the MDT support in the long-term?

NHSE has suggested that the MDT support remains in place whilst the patient is on tirzepatide, which is in line with the MHRA licence (and not less than that approved).

As a new 1st in Class therapy the effectiveness and safety of the removal of the support as provided in the trial is unknown.

- Is there any further information on the design and costs of the services needed for delivering tirzepatide that NHSE would like the committee to be aware of?

NHSE has submitted additional information in the form of an appendix attached to the bottom of this document.

Please complete the following tables with estimated resource use and associated costs for the updated obesity management service delivery model. Specify a range of values where appropriate.

Table 1 – MDT delivered in the community with anti-obesity medication

As noted above the proposed clinical service and associated costs are mapped to the SURMOUNT-1 trial

Number of appointments by profession		Year 1	Year 2	Year 3	Coverage	Cost per slot (£)	Year 1	Year 2	Year 3
GP	10 min slots	21	3	3	-	£ 41.00	£ 861.00	£ 123.00	£ 123.00
Nurse	10 min slots	4.5	3	3	-	£ 18.55	£ 83.47	£ 55.64	£ 55.64
HCA	10 min slots	1	0	0	-	£ 7.14	£ 7.14	£ -	£ -
Nurse group	10 min slots	3	0	0	-	£ 18.55	£ 55.64	£ -	£ -
Clinical pharmacist	10 min slots	3	3	3	-	£ 11.29	£ 33.88	£ 33.88	£ 33.88
Dietician	30 min slots	5	4	4	-	£ 27.19	£ 135.97	£ 108.77	£ 108.77
Psychologist	30 min slots	5.5	3	3	0.33	£ 33.88	£ 62.11	£ 33.88	£ 33.88
Total per patient cost (GP Led)							**£1,239.21**	**£ 355.18**	**£ 355.18**
Total per patient cost (Consultant Led)						**£ 23.33**	**£ 868.21**	**£ 302.18**	**£ 302.18**

The breakdown of appointments is shown in the table below:

Visit	Purpose	Duration	Assumed Resource for costing	Activity / Skill	Assumptions
Stage 1: Patient Assessment, Counselling and Training					
1	HCA Review	10	HCA	Blood Pressure, Height & Weight	
1	Initial consult	45	GP/Consultant	Alternative to GP could be used, for example: - ANP (LTC management) / other health care professionals with LTC management experience. - Senior practice nurses (diabetes specialist) However, GP will be ultimate accountability for patient care. 45 mins to include psychological support assesment.	The screening & eligibility process for the clinical trial is not appropriate in routine setting. Alternative screening and eligibility activity is based on NHSE. clinical input.
1	Blood Test + thyroid test	N/A	N/A		
2	Patient Training	30	Nurse	Checklist review + patient education (could be group sessions)	
2	Patient Education & Dietary/exercise advice	30	Dietician	Dietetic advice and guidance	
2	Clinical Review and prescription validation	15	GP/Consultant	Prescription check	
3	Week 0 - Treatment initiation (2.5mg)	15	Nurse	Patient education could be in video format for some patients.	As per SURMOUNT-1 trial
Stage 2: Titration & Weight Management Support					
4	Week 4 - dose titration (5 mg)	20	GP/Consultant	Same as above - different skills can do this, needs to be a prescriber. Contra-inidcation considerations (polypharmacy) drives requirement for senior oversight. Recognition that this could change as more long term data becomes available.	As per SURMOUNT-1 trial
5	Week 8 - dose titration (7.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 dose titration (10mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
7	Week 16 dose titration (12.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
8	Week 20 dose titration (15mg)	20	GP/Consultant		As per SURMOUNT-1 trial
9	Week 24 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
10	Week 26 - Medicines Review	20	GP		Activity based on clinical input
Stage 3: Maintenance (Every 12 weeks thereafter)					
10,11	Week 36 + 48 (Year 1) - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
12-16	Week 60, 72, 84, 96 (Year 2) - Dietary/exercise advise	30	Dietician		As per SURMOUNT-1 trial
17-21	Week 108, 120, 132, 144 (Year 3) - Dietary/exercuse advise	30	Dietician		As per SURMOUNT-1 trial
Additional Costs					
N/A	Multi Disciplinary Team (MDT) Patient Review	15	GP/Consultant + Nurse + Clinical Pharmacist+ Psychologist	Costing will assume minimum 2 MDT discussions per patient per year. To start from week 26	Activity based on clinical input
N/A	Psychological Support	30	Psychologist / Psychiatrist	Costing will assume 1 in 3 patients will require psychologist support. Where psychologist support is required assume 5 appointments in year 1 (as per DHSC/NHS obesity prescribing pilots).	Activity based on clinical input
N/A	Sharps & disposal	N/A	N/A		Activity based on clinical input

Source for costs as follows:

- GP appointment – standard 9.22 mins – PSCC unit costs 2021/22 per surgery consultation with qualifications - Table 9.4.2 Unit Costs of health and Social Care 2022 (amended 13 July 2023).pdf (kent.ac.uk)
- GP practice nurse appointment – Table 9.3.1 same source
- Dietitian (AfC Band 5) band min for 2023/24 + 40% oncosts based on 37.5 hrs @ 39 weeks = 1,462.5 hours per year
- Psychologist (mix of assistant and counselling psychologist) (AfC band 6) then same approach as dietitian
- Pharmacist (AfC band 6) then same approach as dietitian

Table 2 – MDT delivered in the community without anti-obesity medication

N/A - There is currently no MDT approach to obesity management delivered in primary care in the NHS at present.

Category	No. per year, year 1	No. per year, 2nd & subsequent years	Anticipated duration of support	Costs per visit	Comments
GP visit					
Nurse visit					
Psychologist visit					
Dietician visit					
Other resource – please specify (add rows if needed)					

Table 3 – Specialist weight management services

Eligibility criteria – please specify anticipated eligibility criteria in the context of community-based MDT	NHSE has assumed eligibility as the target population proposed by the company, which is people with a BMI of 30kg/m2 or more with at least 1 weight-related comorbidity.
Anticipated proportion of people needing referral in the context of community-based MDT	NHSE has assumed the eligible population based on a BMI of 30kg/m2 or more with at least 1 weight-related comorbidity.
Anticipated duration of SWMS	NHSE have assumed weight management services remain in place whilst the patient is on treatment.

Appendix 1: Clinical Considerations

Clinical safety as a novel pharmacotherapy

As a novel first in class dual GLP-1 and GIP RA, new to the NHS, compulsory surveillance via the MHRA Yellow Card Scheme as per all new drug therapy will be appropriate.

Position in the clinical pathway

Pharmacotherapy represents one element of the approach to weight management as part of the wider obesity strategy. Therefore, consideration must be made as to where pharmacotherapy-based interventions will sit within the lifestyle and clinical pathway for obesity, how it will connect with other obesity interventions and the settings in which it will be delivered. It is also important to determine how patients who are not eligible or prefer to avoid drug therapy will access alternative evidence-based interventions for weight loss provided by commissioners – including local government as well as the NHS.

Service Requirements: Training & Education

Pharmacotherapy of this nature for the management of obesity has traditionally been delivered in a secondary care setting with access to a multi-disciplinary team with significant clinical experience managing this cohort of patients. Obesity is a complicated disease; aetiology is often complex and multi-faceted as is the approach to sustainable management. It should not be underestimated the significant time and training costs associated with upskilling clinical staff to provide a service that can be delivered safely and effectively alongside pharmacotherapy outside of secondary care.

Service Requirements: Workforce

Requirements for the workforce will be influenced by the size of the eligible population. Health Survey for England data reports that 26% of adults in England are living with obesity[1]. MHRA authorisation for Tirzepatide for adults is for patients with a BMI of 30kg/m² or more (obesity), as well as those with a BMI between 27-30kg/m² (overweight) who also have weight-related health problems. Hence additional workforce for this service will be necessary. Specific consideration should be given to where additional workforce will be sourced for new delivery setting without drawing on existing secondary care services or adding pressure to primary care.

This is perhaps most relevant around access to psychologists given the high association between obesity and psychological and psychiatric issues[2]. It is, therefore, essential that patients have an assessment by the appropriately skilled professional in order for psychological support to be tailored to their needs but to also ensure those that need psychiatric input are referred on. This is critical as the cohort of patients with significant mental health diagnoses were excluded from the SURMOUNT pilot population.

The BMA Mental Health Workforce 2022[3] report suggest the vacancy rate for clinical psychologists is 12% with 57% of staff reporting short staffing of clinical psychologists present during their last worked shift. The NHS Long Term Workforce Plan[4] modelling suggests that education and training places

for clinical psychology needs to expand by 26% by 2031 to meet anticipated demand. Given the likelihood of a reasonable proportion of eligible cohort requiring psychological input, this presents a key workforce constraint to consider.
In addition, the Workforce Plan suggests despite planned expansion of physiotherapy workforce and other allied health professions there will still be a 5% shortfall and 6-10% shortfall in supply by 2036/7 based on anticipated demand. This too, has the potential to impact the service required to deliver accompanying interventions to pharmacotherapy to ensure sustained effects.

Implications for wider NHS Services

An improvement in obesity and obesity related healthcare costs is expected with the introduction of weight loss drugs. Examination and understanding of long-term implications on wider NHS services is essential to ensure future demand can be responded to appropriately.

Unintended complications of new pharmacotherapy or resultant

1. Health Survey for England 2021-22. [Health Survey for England, 2021: Data tables – NHS Digital]
2. Sarwer et al. The Psychosocail Burden of Obesity. Endocrinology Metabolic Clinical Journal North America, Sept 2016. [The Psychosocial Burden of Obesity - PMC (nih.gov)]
3. BMA Measuring Progress Report. [bma-measuring-progress-of-commitments-for-mental-health-workforce-jan-2020.pdf]

NHS Long Term Workforce Plan. [NHS Long Term Workforce Plan (england.nhs.uk)]

Background information:

Lifestyle interventions included in SURMOUNT-1 for all participants (SURMOUNT-1 trial protocol):

Participants will consult with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counselling at Weeks 0, 4, 8 and 12 during dose escalation and then at Week 24 and every 12 weeks thereafter through 72 weeks.

Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact by study staff.

At Visit 3 and subsequent visits, study participants will receive diet counselling by a dietician/nutritionist, or equivalent qualified delegate, according to local standard. Dietary counselling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of:

• maximum 30% of energy from fat

• approximately 20% of energy from protein • approximately 50% of energy from carbohydrates

• an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure (TEE).

To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counselling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

At Visit 3 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week.

Schedule of activities: details of how weight management support was provided for all participants:

Activity	Timing of activity (study treatment weeks)	Additional detail
Providing diary to participant and instructing use	Weeks 0, 12, 24, 36, 48, 60 and 72	Training should be repeated as needed to ensure compliance
Review study diary, including drug compliance	Started week 4, continued every 4 weeks	NA
Lifestyle programme instructions	Weeks 0, 4, 8, 12, 24, 36, 48, 60 and 72	Counselling on diet and exercise to be performed by a dietician or equivalent qualified delegate, according to local standards; to include calculation of individualised energy requirement and methods to change dietary composition and amount of physical activity. Dietary counselling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of: • maximum 30% of energy from fat • approximately 20% of energy from protein • approximately 50% of energy from carbohydrates • an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure (TEE) To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counselling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed. Beginning at week 8, the lifestyle program instruction may be delivered by phone.
Review of diet and exercise goals	Started week 0, continued every 4 weeks	Training should be repeated as needed to ensure compliance

*provisions for changes in study conduct during exceptional circumstances, including pandemics included (relevant due to study period during COVID-19;

start date December 2019; primary completion date April 2022): remote visits, and diaries acquired alternatively, for example by delivery.

Current company and EAG modelling assumptions around weight management support:

Company:

- Background disease-related resource use in the model encompasses general practitioner visits, nurse visits and blood tests. Frequency of resource in each category are based on Ara et al. 2012. Resource use is applied irrespective of treatment for the full-time horizon of the model.

- No other costs which imply treatment setting are included in the company's model.

Table 2: company's estimated background resource cost

Category	Quantity per year	Unit cost	Annual cost	Source
GP visits*	4	£232/hour	£154.67	Quantity per year: Ara *et al.* 2012 Cost of GP visit: GP - Unit costs (including direct care). PSSRU 2022 Cost of nurse visit: Band 6 Nurse. PSSRU 2022 Cost of blood tests: DAPS05, NHS Reference Costs 2021/2022
Nurse visits*	8	£57/hour	£76.00	
Blood tests	1	£2.96	£2.96	
Total annual cost			£233.63	

Section B3.5.2.1, company submission

EAG:

- Estimated specialist weight management service (SWMS) costs from clinical expert opinion, which were applied to all arms in the model for the entire time horizon (see table 2). EAG also presented the following scenarios for comparisons with diet and exercise and semaglutide, either with or without 2-year stopping rules for all active treatments:

a) Removing all SWMS costs from all arms

b) Removing SMWS costs for diet and exercise arm

c) Removing SWMS costs for diet and exercise arm and tirzepatide arm

No alternative background costs were included when SWMS costs were removed.

Table 3: EAG's estimated background resource cost (specialist weight management service costs)

Category	Quantity per year, year 1	Quantity per year, second and subsequent years	Unit cost	Source
Consultant visit	3	2	£152.14	Consultant led dietetics Service non-admitted face to face OP cost
Psychologist visit	3	0	£152.14	
Dietician visit	8	4	£98.43	Non-consultant led dietetics Service non-admitted face to face OP cost
Total annual cost, year 1	**-**	**-**	**£1,645**	**-**
Total annual cost, year 2 and subsequent years	**-**	**-**	**£698**	**-**

Section 5.4.1, EAG report

Costs for digital technologies for weight management support:

No costs associated with the emerging digital technologies for delivering specialist weight management services to manage weight-management medicine were included in the model, by either the company or the EAG.

Details for the indicative costs used in the NICE Early Value Assessments for digital technologies for providing specialist weight management services can be found in table 25 of the assessment report for HTE14 (covering digital technologies with a prescribing function) and table 8.4 of the assessment report for Guideline in Development-HTE10023 (covering digital technologies without prescribing).

NHS England has been asked by NICE to provide the proposed model and costs of the clinical service that is required to deliver tirzepatide treatment in the NHS. This note should be read in conjunction with the attached completed NICE proforma

1. The proposed clinical service and associated costs are mapped to the SURMOUNT-1 trial which is the main evidence source in the company submission. We note that the trial population excluded large groups of patients with co-morbidities and therefore the generalisability of the findings of the trial needs to be interpreted with a degree of caution.

2. This proposed service model does not currently exist in the NHSE. The costs associated with the proposed service are therefore new costs as a direct consequence of having to deliver treatment with tirzepatide.

3. The patient pathway is broadly broken down into 3 stages

   Stage 1 is patient assessment, counselling, and training. Assessment includes both eligibility criteria, exclusion criteria as per the SURMOUNT-1 trial and clinical safety checks. Counselling includes dietary and physical activity education as per the SURMOUNT-1 trial as well as the benefits and risks of tirzepatide. If patients consent, then training on how to self-inject tirzepatide will be given

   Stage 2 is dose titration to the maximum tolerated dose of tirzepatide as in the SURMOUNT-1 trial. The number of visits reflects the SURMOUNT-1 trial. NHSE is aware that gastrointestinal adverse effects are common, and that some patients may need slower dose titration than others, which may require more visits to reach the maximum tolerated dose. NHSE is also aware of the need to monitor for safety given that tirzepatide is a new treatment in the NHS, and to help maximise adherence to treatment and reinforce dietary and physical activity education.

   Stage 3 is maintenance of treatment in responders for whom there will be on-going associated costs for as long as they are treated with tirzepatide. The frequency of visits reflects the SURMOUNT-1 trial with additional MDT overview of progress and prescribing

4. NHSE is aware that patients with obesity have a high burden of psychological issues, such as but not restricted to mood disturbance and low self-esteem. NHSE notes that the SURMOUNT-Trial applied the following exclusion criteria (Jastreboff et al NEJM 2022;387:205-216 Supplementary Appendix). Potential participants were excluded if they:
   - *Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years Note: Patients with MDD or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications*
   - *Have any lifetime history of a suicide attempt*

- *Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1 or 3, prior to randomization*

5. NHSE interpretation of the trial protocol is that a PHQ-9 score of 15 or more (moderate to severe depression) was an independent exclusion criterion

6. NHSE therefore questions the generalisability of the SURMOUNT-1 trial to patients in the NHS who may have significant psychiatric issues or have moderate to severe depression. NHSE recognises that this group of patients will need psychological support if they were to be treated with tirzepatide.

7. Based on this need and using evidence from patients who are screened for bariatric surgery, NHSE estimates that all patients will need some level of initial psychological assessment prior to commencement of tirzepatide, and some level of routine screening for psychological issues arising during the course of treatment. Based on experience with bariatric services and clinical opinion we estimate that 1 in 3 patients will need ongoing psychological support. Clinical opinion is that majority of these patients (estimated at 70%), could be managed by Talking Therapies and the remainder would need more intensive psychological input. NHSE has costed psychological intervention according to these estimates.

Sanjeev Patel
Clinical Advisor to NHSE
Clinical Lead for the Innovative Medicines Fund

Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

Dear Stakeholders,

The appraisal committee discussed the clinical and cost effectiveness of tirzepatide for the treatment of obesity at its meeting on 16 January 2024.

The committee was able to draw the following conclusions on the clinical and cost effectiveness of tirzepatide:

- The target population proposed by the company, that is people with a BMI of 30kg/m^2 or more with at least 1 weight-related comorbidity, is appropriate.
- The primary comparator for tirzepatide is likely to be diet and exercise support delivered via multidisciplinary team (MDT) services in primary care. But semaglutide might also be an appropriate comparator in people eligible for semaglutide in specialist weight management services (see TA875). When semaglutide is a comparator, it should be used according to the recommendations of TA875.
- The subgroup in SURMOUNT-1 reflecting the company's target population had a range of comorbidities but did not include people with type 2 diabetes. This introduced some uncertainty about the generalisability of the clinical effectiveness results and around which comorbidities should be defined as a weight-related comorbidity in the target population.
- It was likely that the highest tolerated dose of tirzepatide would be used and for most people this would be 15 mg.
- Evidence from SURMOUNT-1 shows that tirzepatide is an effective treatment for overweight and obesity compared with placebo at 72-weeks follow up. Network meta-analyses suggest that tirzepatide is more effective than semaglutide for some outcomes, namely weight loss and improvement of high-density lipoprotein levels.

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- The company's model was appropriate for decision making, but the assumption that people enter the model without certain complications or comorbidities does not necessarily reflect the population who would have tirzepatide in clinical practice.
- It is appropriate to assume that people who respond to tirzepatide will continue to take it in the long term for maintenance of weight-loss and no arbitrary stopping rule should be applied for responders to tirzepatide. Also, that a 2-year stopping rule for semaglutide is appropriate in line with recommendations in NICE's technology appraisal on semaglutide for managing overweight and obesity (TA875).
- The natural history of weight increasing with age is likely to occur in the tirzepatide arm as well as the comparator arms. So, it is unlikely that the treatment effect difference between the tirzepatide arms and the comparator arms would continue to increase indefinitely.
- It is uncertain how quickly the benefits associated with tirzepatide (such as weight reduction) would be lost after stopping treatment.
- It is uncertain whether the rate of loss of prediabetes reversal would differ between the diet and exercise support arm and active treatment arms after stopping.
- To estimate the proportion of people stopping tirzepatide due to lack of response (less than 5% of initial body weight loss) after 46 weeks, it is appropriate to use the closest available data from the SURMOUNT-1 trial for the company's target population, which was at 48 weeks.
- Of the 2 sources presented estimating the costs associated with diabetes, the EAG's approach using the UK Prospective Diabetes Study (UKPDS) data is preferred. The company's approach based on hospital admissions may have over-estimated the costs so is unlikely to be appropriate.
- Before it can make a recommendation on tirzepatide, the committee requires further information on the costs associated with delivering tirzepatide in a landscape in which weight management services are changing. It also requires

that further cost effectiveness scenarios are presented to explore some of the uncertainties identified during its deliberations. Therefore, the committee has not prepared draft guidance and has requested that NICE obtain the further information it requires.

NICE has requested further information from NHS England on the anticipated costs of delivering weight management in future. But NICE is also interested in the views of stakeholders on the conclusions the committee has reached so far, and also on the appropriate service delivery model for tirzepatide. In particular:

- The appropriate composition of the multidisciplinary team (MDT) that would deliver tirzepatide in clinical practice, including frequency of contact and follow up with patients, and the extent to which this resembles the support provided in the SURMOUNT-1 clinical trial.
- Whether the same treatment effect of tirzepatide would be expected with a lower level of support than provided in SURMOUNT-1.
- The duration of MDT-support: would it be time limited? Could tirzepatide prescribing continue, for example, into the maintenance phase (once target weight loss has been achieved), or would treatment be stopped if MDT support is no longer available?
- Should MDT-support differ according to whether anti-obesity medications are prescribed or not, and should it differ for each individual for any other reasons?
- What role may digital weight-management technologies play in the delivery of MDT services?
- People with type 2 diabetes were excluded from SURMOUNT-1 but may be eligible for tirzepatide for obesity (if recommended) or type 2 diabetes (NICE TA924). If tirzepatide is recommended for obesity, would adjustment to weight management services be needed for people with type 2 diabetes?

NICE also requests that the company provide analyses exploring uncertainties around the following:

- Proportion of people stopping semaglutide after 6 months due to less than 5% initial body weight loss in the model: explore impact by varying the value for proportion of people stopping semaglutide after 6 months.

- Costs of type 2 diabetes: as noted above, the committee preferred the EAG's approach to estimating the cost of type 2 diabetes but would welcome scenario analyses with other approaches.

- Increase in weight over time and treatment effect waning while on tirzepatide treatment: modelling an increase in weight over time according to natural history in both arms, and analyses exploring treatment effect waning of tirzepatide.

- Weight-regain after stopping treatment: exploring different assumptions for how quickly the benefits associated with tirzepatide (such as weight loss) would be lost after stopping.

- Rate of prediabetes reversal loss: a scenario assuming the rate of loss of prediabetes reversal after stopping treatment is the same in both active treatment and diet and exercise support arms.

- Annualisation of multi-year risk for events: exploring the level of uncertainty introduced into the model due to the compounding of the risk of events occurring over multiple years. For example, by comparing the initial risk of an event in a particular population from the appropriate risk equation with the modelled annualised risk for the same population over the same horizon predicted by the risk equation.

- Consideration of the likely duration of MDT services and whether tirzepatide would stop, or continue, if the duration of MDT services were to be time-limited: explore a range of stopping rules for tirzepatide to account for the uncertainty around how long MDT services will be available and how long tirzepatide would be used in clinical practice.

- Costs associated with different models of services: exploring different models for providing diet and exercise support, including consideration of whether there are

costs in addition to those relating to MDT support if anti-obesity medications are used outside specialist weight management services.

The committee is planning to reconvene to discuss tirzepatide on 12 March 2024. If you have any comments on the issues raised in this letter, please complete and submit the provided response form through NICE Docs, by 22 February 2024.

Kind regards,

Janet Robertson

Associate Director Technology Appraisals

NICE National Institute for Health and Care Excellence

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Stakeholder comment form

Deadline for comments 5pm on 22 February 2024. Please submit via NICE Docs.

Please use this form to comment on the accompanying letter Responses will be circulated to the appraisal committee and will be discussed at the second meeting for this topic on 12 March 2024.	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly and Company Limited (Lilly)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1.	**Executive Summary** As highlighted throughout ACM1, access to NICE-recommended pharmacological treatments for obesity is currently extremely limited in NHS England clinical practice due to capacity constraints and equity issues associated with specialist weight management services. As such, there is a substantial unmet need for people living with this chronic disease. In this context, it is positive news for people living with obesity that the Committee have concluded that: • The target population proposed (i.e., people with a BMI of 30kg/m^2 or more with at least one weight-related comorbidity) is appropriate.

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	• It is appropriate to assume that people who respond to tirzepatide will continue to take it in the long term for maintenance of weight-loss, and no arbitrary stopping rule should be applied for responders to tirzepatide. • The primary comparator for tirzepatide is likely to be diet and exercise support delivered via multidisciplinary team (MDT) services in primary care. We are grateful for the opportunity to provide further input to reaffirm the Committee's conclusions from ACM1 and support a setting-agnostic positioning for tirzepatide that will be paramount to addressing the current unmet need. The following responses seek to address concerns around: • the appropriate composition, intensity and duration of the primary care MDT support that would be required to deliver tirzepatide as an adjunct to diet and exercise in clinical practice, • the costs of managing Type 2 diabetes mellitus (T2DM), and • the long-term efficacy of tirzepatide. Lilly's responses are provided as a top-line summary below, with further details and supporting analyses in subsequent sections of this proforma. In all the requested scenarios, all doses of tirzepatide remain cost effective vs diet & exercise with ICERs well below £20,000 per QALY gained. **Composition, intensity and duration of the diet and exercise MDT primary care support (Response 2)** • Lilly suggests that the delivery of obesity management in primary care (including the delivery of tirzepatide) should use and align with existing models of care and management of other (sometimes more complex) chronic diseases. This could be achieved using an approach that mimics the SURMOUNT-1 lifestyle protocol in terms of intensity and phasing. • This approach could include: ○ **Initiation** by an appropriately trained prescriber, such as a GP (who is well-placed to prescribe tirzepatide given their existing role as the first point of care for people with obesity and are responsible for the management of their weight-related comorbidities); ○ **Dose-escalation period** consisting of one touchpoint every 4 weeks with advice to follow a reduced calorie diet and increased physical activity until the patient reaches an agreed maintenance dose (can be delivered by the primary care MDT); ○ **Medium-term maintenance** consisting of one touchpoint every 3 months for a year (can be delivered by the primary care MDT); ○ **Long-term maintenance** consisting of one annual touchpoint for a yearly review, similar to patients with other chronic diseases.

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	• This approach could be managed for the majority of patients in primary care using an appropriately trained prescriber (such as a GP) and other health care professionals. Most touchpoints (after initiation) could be delivered by a member of the primary care MDT (e.g., practice nurse, dietician, or healthcare assistant), and the lifestyle support could be delivered by phione. **Costs for T2DM (Response 9)** • Lilly is concerned that the EAG's (and Committee's) preferred source for the cost of T2DM represents an overly conservative assumption that does not capture all relevant costs incurred given that it omits direct drug treatment costs for T2DM. • Lilly has therefore explored various scenarios which include costs for TD2M that are more representative of the costs associated with T2DM in clinical practice compared with the UKPDS source preferred by the EAG. • Given the likely and notable underestimation of the annual cost of T2DM by the UKPDS source, Lilly invites the Committee to reconsider this issue. **Long-term efficacy of tirzepatide (Response 10)** • There is no evidence that the treatment effect of tirzepatide wanes over time in people who continue to receive therapy. Data from both SURMOUNT-1 and SURMOUNT-4 have demonstrated that tirzepatide continues to be highly effective at 72 and 88 weeks, respectively.[1, 2] • Lilly has explored various scenario analyses that apply a natural weight gain over time from the literature to people remaining on tirzepatide at different arbitrary timepoints, in order to provide reassurance to the Committee on this issue. • Despite the noteworthy lack of evidence for these scenarios, testing of these assumptions does not change the conclusion that tirzepatide is a cost-effective use of NHS England resources.
2.	**The appropriate composition of the multidisciplinary team (MDT) that would deliver tirzepatide in clinical practice, including frequency of contact and follow up with patients, and the extent to which this resembles the support provided in the SURMOUNT-1 clinical trial.** To enable people with obesity and weight related comorbidities to have access to pharmacological therapies that would improve their health and provide value to NHSE, Lilly considers that the most feasible and practicable approach to delivering obesity management in primary care (including the delivery of tirzepatide) is to use and align with existing models of care for primary care MDT support provided for other chronic diseases, such as T2DM. Within this existing model of care, Lilly would suggest following the SURMOUNT-1 protocol, which represents an appropriate and evidence-based approach for delivering tirzepatide and diet and exercise support in a primary care MDT setting.

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	Specifics of the SURMOUNT 1 Protocol (Lifestyle Programme):[3] • During the first touchpoint, counselling on diet and exercise was performed by a dietician or equivalent qualified delegate. This included a calculation of their individualised energy requirement and methods to change dietary composition and amount of physical activity. • Participants consulted with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counselling at Weeks 0, 4, 8 and 12 during dose escalation and then at Week 24 and every 12 weeks thereafter through to Week 72. • From Week 8, the Lifestyle Programme Instruction could be delivered by phone. • Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the trial were reinforced at each trial contact by study staff. • At Week 8 and subsequent visits, study participants received diet counselling by a dietician/nutritionist, or equivalent qualified delegate, according to local standard. Dietary counselling consisted of advice on healthy food choices and focused on calorie restriction using a hypocaloric diet with macronutrient composition of maximum 30% of energy from fat, approximately 20% of energy from protein, and approximately 50% of energy from carbohydrates. • An energy deficit of approximately 500 kcal/day compared to the patient's estimated total energy expenditure (TEE) (TEE was calculated in SURMOUNT-1 by multiplying the estimated BMR by 1.3 – the NHS England BMI & BMR calculator can also be used). • The hypocaloric diet was continued after randomisation and throughout the treatment period. If a BMI ≤22 kg/m^2 was reached, the recommended energy intake was recalculated with no calorie deficit for the remainder of the trial. • To encourage adherence, it was recommended that a 3-day diet and exercise diary be completed prior to each counselling visit. During each visit, the participant's diet was reviewed and advice to maximise adherence was provided if needed. • At Week 8 and all subsequent visits, participants were advised to increase their physical activity to at least 150 minutes per week. **Considerations for delivery in the NHS with a primary care MDT** The SURMOUNT-1 protocol for diet and exercise support alongside tirzepatide treatment can be implemented with a primary care MDT that aligns with existing models of care. This will reduce unnecessary referrals to SWMS which will free up resources and allow specialist services to focus on more complex cases. In the current NHS clinical setting, this could include the following considerations: • The MDT support could include a GP (or an appropriately trained prescriber) and other health care professionals (such as a dietician, practice nurse, or healthcare assistant), who would support the patient with achieving the NHS Live Well

recommended guidelines in conjunction with published NICE clinical guidelines 189 (CG189).[4, 5]

- **Initiation**: A GP (or an appropriately trained prescriber) would be the most appropriate initial touchpoint for patients with obesity because:
  a) they have extensive experience managing people with obesity per CG189,[4] and associated comorbidities like T2DM per NG28,[6]
  b) they have extensive experience identifying and initiating patients on incretin therapies since their launch 17 years ago, and
  c) they may already be familiar with tirzepatide for T2DM following publication of NICE TA924.[7]

  Per CG189 guidelines, GPs should seek to explore and identify comorbidities, environmental and social factors, psychosocial distress and psychological issues, with the aim of ensuring that individualised patient care is provided prior to commencing tirzepatide treatment.[4]

  When patients are prescribed tirzepatide in primary care via an appropriately trained prescriber, guidance on initiating treatment (such as training in self-administration) could be delivered by a different member of the MDT (e.g., practice nurse, qualified health associate, or healthcare assistant), similarly to how incretins are currently initiated in primary care. This might be on an individual basis or in a group-start setting.

- **Dose-escalation period:** During the dose escalation phase, tirzepatide would be titrated up according to a patient-centred shared management plan that is aligned to both the patient's goals and the summary of product characteristics (SmPC).[8] Diet and exercise support could be provided by the primary care MDT with the following recommendations aligned to the SURMOUNT-1 protocol:
  - One touchpoint every 4 weeks until the patient reaches an agreed maintenance dose
  - A reduced calorie diet (500 calorie deficit)
  - An increase in physical activity (increased to at least 150 minutes of physical activity per week).
- **Medium-term maintenance:** Once a patient has reached an agreed maintenance dose, ongoing diet and exercise support should continue for an additional year, with one touchpoint every 3 months.
- **Long-term maintenance**: After a year on medium-term maintenance, stable patients could transition to an annual review schedule, similar to patients with other chronic diseases (e.g., those stable on treatment for T2DM or hypertension). For patients receiving tirzepatide, it is not anticipated that the efficacy of the treatment would be meaningfully impacted by fewer touchpoints during the long-term maintenance (as detailed in Response 3). Tirzepatide treatment should continue as an adjunct to a reduced-calorie diet and increased

	physical activity, in line with the SmPC. This would enable patients to continue adhering to the NHS Live Well guidance.[5] These interventions are readily available within primary care and the support (including educational materials and a digital app) is already available via the NHS Weight Management Programme. Alternative options include the recent HTE14 which included five digital weight management technologies that could provide additional support. Once an appropriately trained prescriber has initiated tirzepatide, they could refer the patient to these digital weight management technologies who are equipped to mimic the support provided in the SURMOUNT-1 Lifestyle Programme. In line with the Committee's conclusion, that the primary comparator for tirzepatide is likely to be diet and exercise support delivered via MDT services in primary care, Lilly has considered the cost-effectiveness of *adding* tirzepatide to diet and exercise support provided in primary care (see Response 15 for more details). In this scenario, even if all the touchpoints outlined above were conducted by a GP, tirzepatide remains a highly cost-effective treatment..
3.	**Whether the same treatment effect of tirzepatide would be expected with a lower level of support than provided in SURMOUNT-1.** Data from other tirzepatide Phase 3 clinical trials suggest that a lighter-touch diet and exercise programme compared to the SURMOUNT-1 protocol would not meaningfully reduce the efficacy of tirzepatide. To compare between similar patient populations, both SURMOUNT-2 and SURPASS-2 were conducted in patients with T2DM, and both included an element of diet and exercise support. SURMOUNT-2 followed the same lifestyle management protocol as SURMOUNT-1 (details in Response 2), while SURPASS-2 included lifestyle advice only at the first touchpoint. Specifically, SURPASS-2 patients were told not to initiate an organised diet and/or exercise (weight reduction) programme during the study other than the lifestyle and dietary measures for diabetes treatment. While dietary advice may have been reviewed for each patient, there were no additional touchpoints to provide diet and exercise support. Despite the different levels of support, the mean reduction in body weight for tirzepatide 15 mg was similar in both studies: 14.7% and 13.1% in SURMOUNT-2 and SURPASS-2, respectively.[9, 10] Furthermore, it is apparent from the efficacy data of both SURMOUNT-1 and SURMOUNT-2 trials that the observed effect of tirzepatide on weight is primarily driven by the mechanism of action of the drug (demonstrated by the tirzepatide arms), and not by the extent of the support provided alongside it (demonstrated by the placebo arms). The mean body weight reduction was 22.5% and 14.7% for tirzepatide 15 mg versus 3.1% and 3.2% for placebo in SURMOUNT-1 and SURMOUNT-2, respectively.[11, 12] These data suggest that a lower level of support than the SURMOUNT-1 Lifestyle Programme protocol would not meaningfully reduce the efficacy of tirzepatide. Nevertheless, tirzepatide for weight management should still be prescribed as an adjunct to a reduced-calorie diet and increased physical activity, in line with the SmPC.

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4.	**The duration of MDT-support: would it be time limited? Could tirzepatide prescribing continue, for example, into the maintenance phase (once target weight loss has been achieved), or would treatment be stopped if MDT support is no longer available?** To align to the SmPC, tirzepatide for weight management should be administered as an adjunct to a reduced-calorie diet and increased physical activity. As detailed in Response 2, primary care MDT support equivalent to the SURMOUNT-1 protocol could be delivered in a phased approach. After a year on medium-term maintenance, stable patients could transition to an annual review schedule, similar to patients with other chronic diseases (e.g., those stable on treatment for T2DM or hypertension). For patients receiving tirzepatide, it is not anticipated that the efficacy of the treatment would be meaningfully impacted by fewer touchpoints during the long-term maintenance phase (as detailed in Response 3). Therefore, Lilly does not anticipate that the primary care MDT support provided along tirzepatide would be stopped, but the level of support required would change, consistent with models of care for other chronic diseases that are managed by the NHS in primary care.
5.	**Should MDT support differ according to whether anti-obesity medications are prescribed or not?** Primary care MDT support should not differ according to whether anti-obesity medications (AOMs) are prescribed, as Lilly considers that the need for diet and exercise support in patients with BMI ≥30 kg/m^2 with at least one weight related comorbidity remains the same. Considering the changing landscape for obesity management in NHS England clinical practice, it was considered most relevant for the future, and in line with the Final Scope of the appraisal, to consider the cost-effectiveness of *adding* tirzepatide to diet and exercise support provided in primary care. **Should MDT support differ for each individual for any other reasons?** In line with the CG189 guidelines and accompanying quality standards [QS15)], MDT support provided in primary care should be provided on an individualised basis. Primary care clinicians are well positioned to tailor care and treatment to a person's needs and personal preferences, taking into account their circumstances, their ability to access services and their coexisting conditions. Consistent with their role per the CG189 obesity management guidelines and more broadly as primary care practitioners, GPs are familiar with assessing and reviewing a patient's physical and psychological needs and ensuring that individualised care is provided to manage their condition. In this context, to measure a patient's physical and psychological outcomes and their health-related quality of life improvements while on tirzepatide treatment, SF-36v2 was used in SURMOUNT-1 to record patient reported outcomes. Tirzepatide demonstrated improvements from baseline versus placebo in all eight domains of the SF-36v2 (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning,

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	Role-Emotional, and Mental Health), as well as the Physical Component Summary and Mental Component Summary scores.
6.	**What role may digital weight-management technologies play in the delivery of MDT services?** The Early Value Assessment (EVA) [HTE14] highlighted the unmet need for interventions that can address the capacity constraints and unmet need in the obesity pathway. It recommended that five digital weight management technologies could provide potential benefit in delivering weight management services for adults who are eligible for weight management medicine, particularly for those unable or struggling to access specialist weight-management services, while more evidence is generated. Lilly believes that digital weight management technologies are an option to provide diet and exercise MDT support after tirzepatide has been prescribed by an appropriately trained prescriber within primary care. The technology can both ensure continuity of care and provide more flexible access to services and support for people with obesity receiving tirzepatide who are unable to travel or who prefer to access services remotely.
7.	**People with type 2 diabetes were excluded from SURMOUNT-1 but may be eligible for tirzepatide for obesity (if recommended) or type 2 diabetes (NICE TA924). If tirzepatide is recommended for obesity, would adjustment to weight management services be needed for people with type 2 diabetes?** Lilly do not consider that any adjustment would be needed for weight management services for people with T2DM.
Additional Cost-Effectiveness Scenarios Requested by NICE	
Lilly welcomes the additional scenarios requested by NICE to explore any relevant uncertainties. **In all the requested scenarios to explore uncertainties, all doses of tirzepatide remain cost effective vs Diet & Exercise with ICERs well below £20,000 per QALY gained.**	
8.	**Proportion of people stopping semaglutide after 6 months due to less than 5% initial body weight loss in the model: explore impact by varying the value for proportion of people stopping semaglutide after 6 months.** Lilly have explored varying the non-responder discontinuation rate for the semaglutide arm by 5% either side of the base case value, as presented below in Table 1. The prices used for semaglutide in this scenario are as follows: £73.25 for 0.25 mg, 0.5 mg and 1 mg, increasing to £124.53 for 1.7 mg and £175.80 for 2.4 mg (as per listing on the BNF). The impact on cost-effectiveness results is minimal, therefore Lilly considers the base case value appropriate.

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Table 1. Scenario Analyses for Semaglutide Primary Treatment Failure

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: Assumed 10% Primary Treatment Failure			
Tirzepatide (5.0 mg)	£4,691	0.482	£9,728
Tirzepatide (10.0 mg)	£4,266	0.417	£10,222
Tirzepatide (15.0 mg)	£5,905	0.523	£11,280
Scenario 1: Assumed 5% Primary Treatment Failure			
Tirzepatide (5.0 mg)	£4,532	0.480	£9,436
Tirzepatide (10.0 mg)	£4,106	0.415	£9,887
Tirzepatide (15.0 mg)	£5,745	0.521	£11,018
Scenario 2: Assumed 15% Primary Treatment Failure			
Tirzepatide (5.0 mg)	£4,836	0.484	£9,988
Tirzepatide (10.0 mg)	£4,410	0.419	£10,520
Tirzepatide (15.0 mg)	£6,049	0.525	£11,515

Footnote: cost-effectiveness results are presented for tirzepatide (5, 10 and 15 mg) vs semaglutide.
Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year; T2DM: type 2 diabetes mellitus.

9.

Costs of type 2 diabetes: as noted above, the committee preferred the EAG's approach to estimating the cost of type 2 diabetes but would welcome scenario analyses with other approaches.

Lilly acknowledges that there is always some uncertainty with calculating costs, particularly for complex comorbidities such as T2DM, and that various potentially relevant sources exist for quantifying the cost of T2DM. However, Lilly is concerned that the EAG's (and Committee's current) preferred source for the cost of T2DM represents an overly conservative assumption that does not capture all relevant costs incurred for several reasons:

- Firstly, this source (as noted by the EAG) omits "direct drug treatment costs for T2DM". Given the recognised progression of T2DM over time to require multiple pharmacological therapies, many of which have high acquisition costs, Lilly consider this to have notably underestimated the annual cost of T2DM in clinical practice.
- In addition, the EAG preferred cost omits inpatient costs, which the EAG suggests may be incurred for "general health reasons and so likely to be similar for the obese and those with T2DM without any comorbidities". Lilly considers this justification to lack validity, further underestimating the costs associated with T2DM, because:
    - It is uncertain whether inpatient costs are all attributed to complications; inpatient costs not attributable to complications would therefore not have been captured in the model;
    - The UKPDS inpatient costs were attributed to numerous complications that were not all captured in the model supporting this submission (e.g. amputation and eye disorders), and these costs will therefore not be accounted for.

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- Finally, the UKPDS study is based on a low-risk newly-diagnosed T2DM population, which represents a conservative estimate for patients with T2DM in clinical practice. It does not account for T2DM patients who have more advanced disease who would require more intensive treatment to manage micro- and macrovascular complications (e.g., heart failure, renal disease) from having higher HbA1c and longer duration of T2DM.

Given this, Lilly has explored various scenarios to help address any uncertainty and has summarised the results for these scenarios in Table 2. Scenario 1 uses costs that were sourced from Capehorn *et al.* (2021), with an annual cost of £940.86 for treatment of microvascular complications, and £551.89 for insulin and oral treatments. Unlike the UKPDS source, this source accounts for all key costs incurred (including direct costs for T2DM). This source was also used in TA875 and the resulting composite cost was ultimately considered appropriate by the EAG.[13, 14]

Lilly has also explored a more extreme scenario using the EAG preferred UKPDS cost, adjusted to account for the treatment costs for T2DM. The cost of direct drug treatments used in Scenario 2 was sourced from Capehorn *et al.* (2021),[13] as in the previous scenario, leading to a total annual cost of £1,225.89. Results for Scenario 2 are presented below. Importantly, it should be noted that this source remains associated with the numerous limitations highlighted above with regards to the underestimation of costs for complications not otherwise captured in the model, as well as the fact that the UKPDS focuses on a population of newly-diagnosed T2DM patients that does not account for patients with high-risk T2DM populations who incur more costs.

Lilly considers Scenario 1 may be more representative of the costs associated with T2DM in clinical practice. The results of Scenario 2 demonstrate that despite this extreme scenario, which uses the EAG's preference of UKPDS with the numerous limitations listed above, it does not change the outcome of the cost effectiveness results, and all three doses of tirzepatide remain well below £20,000 per QALY gained. We therefore request that the Committee reconsiders this issue.

Table 2. Scenario Analyses for Cost of T2DM

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: £1,771 from NHS Reference Costs			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Capehorn et al (2021) Microvascular Complications + Insulin and Oral Treatments (£1,492.75)			
Tirzepatide (5.0 mg)	£7,828	0.644	£12,153
Tirzepatide (10.0 mg)	£7,430	0.579	£12,829
Tirzepatide (15.0 mg)	£9,117	0.685	£13,304
Scenario 2: UKPDS Non-Hospital Costs + Estimated Treatment Costs (£1,255.89)			
Tirzepatide (5.0 mg)	£8,470	0.644	£13,150

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	Tirzepatide (10.0 mg)	£8,099	0.579	£13,984
	Tirzepatide (15.0 mg)	£9,831	0.685	£14,346

Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year; T2DM: type 2 diabetes mellitus.

10.

Increase in weight over time and treatment effect waning while on tirzepatide treatment: modelling an increase in weight over time according to natural history in both arms, and analyses exploring treatment effect waning of tirzepatide.

There is no evidence that the treatment effect of tirzepatide wanes over time in people who continue to receive therapy. Furthermore, the mechanism of action of tirzepatide (GLP-1/GIP agonism) does not provide a biological rationale for treatment effect waning. Nonetheless, given the Committee's request, a number of scenario analyses have been provided exploring the interaction of their two assumptions:

- Applying natural weight gain over time from the literature to people remaining on tirzepatide
- Testing the effect of applying this weight gain from different arbitrary timepoints: at the end-of-trial (extreme scenario); from the start of Year 3; from the start of Year 5

Lilly re-iterates that all such scenarios are arbitrary in nature and that the assumption that people regain weight while receiving tirzepatide treatment is not evidence-based. Testing these arbitrary assumptions nonetheless demonstrates that tirzepatide is a cost-effective use of NHS England resources, regardless of which scenario is applied.

Table 3. Scenario Analyses for Maintenance of Weight Loss

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: No weight gain while on treatment			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Weight gain in line with diet and exercise after end of trial follow-up			
Tirzepatide (5.0 mg)	£7,407	0.549	£13,493
Tirzepatide (10.0 mg)	£6,854	0.496	£13,823
Tirzepatide (15.0 mg)	£8,612	0.604	£14,268
Scenario 2: Weight gain in line with diet and exercise 2 years after end of trial follow-up			
Tirzepatide (5.0 mg)	£7,320	0.564	£12,980
Tirzepatide (10.0 mg)	£6,773	0.521	£13,009
Tirzepatide (15.0 mg)	£8,535	0.622	£13,724
Scenario 3: Weight gain in line with diet and exercise 3 years after end of trial follow-up			
Tirzepatide (5.0 mg)	£7,316	0.568	£12,881
Tirzepatide (10.0 mg)	£6,773	0.523	£12,943

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	Tirzepatide (15.0 mg) | £8,493 | 0.634 | £13,406 **Abbreviations:** ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year
11.	**Weight-regain after stopping treatment: exploring different assumptions for how quickly the benefits associated with tirzepatide (such as weight loss) would be lost after stopping.** As noted with Document B, Lilly acknowledges that there is some uncertainty surrounding the duration over which the treatment benefit of tirzepatide is lost following discontinuation. Lilly has therefore tested a range of scenarios (Table 4), and across all of them (including the most extreme scenario in which the treatment effect of tirzepatide is lost 1 year after stopping), tirzepatide remains highly cost-effective. **Table 4. Scenario Analyses for Maintained Treatment Benefit**

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: Treatment effect lost after 3 years			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Treatment effect lost after 2 years			
Tirzepatide (5.0 mg)	£7,410	0.634	£11,688
Tirzepatide (10.0 mg)	£6,986	0.231	£12,372
Tirzepatide (15.0 mg)	£8,649	0.670	£12,909
Scenario 2: Treatment effect lost after 1 year			
Tirzepatide (5.0 mg)	£7,619	0.611	£12,473
Tirzepatide (10.0 mg)	£7,325	0.525	£13,949
Tirzepatide (15.0 mg)	£9,035	0.651	£13,877

Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year

12.	**Rate of prediabetes reversal loss: a scenario assuming the rate of loss of prediabetes reversal after stopping treatment is the same in both active treatment and diet and exercise support arms.** The Final Scope for this appraisal specifies that tirzepatide as an adjunct to diet and exercise is compared with diet and exercise, as well as to two other GLP-1 RAs, each as an adjunct to diet and exercise. The Committee concluded that diet and exercise alone is the most relevant comparator. When it comes to considering the Committee's request, this raises a problem: it is not possible to "discontinue" diet and exercise, as the support will always be needed by a person with this chronic disease. It is only possible to discontinue active treatment (but not the diet and exercise support it is adjunct to). As a result of this, the model has to apply assumptions regarding the loss of prediabetes

reversal in the model for the diet and exercise arm, and it is not possible to exactly replicate the approach in the active treatment arm.

While exact alignment between arms is not possible, an additional scenario has been presented below (Table 5) in which the time point for loss of reversal of prediabetes in the diet and exercise arm has been aligned to the timepoint at which the diet and exercise arm average weight returns to baseline (8 years). While this scenario is likely to overstate the duration of prediabetes reversal in the diet and exercise arm, tirzepatide is still shown to be cost-effective.

Table 5. Scenario Analyses for Reversal of Prediabetes in Diet and Exercise

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: Prediabetes Reversal at 2 Years			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Prediabetes Reversal aligned with Average Return to Baseline Weight (8 Years)			
Tirzepatide (5.0 mg)	£8,489	0.641	£13,239
Tirzepatide (10.0 mg)	£8,063	0.576	£13,993
Tirzepatide (15.0 mg)	£9,702	0.682	£14,218

Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year

13.

Annualisation of multi-year risk for events: exploring the level of uncertainty introduced into the model due to the compounding of the risk of events occurring over multiple years. For example, by comparing the initial risk of an event in a particular population from the appropriate risk equation with the modelled annualised risk for the same population over the same horizon predicted by the risk equation.

Unfortunately, Lilly has not been able to fulfil NICE's request to compare the initial risk of an event in a particular population from the appropriate risk equation with the modelled annualised risk for the same population over the same horizon predicted by the risk equation. The reason for this is three-fold:

- Inputs for binary or categorical variables in risk equations (for example, patient race) cannot accurately reflect a patient population, which likely includes a proportion of patients in each possible category for these variables
- The long-term outcomes for the modelled patient population do not necessarily align with outcomes for the patient cohorts used to derive the risk equations, as the modelled long-term trajectories of surrogate endpoints (weight, SBP, HDL and total cholesterol) are not in line with general population trends

- The ten-year risk of developing complications observed in the model is reduced by mortality, which reduces the overall number of observed complication events

Given these limitations with the analyses suggested by the Committee, Lilly conducted various additional analyses to further explore the level of uncertainty introduced due to the compounding of risk events occurring over multiple years; a summary of the methodology and results of these analyses are presented below. In the base case, three risk equations are affected by this issue: T2DM (QDiabetes, 10 years), Initial CV Event for non-T2DM patients (QRisk3, 10 years), and obstructive sleep apnoea [OSA] (Erridge et al. 5 years). For both scenario analyses, T2DM was selected as an illustrative example given that the incidence of T2DM has the greatest impact on cost-effectiveness results compared to the other modelled events.

Analysis #1

The first analysis undertaken by Lilly involved determining the extent to which the per-cycle probability of developing T2DM would have had to be overestimated in the model in order for tirzepatide to no longer be cost-effective compared to diet and exercise (at a willingness-to-pay threshold of £20,000). The results determined that the per-cycle probability of developing T2DM would have to be overestimated by 87% or more for tirzepatide to no longer be cost effective across all doses. Exploring this scenario shows that this does not change the overall cost effectiveness results.

Analysis #2

The second analysis undertaken involved reducing the number of T2DM events occurring over the modelled time horizon by 25% and 50%, the results of which are shown below in Table 6. In both scenarios, tirzepatide remains cost-effective against diet and exercise, at all doses.

These analyses demonstrate that tirzepatide remains highly cost-effective, even in extreme unrealistic scenarios that assume the risk of T2DM has been substantially overestimated in the model due to compounding the risk of events. These analyses help to remove any uncertainty around this issue and support Committee decision-making by demonstrating that while the issue raised by the EAG is valid, its effect is immaterial.

Table 6. Scenario Analyses for Multi-Year Risk for Events

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: No adjustment to risk equation			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Reduction of T2DM incidence in all arms by 25%			
Tirzepatide (5.0 mg)	£7,821	0.636	£12,295
Tirzepatide (10.0 mg)	£7,572	0.572	£13,235
Tirzepatide (15.0 mg)	£9,139	0.674	£13,566

	Scenario 2: Reduction of T2DM incidence in all arms by 50%			
	Tirzepatide (5.0 mg)	£8,578	0.618	£13,882
	Tirzepatide (10.0 mg)	£8,329	0.562	£14,832
	Tirzepatide (15.0 mg)	£10,092	0.655	£15,411

Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year

14.

Consideration of the likely duration of MDT services and whether tirzepatide would stop, or continue, if the duration of MDT services were to be time-limited: explore a range of stopping rules for tirzepatide to account for the uncertainty around how long MDT services will be available and how long tirzepatide would be used in clinical practice.

Given the chronic nature of obesity, it would be illogical to suggest that tirzepatide be stopped, and Lilly notes that during the first Committee meeting, it was generally agreed that arbitrary time limits on therapy were not appropriate. Lilly also notes that the placebo data in the SURMOUNT-1 trial, alongside the clear dose–response relationship for tirzepatide arms, clearly show that the vast majority of the observed effect of tirzepatide is driven by the mechanism of action of the drug, and not by the nature of the support offered alongside it (see Response 3).

It is for the NHS to determine its service models, but Lilly recommends that diet and exercise continues throughout the duration of treatment, in line with the SmPC for tirzepatide. However, as previously detailed in Response 2, Lilly expects that primary care MDT support could be phased in intensity.

While urging the Committee to avoid including any arbitrary stopping rules in its guidance, Lilly has nonetheless provided scenario analyses in Table 7 with some arbitrary stopping rules applied (5 years, 10 years) in order to demonstrate tirzepatide remains highly cost-effective regardless of stopping rules.

Table 7. Scenario Analyses for Arbitrary Stopping Rules

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: No stopping rule for tirzepatide			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Discontinuation of tirzepatide at 5 years			
Tirzepatide (5.0 mg)	£1,754	0.292	£6,009
Tirzepatide (10.0 mg)	£2,035	0.248	£8,220
Tirzepatide (15.0 mg)	£2,359	0.288	£8,196
Scenario 2: Discontinuation of tirzepatide at 10 years			
Tirzepatide (5.0 mg)	£3,369	0.396	£8,518
Tirzepatide (10.0 mg)	£3,653	0.373	£9,789

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	Tirzepatide (15.0 mg)	£4,380	0.431	£10,160
	Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year			
15.	**Costs associated with different models of services: exploring different models for providing diet and exercise support, including consideration of whether there are costs in addition to those relating to MDT support if anti-obesity medications are used outside specialist weight management services.** Lilly has provided a scenario analysis in Table 8 assuming the diet and exercise MDT primary care support provided alongside tirzepatide is aligned with the approach outlined in Response 2. It should be noted that although Lilly anticipate that primary care MDT diet and exercise support would be provided by an appropriately trained prescriber alongside other health care professionals (such as a dietician, practice nurse, or healthcare assistant), for modelling purposes Lilly has applied more conservative cost and resource use assumptions (i.e. touchpoints are costed at GP rates irrespective of who is providing the touchpoint). Cost and resource use for this approach are outlined below: • Months 1–3 (initiation and dose-escalation period): touchpoint every 4 weeks, costed as a GP (however after initiation, can be with any member from the primary care MDT thereafter) • Months 4–16 (medium-term maintenance): touchpoint every 3 months (virtual or telephone) costed as a GP (however can be with any member from the primary care MDT) • Months 16+ (long-term maintenance): annual GP visit • It is assumed that the touchpoints detailed above will be approximately 10–15 minutes in duration and would be carried out either over the telephone or virtual unless requested by the patient or HCP • Costs for GP/nurse/primary care MDT are as per the Company submission • When these costs are applied, they are applied to diet and exercise and tirzepatide arms irrespective of whether a patient 'remains' on tirzepatide. Further, the existing resource use in the model is set to 0 (hence the decrease in total costs in this scenario) When these costs are applied, the conclusion on the cost-effectiveness of tirzepatide is not changed – tirzepatide 5, 10 and 15 mg remain highly cost-effective relative to diet and exercise only. **Table 8. Scenario Analyses for Primary Care MDT Costs**				
	Intervention	**Incr. costs (£)**	**Incr. QALYs**	**ICER (£/QALY)**
	Updated Company Base Case: No MDT Costs			
	Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
	Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
	Tirzepatide (15.0 mg)	£8,373	0.685	£12,218

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	Scenario 1: Primary Care MDT Costs Incorporated			
	Tirzepatide (5.0 mg)	£7,103	0.644	£11,028
	Tirzepatide (10.0 mg)	£6,689	0.579	£11,549
	Tirzepatide (15.0 mg)	£8,316	0.685	£12,135
	Footnotes: The timepoints above have been converted into weeks in the model **Abbreviations:** ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality- adjusted life year			

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: In the interests of openness and transparency, and to promote understanding of how recommendations are developed we intend to publish stakeholder comments received in response to the accompanying letter. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

1. Eli Lilly. Data on File. SURMOUNT-4 Clinical Study Report. 2023.
2. Eli Lilly. Data on File. SURMOUNT-1 Clinical Study Report. 2022.
3. Eli Lilly. Data on File. SURMOUNT-1 Protocol. 2021.
4. National Institute for Health and Care Excellence (NICE). Obesity: identification, assessment and management [CG189]. Available at: https://www.nice.org.uk/guidance/cg189. Last accessed: August 2023.
5. National Health Service (NHS). Live Well. Available at: https://www.nhs.uk/live-well/. Last accessed: February 2024.

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6. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management (NG28). Available at: https://www.nice.org.uk/guidance/ng28. Last accessed: August 2023.
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8. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics. Mounjaro (tirzepatide). Available at: https://mhraproducts4853.blob.core.windows.net/docs/2631e86db2378c4b5dac1e847d3c96ff63db38f5. Last accessed: November 2023. 2023.
9. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. New England Journal of Medicine 2021;385:503-515.
10. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet 2023.
11. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nature medicine 2022;28:2083-2091.
12. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine 2022;387:205-216.
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14. National Institute for Health and Care Excellence (NICE). Semaglutide for managing overweight and obesity [TA875]. Available at: https://www.nice.org.uk/guidance/TA875/. Last accessed: March 2023.

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Please use this form to comment on the accompanying letter Responses will be circulated to the appraisal committee and will be discussed at the second meeting for this topic on 12 March 2024.	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Obesity and metabolic surgery society (BOMSS)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are broadly in support of the direction of the guidance regarding Tirzepatide for obesity
2	We should make tirzepatide available by developing MDT services that are safe and cost-effective. The minimum requirements to achieve this includes: one physician/GP, a specialist

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	nurse (that can ideally prescribe) and a dietitian (again ideally that can prescribe). The MDT should also have access to psychological expertise as necessary.
3	The effect of the medication with this MDT composition is likely to be very similar to what was observed in the SURMOUNT -1 Trial. We know from other RCTs, that intensive MDT support adds only marginal weight loss or health gains.
4	Beyond 1 year of treatment, and assuming the patient is stable, the demands on the service will decrease. The patient can be assessed every 6 months by a single member of the team, whilst however still having access to the other members as necessary
5	We completely agree that any effective medication for obesity should be taken to long term for maintenance of weight-loss and no arbitrary stopping rule should be applied for responders to tirzepatide.
6	Considering the lack of resources, digital interventions should play a very important role in the management of people on pharmacotherapy as they can offer excellent support to patients and save time for healthcare professionals

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Please use this form to comment on the accompanying letter Responses will be circulated to the appraisal committee and will be discussed at the second meeting for this topic on 12 March 2024.	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Diabetes UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Eli Lilly - £49,259.33 Funding our Tackling Inequalities Commission Partnership ongoing Sanofi & Novo Nordisk – No funding received in last 12 months Partnership ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	*What role may digital weight-management technologies play in the delivery of MDT services?* Digital weight management services can play an important role in the delivery of MDT services. Research comparing the effectiveness of digital/remote and F2F services found the mean baseline

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	weight of those using digital weight management services was higher than those using remote or F2F, likely due to the weight stigma resulting in avoidance of group-based environments. Research by Diabetes UK found that for people with type 2 diabetes stigmatising exchanges with healthcare professionals can have a huge impact on both accessing and completing weight management services. For technologies to work it is important that people are referred without experiencing stigma within primary care. In addition, many people with type 2 diabetes report that receiving person-centred support, including emotional support, was key to successfully achieving their weight loss aims. Therefore, digital weight management services must ensure services are tailored to individual patients and provide appropriate mental health support. Research by Manchester University did see greater weight loss for the remote and digital groups compared to the F2F groups which reenforces the effectiveness of digital weight management services. However, although remote delivery had greater completion rate than F2F, digital delivery had a lower completion rate. As such a combined approach that maximises both the accessibility and support needed for patients utilising these services is needed. However, our own report on the NHS Diabetes Prevention Programme shows that key to patients was to have a choice between digital or face to face services, reenforcing the importance of clinicians considering personal preference to increase adherence. Additionally, many said they would prefer face-to-face sessions over digital due to the ability to have conversations and discuss things more easily face-to-face and so, despite potential other benefits of digital services, face-to-face groups should not be removed altogether. Alongside this, research has found that people who are limited users of the internet are 1.5 times more likely to be from Black, Asian or other minority ethnic backgrounds, and many of these have English as a second language and will require further support. There is also higher prevalence of diabetes amongst people with learning disabilities and there are higher proportions in the more severe category of obese (37% of people with learning disabilities compared to 30.1% of people without learning disabilities). Both groups are, therefore, at risk of being digitally excluded.
2	*People with type 2 diabetes were excluded from SURMOUNT-1 but may be eligible for tirzepatide for obesity (if recommended) or type 2 diabetes (NICE TA924). If tirzepatide is recommended for obesity, would adjustment to weight management services be needed for people with type 2 diabetes?* If tirzepatide is recommended for obesity, adjustments to weight management services for people with type 2 diabetes would not be needed as this treatment is based on a person living with obesity not with diabetes. The same MDT support would be needed for individuals taking tirzepatide for obesity as it would for other weight loss medications due to them being specialised in supporting weight loss. An individual with diabetes will still be supported by their diabetes specialist team however this may not include clinicians that have the specialist skills needed to support sustained weight loss.
3	
4	
5	
6	

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- Please underline all confidential information in turquoise. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'confidential information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: In the interests of openness and transparency, and to promote understanding of how recommendations are developed we intend to publish stakeholder comments received in response to the accompanying letter. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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NICE National Institute for Health and Care Excellence

Tirzepatide for managing overweight and obesity [ID6179]

Stakeholder comment form

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Please use this form to comment on the accompanying letter Responses will be circulated to the appraisal committee and will be discussed at the second meeting for this topic on 12 March 2024.	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novo Nordisk Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Appropriate service delivery model for tirzepatide** Thank you for giving us an opportunity to respond to the committee conclusions relating to the 16 January 2024 meeting to discuss tirzepatide for managing overweight and obesity [ID6179]. Novo Nordisk welcomes the committee's request for further information and additional analyses exploring the uncertainties in the company submission and economic modelling. We particularly appreciate the deeper consideration of the anticipated healthcare professional support and practicalities of delivering weight management services in the future, given the recent NHS policy initiatives launched in this area that aim to accelerate the development of – and access to – new care models for people living with obesity. In our experience, tier 2 weight management services are focused on diet, lifestyle, and behaviour rather than pharmacological intervention. These interventions are usually provided for 10-12 weeks and in most cases are not clinically led nor have a designated prescriber. A recent freedom of information request has shown that nearly 80% of tier 2 services are run by local councils **(1)**. Alternatively, GPs can refer patients to the NHS Digital Weight Management programme for tier 2 support. These services do not provide access to pharmacological treatments either. Given the complexity and the duration of the titration period for anti-obesity medicines, (liraglutide, semaglutide and tirzepatide), this setting does not align with the precedent agreed by the committee on the setting of care in TA875, the therapeutic indication of tirzepatide which requires the provision of the treatment as an adjunct to a reduced-calorie diet and increased physical activity **(2)** or the way patients were treated in SURMOUNT 1. Indeed, in SURMOUNT 1, dietetic consultations were carried out at weeks 0, 4, 8, 12, and then every 12 weeks in addition to consultations with experienced clinicians to ensure appropriate dose titration, advice regarding possible adverse events and review of co-morbidities given that nearly two thirds of the SURMOUNT 1 population had one or more weight related complications **(2)**. The financial impact on primary care needs to be carefully considered as part of this assessment, as the costs associated with this additional support have not been calculated. Furthermore, the education and training of primary care clinical teams who currently are not involved in the prescribing and management of pharmacotherapy for weight management needs to be addressed. Without investment in training

	and supporting the primary care workforce there could be an impact on the safe and appropriate use of weight management medications. There is a recognition that sustainable system transformation within obesity is critical to improve patient outcomes and reduce costs to the NHS. The Government, NHS England and NIHR have invested significant resources to build the evidence base to inform new model(s) of care for obesity in England with the following timelines: • The NICE Health Technology Evaluations (HTE) anticipates a four-year evidence generation period prior to assessing whether the technologies to provide access to weight management medicines can be used routinely on the NHS **(4)**. • The NHSE obesity pilot will help determine if medications can be used safely and effectively in non-hospital settings as well as a range of other weight management interventions **(2)**. • Early indications suggest that PCNs will receive £1109 for each patient who takes part in the pilot if general practitioners "identify patients and initiate prescribing." **(6)** • The National Institute for Health and Care Research (NIHR) will spend approximately three years evaluating the pilot for use of obesity medications outside of hospital setting to build a robust evidence base on the feasibility, acceptability, clinical outcome and cost to the NHS **(2)**. As such, until the evidence from these pilot programmes is analysed for feasibility, acceptability, clinical outcomes and cost, it would be premature and disruptive to divert from the model of care recommended in NICE guidelines. Existing and upcoming NICE guidance requires weight management medicines to be initiated in specialist weight management services, with the support of a multidisciplinary team (MDT). The 2023 NICE HTE Digital technologies for delivering specialist weight-management services to manage weight-management medicine: early value assessment states **(3)**: • 'Weight management medicine can only be accessed alongside a specialist weight-management service'. • 'Digital weight-management technologies are an option to deliver specialist weight-management services…they can be used for adults who are eligible for weight-management medicine'. • 'The technologies [delivering specialist weight-management services] provide support from a MDT of qualified healthcare professionals. This must include psychological support and monitoring to reduce the risk of harm, including from disordered eating'.

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	Mirroring the above guidance, the draft NICE guideline on overweight and obesity management (GID-NG10182), which is due to be published in March 2024, also recommends weight management medicines are initiated in specialist weight management services, under the care of a MDT **(4)**: • 'Consider referral to specialist overweight and obesity management services if: […] treatment with weight-loss medicines is being considered (p34). • 'Ensure the multidisciplinary team within a specialist overweight and obesity management service includes or has access to health and social care professionals who have expertise in conducting medical, nutritional, psychological and surgical assessments in people living with obesity and are able to assess whether surgery is suitable' (p75). Novo Nordisk hopes for a positive evaluation of these new model of care pilots in order to inform a sustainable, outcomes-led and clinically accepted future service model, but to do so, they must benefit from their full and stated evaluation. This will ensure patients receive a positive experience when taking pharmacotherapy and achieve the clinical outcomes they expect based on the trial evidence. We would also advocate for the three-year evaluation period to be used to overcome existing challenges in establishing equitable access to NICE-recommended obesity medicines in England, evidenced by the NHS Digital Innovation Scorecard. **(5)** The inequity in access to weight management medicines on the NHS has also been considered by the Society for Endocrinology and Obesity Management Collaborative which have published a joint statement to help healthcare professionals and commissioners 'ease the impact of rolling out GLP-1 analogues and future drugs for obesity on NHS resources' and 'offer some suggestions on the prioritisation of patients most in need of weight loss for specific medical reasons'. **(6)** The scale of the challenge within the current service – where commissioners and healthcare professionals' risk-stratify eligible patients to manage local resources – should be considered as part of any future review and expansion of service. For the reasons outlined above, Novo Nordisk believes that these mechanisms provide an appropriate way to support the managed entry of new anti-obesity medicines that ensures they are given to the patients most in need, appropriately manages NHS budgets and ensures that patients receive a positive experience in weight management services which aligns with the outcomes demonstrated in the clinical trials. It also ensures that the full benefits of these treatments are realised as part of a programme to promote long term sustainable weight loss.
2	**Generalisability of SURMOUNT-1** Given the proposed positioning of tirzepatide by the company, i.e., adults with BMI ≥30 and at least one weight-related comorbidity, there remain questions about

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	how reflective the trial cohort is likely to be of patients expecting to receive treatment with tirzepatide in primary care. SURMOUNT-1 enrolled participants with a mean body-mass index (BMI) of 38.0 (SD: ±6.81). 34.5% of participants enrolled had a baseline BMI of ≥30 to <35, with the majority (60%) having a baseline BMI ≥35. **(7)** Data published by NHS England's Quality and Outcomes Framework show the majority (64%) of people in England living with obesity were categorised as having obesity Class-1 (BMI of 30 to < 35) compared with just 24% in Class-2 (BMI of 35 to < 40). **(8)** The Steel et al (2017) **(9)** data show that only 1.7% of patients treated in Specialist Weight Management Services (SWMS) had a BMI <35. These findings suggest that the patient population enrolled in SURMOUNT-1 had a much higher baseline BMI than what would be expected across primary care clinical practice. Instead, this population may be more reflective to a population with higher baseline BMI treated within SWMS. As such, it may be informative for the company to provide scenario analyses exploring the clinical and cost-effectiveness of tirzepatide specifically in the BMI ≥30 to <35 and BMI ≥35 groups separately. This may then allow the committee to determine whether consistent weight loss is observed across different patient groups and specifically in patients with underlying clinical characteristics more in line with what would be expected in clinical practice.
3	**Long-term treatment duration and weight regain** The SURMOUNT-1 clinical trial enrolled patients with a mean age of 44.9 years (±12.5 years), with between 88.4% and 89.8% of participants completing the initial treatment period of 72-weeks. **(7)** As noted by the committee, in the company submission people who respond to tirzepatide are expected to continue to take it in the long term for maintenance of weight loss with no additional stopping rule being applied for responders. However, it was unclear from the evidence presented during the committee meeting whether the company model predicts a clinically plausible proportion of patients remaining on treatment, and therefore continuing to benefit from tirzepatide at various timepoints throughout the extrapolated period. There remains considerable uncertainty over whether patients would continue to remain on the highest dose of tirzepatide over time and therefore continue to achieve the same efficacy throughout the entirety of the maintenance phase or whether there would be a waning of treatment effect that may then impact rates of discontinuation. The Company also suggested that the maintenance dose could be flexible therefore it is uncertain whether patients will continue to achieve the same efficacy. It would therefore be informative if clarity could be provided as to the underlying assumptions and the clinical plausibility of values predicted by the company model relating to long-term rates of discontinuation and the specific factors driving discontinuation over time such as AEs, patient choice etc. Additionally, it would be informative if the Company would provide scenarios exploring the waning of efficacy over the maintenance phase if a proportion of patients chooses to reduce their dose.

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	It is reassuring to see that NICE have concluded that 'the natural history of weight increasing with age is likely to occur in the tirzepatide arm as well as the comparator arms' and that NICE have asked the company to explore different assumptions for how quickly the benefits associated with tirzepatide (such as weight loss) would be lost after stopping.
4	**Willingness to pay threshold** NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will consider the degree of certainty around the ICER. In the appraisal of semaglutide 2.4mg for the treatment of obesity (TA875) NICE determined that there would need to be a 'high level of confidence that the ICER was at the lower end of the range for acceptable cost effectiveness (£20,000 to £30,000 per QALY gained)', noting uncertainties particularly around the rate of weight regain, long-term treatment effectiveness and the possible implications for NHS delivery of services. **(10)** The committee has concluded that similar uncertainties are prevalent in the underlying evidence base (with the additional uncertainty introduced by the company's modelling of long-term treatment duration) and implementation strategy for tirzepatide; therefore, Novo Nordisk would request that to ensure consistency across the appraisals similar considerations are taken into account when determining the decision-making threshold.
5	**Correction on early responder rates for semaglutide 2.4mg** On slide 25 of the ACM presentation slide deck, NICE presented data informing the company's economic model pertaining to the proportion of patients discontinuing treatment due to non-response (failure to achieve 5% weight loss) at 6-months. It is quoted that for liraglutide 3.0mg 17% of patients are assumed to discontinue at 6-months based on TA875 and 10% for semaglutide 2.4mg based on expert opinion. However unpublished post-hoc analyses provided in the company submission for TA875 (redacted due to their confidential nature) showed that [redacted] of liraglutide treated patients discontinued after 16-weeks (consisting of a 4-week titration period followed by a 12-week maintenance dose) and [redacted] of semaglutide treated people discontinued treatment after 28 weeks (consisting of a 16-week titration period followed by a 12 week maintenance dose).These figures are again provided here in confidence to ensure the committee are basing their decisions on estimates of cost-effectiveness that utilise the most accurate underlying data possible.

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information in turquoise. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'confidential information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Tirzepatide for Managing Overweight and Obesity [ID6179]

Lilly Response to NHS England Stakeholder Responses

Executive Summary

Lilly would like to thank NICE for the opportunity to respond to the NHSE cost estimates of the services that would be needed to support the prescribing of tirzepatide in clinical practice. Lilly trusts that this additional response will allay any concerns NICE and the NHSE have related to the service provision of tirzepatide for the treatment of obesity and support the Committee in their intention to further explore the costs of the MDT primary care support that would be provided alongside tirzepatide prior to ACM2.

This response has three key sections. First, Lilly will address NHSE's proposed MDT costs that are detailed in 'ID6179 Questions for NHSE 26Jan24 NHSE Submission FINAL v2.0 200224' (hereby referred to as 'Questions for NHS England Document'), including a discussion of any proposed amendments, and presentation of accompanying cost-effectiveness results. Next, Lilly will respond to the key concerns raised in 'ID6179 NHSE submission tirzepatide FINAL v0.1 200224' (hereby referred to as 'NHS England Submission Letter'). Finally, Lilly will address any additional issues discussed within the Questions for NHS England document. Importantly, it should be noted that some of these issues have already been addressed in Lilly's Stakeholder Comments (submitted 23rd February 2024); therefore, Lilly has referred to these responses where possible and would suggest that these documents are read in conjunction.

Response to NHSE Estimates of MDT Costs and Proposed Service Provision

In response to NHSE's cost estimates for the MDT support delivered in primary care for tirzepatide (specifically the breakdown of appointments) detailed in the Questions for NHS England Document, Lilly wishes to re-iterate that significant weight loss with tirzepatide treatment will improve patient health and quality of life, and is also anticipated to lead to reduced resource use through avoidance of comorbidities, many of which are resource-intensive and contribute to a significant cost burden for NHSE. In addition, Lilly suggests that various revisions are made to the number, duration and assumed required resource of appointments, as detailed in red in Table 1. Justifications for each of Lilly's suggested revisions is provided in the far right-hand column and are then supplemented in the subsequent sections of this response. In addition, Lilly has highlighted which touchpoints are relevant for patients receiving diet and exercise support, the specified comparator for tirzepatide in the final scope for this appraisal.

It is important to note that NHSE's cost and resource use estimates for the MDT support provided for patients with obesity **are akin to MDT support provided in a secondary care setting, such as in SWMS**. Lilly would therefore like to re-iterate that for the majority of patients with obesity, it is expected that an MDT-led approach akin to that provided in primary care for patients with other chronic disease would be adequate and is in line with the SURMOUNT-1 protocol. This MDT-led approach in primary care aligns with what is currently available to people with obesity in primary care (as per CG189)[1] and relies on collaboration between primary care healthcare professionals, usually through the exchange of patient notes, rather than requiring additional resource-intensive in-person meetings. To provide evidence that primary care has an existing weight management service/workforce model for managing people with obesity, and this existing model replicates Lilly's proposal in Table 1, Lilly has funded General Practitioner Market Research[17]. This additional information from a representative sample (n=381) of primary care GPs in England and Wales, should alleviate any concerns NICE has around the implementation

of new and effective anti-obesity medications within primary care using the proposed service model in Table 1.

Cost-effectiveness results based on the visits summarised in Table 1 are presented in the following section of this response, alongside any relevant scenario analyses.

Table 1. Proposed appointments for MDT support delivered in primary care for patients with obesity in line with SURMOUNT-1 protocol

Visit	Purpose	Duration (mins)	Assumed resource	Activity/Skill	Required for D&E, or specific to those on tirzepatide	Justification for amendment(s)
Stage 1: Patient Assessment Counselling and Training						
~~1~~	~~HCA Review~~	~~10~~	~~HCA~~	~~Blood Pressure, Height & Weight~~	N/A	• Lilly does not consider an Health Care Assistant (HCA) review as a treatment-specific requirement for tirzepatide; instead, an HCA review would be required for any intervention in any therapy area (As per CG189 and good clinical care for obesity management with or without pharmacotherapy)[1] • Lilly therefore proposes removing this cost.
1	Initial consult and assessment	10	GP/ Consultant	Alternative to GP could be used, for example: • Advanced Nurse Practitioner (ANP) (Long Term Condition (LTC) management) / other healthcare professionals with LTC management • Senior practice nurses (diabetes specialist) • However, GP will be ultimately accountable for patient care. • 10 mins to include psychological support assessment as per CG189.	Relevant for both tirzepatide and diet and exercise	• This appointment would represent the starting point in the patient journey. It is expected that a 10-minute (rather than a 45-minute) consultation would be appropriate and realistic to enable a GP to assess their patient (including for psychological needs) as per CG189 and discuss treatment options, aligned with real-world primary care practice in the UK.[2] • For patients opting for tirzepatide treatment, this appointment would also be used to write-up an initial repeat prescription and schedule a second appointment for administration training by a nurse. In some surgeries, it may be possible for administration training to be carried out on the same day, enabling a patient to begin treatment immediately. • This consultation would be required for both patients opting to receiving tirzepatide, as well as those choosing diet and exercise intervention only, as both patient populations would require an initial consultation, an assessment for their obesity, and consequently a treatment decision.
~~1~~	~~Blood Test + thyroid test~~	~~N/A~~	~~N/A~~		N/A	• Blood and thyroid tests are not required for tirzepatide (not specified in the SmPC), so they should not be considered as a treatment-specific requirement. • Lilly therefore proposes removing this cost.
~~2~~	~~Patient Training~~	~~30~~	~~Nurse~~	~~Checklist review + patient education (could be group sessions)~~	N/A	• This is considered a duplicate of the 'Week 0 – treatment initiation (2.5mg)' cost in Week 3 as both comprise patient training/education. • Lilly therefore proposes removing this cost.

2	Patient education and dietary/exercise advice	30	Dietician or suitably qualified HCA	Diet advice and guidance	Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA.
~~2~~	~~Clinical Review and prescription validation~~	~~15~~	~~GP/Consultant~~	~~Prescription check~~	N/A	• Current prescribing practice in primary care does not require a separate prescription check. • Lilly therefore proposes removing this cost.
3	Week 0 - Treatment initiation (2.5mg)	20	Nurse	Patient education could be in video format for some patients.	Relevant for tirzepatide only	• Based on extensive patient and HCP feedback from Lilly's other injectable products, 40 minutes would be excessive for patients to receive training for the administration of tirzepatide. Lilly has therefore reduced this appointment duration to 20 minutes.[3, 4]
Stage 2: Titration & Weight Management Support						
4	Week 4 - dose titration (5 mg)	30	Nurse	Same as above - different skills can do this~~, needs to be a prescriber. Contra-indication considerations (polypharmacy) drives requirement for senior oversight. Recognition that this could change as more long term data becomes available.~~	Relevant for tirzepatide only	• To reflect the fact that some patients may experience adverse events during the dose titration phase, Lilly suggests that a 30-minute virtual appointment is provided when patients titrate from tirzepatide 2.5 mg to 5 mg so that patients can consult with the nurse about any issues they may be experiencing.
5	Week 8 - dose titration (7.5 mg)	15	Nurse			• Following the first dose titration from tirzepatide 2.5mg to 5mg (the first maintenance dose), Lilly has conservatively assumed that a 15-minute virtual consultation with a nurse would be the most that is required to check that the patient needs to proceed to the next titration step. • Consistent with the use of GLP-1 RAs in T2DM, it is assumed that titration would be carried out unless a patient experiences any issues (i.e. to achieve a patient's maximum tolerated dose). As such, Lilly consider that these appointments could be carried out virtually by a nurse, with the purpose of ensuring that the patient is not experiencing any issues (adverse events or otherwise) before dose escalation. • Although dose titration appointments are expected to vary by patient based on a patient-centred shared management plan that is aligned to both the patient's goals and the summary of product characteristics (SmPC), Lilly have presented a more realistic scenario that is more aligned with the use of GLP-RAs in T2DM where no nurse consultation is provided at Weeks 8, 12, 16 and 20 and is instead replaced with a single 15-minute nurse consultation at Week 26.
6	Week 12 dose titration (10 mg)	15	Nurse			
6	Week 12 - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA

7	Week 16 dose titration (12.5 mg)	15	Nurse		Relevant for tirzepatide only	• As per visit 4–6 above
8	Week 20 dose titration (15 mg)	15	Nurse			
9	Week 24 - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA
~~10~~	~~Week 26 - Medicines Review~~		~~GP~~		N/A	• This is considered a duplicate of the 'Muti Disciplinary Team (MDT) Patient Review' in the Additional Cost section below as both comprise an MDT review. Annual review is expected frequency, consistent with other chronic diseases in primary care. • Lilly therefore proposes removing this cost.
Stage 3: Maintenance (every 12 weeks thereafter)						
10,11	Week 36 + 48 (Year 1) - Dietary/exercise advice	30	Dietician or suitably qualified HCA		N/A	As per the SURMOUNT-1 protocol, it expected that dietary and exercise advice could be provided by a suitably qualified HCA
12-16	Week 60, 72, 84, 96 (Year 2) - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• As per the SURMOUNT-1 protocol, it expected that dietary and exercise advice could be provided by a suitably qualified HCA
17-21	~~Week 108, 120, 132, 144 (Year 3) - Dietary/exercise advise~~		~~Dietician~~		N/A	• It is expected that patients would have achieved their target weight loss by the end of Year 2 in the Maintenance Phase, and would be well-equipped to manage their diet and exercise, following NHS Live Well Guidance, without further intervention. Therefore, it is not anticipated that additional dietary and exercise advice would be required beyond Year 2 in the Maintenance Phase • Lilly therefore proposes removing this cost.
Additional Costs						

N/A	MDT patient review	10	GP/Consultant ~~+ Nurse + Clinical Pharmacist + Psychologist~~	Costing will assume ~~minimum~~ 1 MDT ~~discussions~~ per patient per year. To start from week 52	Relevant for tirzepatide only	• In primary care, an MDT patient review would likely involve a GP independently reviewing patient notes from supporting nurse(s), dietician(s) or other HCAs, rather than requiring an in-person meeting with all three professionals present. Lilly therefore proposes removing nurse, clinical pharmacist and psychologist costs. • Consistent with annual reviews performed in primary care for other chronic diseases, it is also expected that such a review would occur on an annual basis from the end of Year 1, rather than from Week 26 where the maintenance phase has not yet been reached.
N/A	~~Psychological support~~		~~Psychologist / Psychiatrist~~	~~Costing will assume 1 in 3 patients will require psychologist support. Where psychologist support is required assume 5 appointments in year 1 (as per DHSC/NHS obesity prescribing pilots)~~	N/A	• Patients requiring psychological support would be provided it (as per CG189 and good standards of clinical care), regardless of whether they receive tirzepatide treatment or not. It is not a cost that is specifically attributed to the use of tirzepatide (and would apply equally to diet and exercise, or even no intervention). • Lilly therefore proposes the removal of this cost as it is not relevant to consider in the economic analysis for tirzepatide.
N/A	Sharps & disposal	N/A	N/A		N/A	N/A – no amendments proposed

Cost-Effectiveness Results

Scenario 1 – Lilly-proposed MDT support without nurse titration touchpoints:

Table 3 presents the cost-effectiveness results for tirzepatide 5, 10 and 15 mg versus diet and exercise using the MDT support costs outlined in Table 1, which have been adjusted from NHSE's proposed costs based on existing evidence and to align with primary care clinical practice.

Although it is expected that dose titration will vary by patient according to a patient-centred shared management plan that is aligned to both the patient's goals and the SmPC, this scenario does not include a nurse consultation at Weeks 8, 12, 16 and 20, and instead includes a single 15-minute nurse consultation at Week 26 as this is this was considered to be a more realistic scenario which may be more practicable in NHSE clinical practice. Crucially, this is also more aligned with the current support provided for patients with T2DM who are initiating tirzepatide. This scenario (as well as those below) use the same unit cost sources proposed by NHSE on Page 11 of the document named 'ID6179 Questions for NHSE 26Jan24 NHSE Submission FINAL v2.0 200224'.

Overall, these results demonstrate that the revised costing of the MDT-led approach in primary care does not change the conclusion that tirzepatide is a highly cost-effective use of NHS England resources.

Table 2. Scenario analyses exploring removal of dose titration appointments for MDT support delivered in primary care for patients with obesity

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,094	15.997	-	-	-
Tirzepatide (5.0 mg)	£28,702	16.641	£7,607	0.644	£11,811
Tirzepatide (10.0 mg)	£28,232	16.576	£7,138	0.579	£12,325
Tirzepatide (15.0 mg)	£29,874	16.682	£8,780	0.685	£12,812

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 2 – Lilly-proposed MDT support costs:

Table 3 presents a scenario analysis in which the frequency of appointments and cost sources remain consistent with Scenario 1, but assuming that four touchpoints take place during the titration period, aligned with NHSE's proposed number of touchpoints during this period.

While Lilly would re-iterate that this scenario is not aligned with the use of GLP-RAs in primary care for T2DM, this scenario analysis finds that tirzepatide remains a highly cost-effective use of NHS England resources, with ICERs that remain generally consistent with Scenario 1.

Table 3. Cost-effectiveness results for tirzepatide based on revised appointments for MDT support delivered in primary care for patients with obesity

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER vs D&E (Cost/QALY)
Diet and Exercise	£21,094	15.997	-	-	-
Tirzepatide (5.0 mg)	£28,658	16.641	£7,564	0.644	£11,743
Tirzepatide (10.0 mg)	£28,233	16.576	£7,139	0.579	£12,327

Tirzepatide (15.0 mg)	£29,929	16.682	£8,834	0.685	£12,891

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio

Scenario 3 – NHSE-proposed MDT support costs applied for both treatments:

Table 4 presents a scenario analysis in which the NHSE's proposed costs have been applied to the tirzepatide arm as well as the diet and exercise arm (where relevant, adding ~£600 to the diet and exercise arm total costs). This scenario is more aligned with Lilly's proposed MDT costs, but remains overly conservative for reasons outlined in Table 1. Nevertheless, this scenario analysis finds that tirzepatide remains a highly cost-effective use of NHS England resources.

Table 4. Estimates of NHSE costs ICER results

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,767	15.997			
Tirzepatide (5.0 mg)	£30,514	16.641	£9,747	0.644	£15,133
Tirzepatide (10.0 mg)	£29,896	16.576	£9,130	0.579	£15,764
Tirzepatide (15.0 mg)	£31,781	16.682	£11,015	0.685	£16,073

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 4 – NHSE-proposed MDT support costs applied to tirzepatide only:

Table 5 presents a scenario analysis in which NHSE's proposed costs have been applied to the tirzepatide arm only, aligned with NHSE's proposition. Although this scenario is considered unrealistic for the reasons outlined in Table 1 and due to the fact that individuals with obesity not treated with tirzepatide would still incur some of the same costs, this scenario analysis finds that tirzepatide remains a highly cost-effective use of NHS England resources.

Table 5. Estimates of NHSE costs ICER results only applied to TZP arm:

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,184	15.997			
Tirzepatide (5.0 mg)	£30,514	16.641	£10,330	0.644	£16,038
Tirzepatide (10.0 mg)	£29,896	16.576	£9,712	0.579	£16,770
Tirzepatide (15.0 mg)	£31,781	16.682	£11,598	0.685	£16,923

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Summary

Overall, these results demonstrate that tirzepatide is a highly cost-effective use of NHSE resources, even when overly conservative and unrealistic assumptions surrounding the level of MDT support provided alongside tirzepatide treatment are used in a primary care setting. Compared to the ICERs when the NHSE-proposed MDT costs (Scenario 4) are used, the ICERs for Lilly's proposed MDT costs (Scenario 1) only vary by ~£5,000 for tirzepatide 5 mg and ~£4,000 for tirzepatide 10 and 15 mg versus diet and exercise, driven by an additional ~£2,000 tirzepatide cost and a reduction of ~£1,000 in diet and exercise costs in the extreme NHSE scenario. These scenario analyses therefore exemplify the significant costs that are averted from

tirzepatide treatment in the long-term due to the avoidance of costly comorbidities, which greatly outweigh any variation in the level of diet and exercise support provided alongside tirzepatide.

Responses to NHS England Submission Letter

This section focusses on responding to the ***key issues*** raised in the NHSE England Submission Letter, with the aim of supplementing the justifications provided in Table 1. Responses to any additional issues raised in the Questions for NHS England Document are provided in the next part of this response.

1. ***"The proposed clinical service and associated costs are mapped to the SURMOUNT-1 trial which is the main evidence source in the company submission. We note that the trial population excluded large groups of patients with co-morbidities and therefore the generalisability of the findings of the trial needs to be interpreted with a degree of caution."***

Response:

The Company wish to clarify that in contrast to NHSE's interpretation, SURMOUNT-1 only excluded a small number of comorbidities for the overall population. Specifically, as per the SURMOUNT-1 protocol, only the following five conditions were excluded:

- Type 1 Diabetes or Type 2 Diabetes
- a history of chronic or acute pancreatitis
- family history or personal history of MTC or multiple endocrine neoplasia syndrome type 2
- a history of *significant active or unstable* MDD or other severe psychiatric disorders within the last 2 years, or
- any lifetime history of a suicide attempt

The other eligibility criteria in the SURMOUNT-1 protocol related to comorbidities (i.e. where patients has to have at least one of the following comorbidities: OSA, CVD, hypertension or dyslipidaemia) **only applied to patients with a BMI <30 and ≥27 kg/m^2** – i.e. this criteria did not apply to patients with a BMI ≥30 kg/m^2. As such, there was no restriction on the number or type of comorbidities that patients with a BMI ≥30 kg/m^2 could have, provided they did not have the five excluded conditions listed above.

Given this, the patient population from SURMOUNT-1 had a broad range of baseline weight-related comorbidities that are reflective of those seen in clinical practice (including but not limited to hypertension, dyslipidaemia, OSA, ASCVD, osteoarthritis, anxiety/depression, PCOS, NAFLD, asthma/COPD, and gout), as well as a broad range of pre-existing conditions (listed in Table GPHK.8.11 on Page 553 in the SURMOUNT-1 CSR).[5] In fact, within SURMOUNT-1, 62.8% of participants had one or more comorbidities.[5]

2. ***"This proposed service model does not currently exist in the NHSE. The costs associated with the proposed service are therefore new costs as a direct consequence of having to deliver treatment with tirzepatide."***

Response:

Contrary to NHSE's suggestion, Lilly's proposed service model for tirzepatide in primary care aligns with what is currently available and recommended for patients with obesity in primary care as per CG189.[1] Unlike a secondary care MDT, a primary care MDT-led approach may include (but is not limited to) GPs, pharmacists, healthcare assistants, and practice nurses who collaborate through the exchange of patient notes.

Importantly, these healthcare professionals already manage patients with overweight or obesity by providing lifestyle support, including dietary and exercise advice. Moreover, there are several resources available to support discussions in primary care in both matters:

- Dietary advice – The NICE Clinical Knowledge Summary on Obesity provides specific dietary advice and is a useful resource for primary care physicians.[6] Should further advice tailored to the individual be required, community dietician services are accessible to primary care on referral.
- Exercise – Guidance and support are available in the NICE Physical activity: brief advice for adults in primary care (PH44),[7] NICE Clinical Knowledge Summary on Obesity,[6] and the UK Chief Medical Officers Physical Activity Guideline.[8] Primary care clinicians are well placed to provide individualised advice on local facilities and, where available, exercise programmes on referral, as described in the NICE guideline on Physical Activity: exercise on referral (PH54)

These resources describe recommended practices for the management of patients with overweight or obesity, with or without the use of anti-obesity medications. As per Table 1, these costs should therefore not be specifically associated only with the use of tirzepatide.

To provide NICE with reassurance that the proposed service model exists within primary care for people with obesity and at least one weight-related comorbidity, Lilly conducted Market Research with GPs in England and Wales. Respondents were provided with the hypothetical situation of managing a patient with a BMI ≥30 kg/m2 with at least one weight related comorbidity. Out of 381 respondents, 90% were aware of CG189. Of these, a further 73% followed these guidelines always or very frequently. In terms of what GPs currently offer these patients, 78% already offer specific diet and exercise advice, and 94% has access to a dietician or qualified healthcare professional to provide diet and exercise support. To verify existing weight management services in primary care and the community are already being utilised for people with obesity, 88% of GPs confirmed that they use community-based diet and exercise services. For the full report and methodology, please see the Lilly Market Research Report [17].

Primary care services currently manage the obesity population and therefore must have a service model in place. In particular, the target population are already being seen within primary care for the management of their comorbidities and therefore no further resource investment would be required.

3. "The patient pathway is broadly broken down into 3 stages."

> ***"Stage 1 is patient assessment, counselling, and training. Assessment includes both eligibility criteria, exclusion criteria as per the SURMOUNT-1 trial and clinical safety checks. Counselling includes dietary and physical activity education as per the SURMOUNT-1 trial as well as the benefits and risks of tirzepatide. If patients consent, then training on how to self-inject tirzepatide will be given"***

Response:

Lilly agrees that patient assessment would take place when a patient with obesity and one weight-related comorbidity presents to primary care. However, Lilly would like to emphasise that regardless of intervention choice, this assessment should follow CG189, in which it is recommended that primary care providers explore and identify any comorbidities and underlying factors (e.g., environmental and social factors, psychosocial distress and psychological issues) with the aim of providing individualised patient care. Once any comorbidities and underlying factors are identified and managed, then either lifestyle intervention alone or adjunct to treatment

with a pharmacological interventions (e.g. tirzepatide if recommended) can be discussed. Lifestyle intervention could include behavioural interventions, physical activity, and dietary approaches.

The decision to start treatment should be made after discussing the potential benefits and limitations with the patient, including the mode of action, clinical efficacy, adverse effects, and monitoring requirements. Once the decision is made to initiate tirzepatide, we would suggest that Lilly's "Initiation" phase, as detailed in our previous response (Stakeholder Comments), is followed. Tirzepatide treatment should:

- Form part of an integrated approach to weight management, which should include advice, support, counselling on diet and physical activity, and behavioural strategies as per SURMOUNT-1 protocol.
- Be monitored for the effect of pharmacological intervention, and reinforce lifestyle advice and adherence through touchpoints, as per SURMOUNT-1 protocol.

Training on the administration of tirzepatide can be provided in a number of ways, similar to how incretin therapies (including tirzepatide) are currently initiated in primary care for patients with T2DM. This includes 1:1 training, group starts, and digital video resources.

> ***"Stage 2 is dose titration to the maximum tolerated dose of tirzepatide as in the SURMOUNT-1 trial. The number of visits reflects the SURMOUNT-1 trial. NHSE is aware that gastrointestinal adverse effects are common, and that some patients may need slower dose titration than others, which may require more visits to reach the maximum tolerated dose. NHSE is also aware of the need to monitor for safety given that tirzepatide is a new treatment in the NHS, and to help maximise adherence to treatment and reinforce dietary and physical activity education."***

Response:

NHSE's proposed Stage 2 should reflect Lilly's previously proposed stages of delivery of tirzepatide within primary care, specifically the "Dose-Escalation Period" outlined in Response 2 as part of Lilly's Stakeholder Comments. Lilly agrees that tirzepatide would be titrated up according to a patient-centred shared management plan that is aligned to both the patient's goals and the summary of product characteristics (SmPC), but this does not necessarily necessitate additional touchpoints. Lilly recommends that the number of touchpoints should be no greater than the SURMOUNT-1 protocol, with a touchpoint every 4 weeks until the patient reaches an agreed maintenance dose.

Lilly would also like to highlight that SURMOUNT-1 did not titrate all patients to a maximum tolerated dose as noted by NHSE. Instead, in SURMOUNT-1, participants were randomised to either 5 mg (n=630; 24.8%), 10 mg (n=636; 25.1%), 15 mg (n=630; 24.8%) tirzepatide or placebo (n=643; 25.3%) to align with regulatory trial design requirements. All doses showed clinically meaningful and statistically significant weight reductions compared to placebo.[9]

Regarding gastrointestinal side effects, SURMOUNT-1 demonstrated that these are generally mild to moderate in severity, occur more often during dose escalation and decrease over time. As such, it is anticipated that experienced clinicians, including nurses, would be able to counsel patients on these side effects and provide supportive guidance, which would limit the need for additional touchpoints beyond those in the SURMOUNT-1 protocol. Moreover, as incretin therapies have been in routine clinical practice for 17 years, there is now substantial experience of initiating and titrating incretin therapies in primary care. Consequently, primary care teams are best placed to provide this support efficiently and meet patient needs.

Finally, as per the SURMOUNT-1 protocol, Lilly agrees that adherence to treatment and diet and exercise should be reinforced. However, this would not require additional touchpoints or resources compared to existing CG189 recommendations, given that the CG189 guidelines already recommend reinforcing lifestyle or behavioural interventions as best practice and is a service model already being followed by primary care.

> ***"Stage 3 is maintenance of treatment in responders for whom there will be on-going associated costs for as long as they are treated with tirzepatide. The frequency of visits reflects the SURMOUNT-1 trial with additional MDT overview of progress and prescribing"***

Response:

Lilly would like to draw attention to the "Medium-term Maintenance" and "Long-term Maintenance" stages included in Response 2 provided in Lilly's Stakeholder Comments, as these broadly align with NHSE's proposed Stage 3. As per this response, after a year on medium-term maintenance, stable patients could transition to an annual review schedule, similarly to patients with other chronic diseases (e.g., those stable on treatment for T2DM or hypertension).

For patients receiving tirzepatide, it is not anticipated that the efficacy of the treatment would be meaningfully impacted by fewer touchpoints during the Long-term Maintenance stage (as detailed in Response 3 of Lilly's Stakeholder Comments). Tirzepatide treatment should continue as an adjunct to a reduced-calorie diet and increased physical activity, in line with the SmPC. This would enable patients to continue adhering to the NHS Live Well guidance.

Given the above, the only ongoing costs associated with tirzepatide treatment during Stage 3 would be an annual review appointment with a primary care healthcare professional, as detailed in Lilly's proposed costs (Table 1). This is a conservative assumption given that it is anticipated for patients with comorbidities this annual appointment would already take place to manage their other conditions and would not be specifically attributed to treatment with tirzepatide.

4. ***"NHSE is aware that patients with obesity have a high burden of psychological issues, such as but not restricted to mood disturbance and low self-esteem. NHSE notes that the SURMOUNT-Trial applied the following exclusion criteria (Jastreboff et al NEJM 2022;387:205-216 Supplementary Appendix). Potential participants were excluded if they:"***

Response:

Lilly has been unable to find evidence to corroborate the NHSE suggestion that patients with obesity have a high burden of psychological issues. With one in six adults in England suffering from a common mental disorder (CMD),[10] it is important to distinguish these CMDs from psychological issues that are directly linked to obesity. Fezeu *et al.* (2015) conducted a UK prospective analysis which demonstrated that abdominal obesity was not associated with an increased future risk of CMD and instead suggested that the direction of association between CMDs and adiposity is actually that CMD leads to an increased future risk of adiposity, rather than the converse.[11] Regardless, it is expected that primary care would be aware of and/or assess for CMD as part of routine care for patients with overweight or obesity, as per CG189.[1] In this respect, patients requiring psychological support would be provided it regardless of whether they receive tirzepatide treatment or not. Costs for psychological support are therefore not attributed to the use of tirzepatide and should not be considered within the economic analysis.

Separately, Lilly would like to clarify that contrary to NHSE's suggestion, there was no exclusion criteria for psychological issues. Rather, the SURMOUNT-1 protocol included the following

statement: "*Patients with Major Depressive Disorder (MDD) or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications*." Accordingly, there were in fact a proportion of patients with psychological issues within the SURMOUNT-1 trial, with 21.6% of participants reporting a pre-existing psychiatric disorder including, but not limited to, depression, anxiety, insomnia, and MDD. No additional support was provided to these participants. Consequently, with primary care already following CG189 (as evidenced by Lilly Market Research[17]) and abiding to the SURMOUNT-1 protocol, there is no expectation for further resource investment or issues with implementation.

5. ***"NHSE interpretation of the trial protocol is that a PHQ-9 score of 15 or more (moderate to severe depression) was an independent exclusion criterion"***

Response:

Lilly suggests that further clarity is required on this point, as the NHSE interpretation of this eligibility criteria is incomplete. Specifically, Lilly would like to bring an additional part of the SURMOUNT-1 protocol to the attention of NICE and NHSE, which stipulates that participants with a PHQ-9 score of 15 or more should be referred to a "*Mental Health Professional (MHP) to assist in deciding whether the subject should be discontinued from study drug. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the Investigator (in agreement with the MHP), may be continued in the trial on randomized therapy*".[12]

As such, a PHQ-9 score of 15 or more was not an exclusion criterion in itself, but resulted in participants being referred to a mental health professional for treatment (as would be expected in primary care). At the discretion of the Investigator, patients were then randomised back into the trial. In total, 4 patients had a PHQ-9 score ≥15, and 2 of these patients continued to be randomised into SURMOUNT-1. No additional psychological support was provided for the participants who were re-randomised to tirzepatide as part of the SURMOUNT-1 protocol.

Lilly would also like to note that while the PHQ-9 is a tool validated for use in primary care, it is not typically used as a screening tool for depression. Rather, it is used to monitor the severity of depression and response to treatments (PHQ-9 Depression Test Questionnaire | Patient). It is therefore not expected that this eligibility criteria would be translated into clinical practice; instead, an assessment of psychological needs would be carried out in accordance with CG189.

Lastly, it is noted that clinical trials for obesity (as well as other conditions) have similar protocols and associated eligibility criteria, indicating that the inclusion of a criterion based on patients' psychological wellbeing is tied to research purposes rather than any specific therapy.

6. ***"NHSE therefore questions the generalisability of the SURMOUNT-1 trial to patients in the NHS who may have significant psychiatric issues or have moderate to severe depression. NHSE recognises that this group of patients will need psychological support if they were to be treated with tirzepatide."***

Response:

As previously stated, patients requiring psychological support would be provided it (as per CG189 and good standards of clinical care), regardless of whether they receive tirzepatide treatment or not. Provision of psychological support is therefore not directly attributed to tirzepatide treatment and indeed would be required for those patients with psychological needs wishing to initiate diet and exercise.

Furthermore, as noted in Response 4, 21.6% of participants in SURMOUNT-1 had a pre-existing psychiatric disorder including, but not limited to, depression, anxiety, insomnia, and MDD, (similar to the 1 in 6 adults in England suffering from a common mental disorder).[10] No additional support was provided to these participants even though they had a pre-existing psychiatric disorder.

7. ***"Based on this need and using evidence from patients who are screened for bariatric surgery, NHSE estimates that all patients will need some level of initial psychological assessment prior to commencement of tirzepatide, and some level of routine screening for psychological issues arising during the course of treatment. Based on experience with bariatric services and clinical opinion we estimate that 1 in 3 patients will need ongoing psychological support. Clinical opinion is that majority of these patients (estimated at 70%), could be managed by Talking Therapies and the remainder would need more intensive psychological input. NHSE has costed psychological intervention according to these estimates."***

Response:

Lilly's suggested population of BMI ≥30 kg/m^2 with at least one weight related comorbidity alongside the SURMOUNT-1 baseline characteristics does not match the current NICE recommendations for bariatric surgery, nor the baseline demographic characteristics of patients that underwent bariatric surgery from January 2015 – December 2019 (BMI 48.0±7.9 versus 38.0±6.81 in SURMOUNT-1).[13] Additionally, access to bariatric services is limited and therefore screening within this population is unlikely to be representative of the broader population eligible for tirzepatide. Bariatric surgery is also an invasive procedure that requires life-long follow-up; patients eligible for bariatric surgery are therefore not a suitable population from which to generalise the psychological needs for patients who would be eligible for tirzepatide treatment in primary care.

With regards to depression as a psychological condition in all people with obesity that may need support, using the entire SURMOUNT-1 participant population (n=2,539) at baseline, over 90% had a PHQ-9 score of 9 or less. As per Kroenke *et al.* (2001), this equates to "no–mild" depression and therefore no intervention/watchful waiting is recommended including no need for ongoing psychological support.[14]

Unlike NHSE's estimate of 1 in 3 bariatric patients requiring ongoing psychological support, only 1 in 1270 patients in SURMOUNT 1 had a PHQ-9 score of ≥15, which is the cut-off for bariatric surgery candidates who may require further assessment of depressive symptoms[2]. 21.6% of participants in the SURMOUNT-1 trial had a pre-existing psychiatric disorder.

As noted previously, it is also anticipated, as per CG189, that a GP would have already assessed a patient choosing to initiate tirzepatide for their psychological needs; the addition of tirzepatide to the management plan would therefore not alter ongoing management for psychological issues.

Finally, there is currently no evidence to suggest that tirzepatide has additional risks for mental wellbeing that would require a different approach to current primary care management. In fact, during the SURMOUNT-1 trial, it was reported that patients receiving tirzepatide experienced an improvement from baseline in all eight domains of the SF-36v2 (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health), as well as the Physical Component Summary and Mental Component Summary scores.[5]

Responses to Questions for NHS England Document

1. ***"Currently no MDT approach to obesity management routinely delivered in the NHS, at present, in primary care. However, weight management pilots are being designed to evaluate Specialist Weight Management Service (SWMS) delivery outside of a secondary care setting. The nature of these pilots is still being defined and, whilst it has not been included in the response, the pilots could potentially provide a mechanism for firming up assumptions about the model of care delivery required to support treatment with tirzepatide, or other weight loss drugs."***

Response:

Aligned with Response 1, Lilly disagrees with the NHSE statement that *"there is no MDT approach to obesity management delivered in the NHS, at present, in primary care"* as we consider that the proposed service model for tirzepatide aligns with what is currently available to patients in primary care as per CG189.[1] As part of these guidelines, GPs (alongside their MDT, including nurses, pharmacists, and healthcare assistants) routinely deliver overweight and obesity management and treatment within primary care.

While we appreciate that the pilot to deliver SWMS services outside of a secondary setting is being investigated by NHSE, Lilly would like to highlight that SWMS's were established to assess patients' suitability and readiness for **bariatric surgery**. As alluded to in Response 7, patients being screened for bariatric surgery are not representative of the majority of patients that will be seen within primary care; therefore, SWMS should not be used as the model of care on which to base the primary care service model. For this reason, rather than trying to replicate SWMS outside of a secondary care setting, Lilly recommends that NHSE and NICE consider the current model of care already available in primary care and, where necessary, expand these services as part of the pilot or via future NHSE investments within weight management services.

Primary care currently manages the obesity population and therefore must have a service model in place that follows CG189 and already utilises a MDT approach based in primary care. As previously mentioned, Lilly conducted Market Research with GPs in England and Wales. Respondents were provided with the hypothetical situation of managing a patient with a BMI ≥30 kg/m2 with at least one weight related comorbidity[17]. Out of 381 respondents, 90% were aware of CG189. Of these, a further 73% followed these guidelines always or very frequently. In terms of what GPs currently offer these patients, 78% already offer specific diet and exercise advice, and 94% has access to a dietician or qualified healthcare professional to provide diet and exercise support. This Lilly Market Research provides evidence that primary care has an existing weight management service/workforce model for managing people with obesity, and this existing model replicates Lilly's proposal in Table 1 (an MDT-led approach).

Lilly agrees that commissioned SWMS services should continue in their current format, and should any bariatric candidates present in primary care, they should be escalated as per local clinical pathways.

[redacted]

2. ***"A pilot of weight management drugs is currently being developed by DHSC/NHSE to assess how and what components of a typical SWMS and an MDT approach in specialist care can be delivered outside of a specialist setting. The pilots were being designed in line with the NICE recommendation for semaglutide in specialist weight management services."***

Response:

As above, Lilly recommend that rather than trying to replicate SWMS outside of a secondary care setting, NHSE and NICE should consider the current model of care already available in primary care and, where necessary, expand these services as part of the pilot or via future NHSE investments within weight management services.

NHSE has highlighted that some digital weight management technologies have already been deployed locally within the NHS, including as part of the Adult Weight Management Services Grant by the Government. This has seen the use of digital weight management technologies by over 140,000 patients within primary care and the community since 2021.[15] Nevertheless, we would be cautious with the approach of replicating the current SWMS model more widely, as Tier 3 services have been shown to be ineffective in achieving weight loss outcomes – with only 10% of participants (n=11,735) achieving ≥10% weight loss at 6 months.[16] Considering this, Lilly suggests that the NHSE pilot should consider new approaches to providing diet and exercise in the primary care setting (such as the proposed approach in Table 1), which could be offered as an adjunct to tirzepatide treatment.

3. ***"The pilot programme will adapt the multidisciplinary team approach stated by NICE [CG189] for the purpose of evaluating access and acceptability (through NIHR evaluation) through a General Practitioner (not with special interest) led process for assessment for patient eligibility and appropriateness to be managed/prescribed the associated weight loss drugs and either…."***

Response:

While Lilly appreciates that the pilot to deliver SWMSs outside of a secondary setting is being investigated by NHSE, Lilly would re-iterate that SWMSs were established to assess patients' suitability and readiness for bariatric surgery and that patients being screened for bariatric surgery are not representative of the majority of patients that will be seen within primary care (Response 7). [redacted]. Nevertheless, it is reassuring that NHSE are willing to shape the pilots going forward, should tirzepatide be accessible via MDT services within primary care. Lilly broadly agrees with the NHSE proposal that a GP (not with special interest) would lead the assessment for patient eligibility and suitability for tirzepatide. Lilly also agrees that primary care may choose to assume all associated prescribing responsibilities, from initiation through to titration, maintenance, and continued medical management.

4. ***"Wrap around MDT care speciality service provision outside of prescribing of the drug will be provided by either:***

a) Locally (ICB) procured wrap around MDT services specifically for the pilot patients only

b) A Nationally procured digital delivery of wrap around MDT care specifically for the pilot patients only"

Response:

Lilly proposes that the "wrap around MDT care speciality service provision" should encompass digital weight management technologies that purely provide the diet and exercise support, as per the SURMOUNT-1 protocol. This proposal aligns with the NICE EVA that highlighted up to 9 digital weight management technologies that can provide multidisciplinary programmes to increase physical activity levels and improve eating behaviours and diet. Leveraging digital weight management technologies in this way would not require any additional touchpoints beyond those outlined in Table 1, and as such, tirzepatide would represent a cost-effective use of NHS resources when used alongside digital weight management technologies.

5. ***"NHSE has suggested that the MDT support remains in place whilst the patient is on tirzepatide, which is in line with the MHRA license (and not less than that approved)".***

Response:

As per the "Long-term Phase" detailed in Lilly's Stakeholder Comments, an annual review would be considered appropriate and in line with how other chronic diseases are managed in primary care. Furthermore, there is no mention of MDT support within the tirzepatide MHRA license; our license states that tirzepatide can be used for weight management, including weight loss and weight maintenance, **as an adjunct to a reduced-calorie diet and increased physical activity** in adults with an initial BMI of ≥30 (obesity), or ≥27 to <30 (overweight) in the presence of at least one weight-related comorbidity.

6. ***"Specific consideration should be given to where additional workforce will be sourced for new delivery setting without drawing on existing secondary care services or adding pressure to primary care. This is perhaps most relevant around access to psychologists given the high association between obesity and psychological and psychiatric issues. It is, therefore, essential that patients have an assessment by the appropriately skilled professional in order for psychological support to be tailored to their needs but to also ensure those that need psychiatric input are referred on. This is critical as the cohort of patients with significant mental health diagnoses were excluded from the SURMOUNT pilot population."***

Response:

First, Lilly would like to highlight an inaccuracy in the NHSE statement, given that within the SURMOUNT-1 population, 21.6% of participants had a pre-existing psychiatric disorder including, but not limited to, depression, anxiety, insomnia, and MDD (Response 6).

Second, regarding NHSE's stance that it is essential that people with obesity have an assessment by the appropriately skilled professional for psychological support to be tailored to their needs: this must occur, as per CG189, regardless of any weight management intervention – including any diet and exercise. Therefore, as per Table 1, Lilly has excluded any psychological support or assessment from the tirzepatide arm, as this would be required for the diet and exercise comparator as well.

In relation to workforce and capacity constraints, the Lilly Market Research surveyed GPs in England and Wales with the hypothetical option of other effective weight management drugs being available in primary care for a patient with a BMI ≥30 kg/m2 with at least one weight related comorbidity.[17] Out of 381 respondents, 100% said that offering patients additional effective treatments in primary care would add value to their patients. Furthermore, 93% of GPs said that this would add value to their practice. When asked further on whether this perceived value of additional effective anti-obesity medications would help tackle capacity constraints, only

3% of GPs responded with “not at all”. Lastly, even with the immense pressure that primary care is currently under, 80% of surveyed GPs stated it was either “extremely important”, “very important”, or “important” that their practice was able to initiate effective anti-obesity medications.[17] For the full report and methodology, please see the attached Lilly Market Research document.

This Lilly Market Research provides evidence that primary care has an existing weight management service/workforce model for managing people with obesity, and this existing model replicates Lilly’s proposal in Table 1. We hope this additional information from a representative sample of primary care GPs, alleviates any concerns NICE have around the implementation of new and effective obesity medications within primary care.

7. ***“Yes, there will need to be an assessment for eligibility that includes inclusion and exclusion criteria and in particular psychological assessment informed by the relevant NICE recommendations but will also need to take account of system capacity.”***

Response:

Lilly would like to highlight that per CG189, prior to any lifestyle or medical intervention, primary care should seek to explore and identify comorbidities, environmental and social factors, psychosocial distress and psychological issues, with the aim of ensuring that individualised patient care is provided. This approach aligns with Lilly’s proposed Initiation phase (see Lilly’s Stakeholder Comments), where it is proposed that a GP assesses the patient for comorbidities (including psychological issues) prior to starting any intervention. If a patient is considered a suitable candidate for SWMS, then the GP would continue to escalate that patient as per local weight management clinical pathways.

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Evidence request for the company

1. Please present scenario analyses listed in table 1 to demonstrate the cost effectiveness of tirzepatide in the context of various assumptions around obesity management services. Feel free to provide any additional scenarios that you believe would be useful for committee decision making.

Table 1: requested scenarios to demonstrate various assumptions around obesity management services

No.	Intervention arm (all include GP assessment)	Comparator arm (all include GP assessment)
1	NHSE proposed resource use for obesity services while on tirzepatide*, then no resource use after stopping tirzepatide	No resource use for obesity services (reflecting current standard of care = no diet and exercise intervention for majority)
2	NHSE proposed resource use for obesity services while on tirzepatide, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model	NHSE proposed resource use for obesity services minus GP titration appointments for 2 years, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model
3	NHSE proposed resource use for obesity services while on tirzepatide, then 1 GP visit per year until 2, 4 or 6 years in model	1 GP visits per year until 2, 4 or 6 years in model
4	Company proposed resource use for obesity services while on tirzepatide: First 3 months: 1 GP visit, then nurse every 4 weeks	Company proposed resource use for obesity services for 2 years in model

	4-16 months: 1 GP visit, then nurse every 3 months >16 months: 1 GP visit annually	
5	Company proposed resource use for obesity services while on tirzepatide, then 1 GP visit per year until 2, 4 or 6 years in model	1 GP visits per year until 2, 4 or 6 years in model
6	SWMS NHSE consultant led costs** for 2 years, then company proposed resource use from year 2 while on tirzepatide: First 3 months: 1 GP visit, then nurse every 4 weeks 4-16 months: 1 GP visit, then nurse every 3 months >16 months: 1 GP visit annually	SWMS NHSE consultant led costs** (+ semaglutide) for 2 years, then no resource use for obesity services
7	SWMS NHSE consultant led costs** for 2 years, then NHSE proposed resource use while on tirzepatide minus GP titration appointments, then 1 GP visit per year until 2, 4 or 6 years in model	SWMS NHSE consultant led costs** (+ semaglutide) for 2 years, then 1 GP visit per year until 2, 4 or 6 years in model

* See NHSE proposed clinical services and costs and breakdown of appointments below (appendix, tables 2 and 3)

**NHSE consultant led costs set out in appendix, table 3

2. Please amend the economic model so that resource associated with ongoing obesity management services (e.g. dietician appointments) can be included in all treatment arms with a prespecified duration.

3. Please provide the following baseline demographic information for the population in SURMOUNT-1:
    - Baseline comorbidities which made a participant eligible to be included within the target population
    - Distribution of comorbidities for:
        - people with a BMI of 30 to 34.9 mg/kg^2
        - people with a BMI of ≥35 mg/kg^2
    - Proportion of people who had a previous mental health condition for:
        - the total target population
        - people with a BMI of 30 to 34.9 mg/kg^2
        - people with a BMI of ≥35 mg/kg^2
    - Detailed gradation of the BMI distribution, providing the proportion who had BMI 30 to 30.9 mg/kg^2, 31 to 31.9 mg/kg^2 etc. Please comment on how this compares with the BMI distribution of the population in primary care in England.

4. Please provide evidence on the distribution of all relevant weight-related comorbidities in people with a BMI of ≥30mg/kg^2 in primary care and compare this with the baseline comorbidities in the target population in the SURMOUNT-1 trial.

5. Please provide evidence on the prevalence of type 2 diabetes amongst people with a BMI of ≥30 mg/kg^2 and ≥35 mg/kg^2 in England.

6. Please update the model so that people entering the model reflect the SURMOUNT-1 baseline comorbidities with respect to all the complications within the model. Where these baseline comorbidities were not recorded in SURMOUNT-1, adopt the same approach as for the other baseline comorbidities not recorded during SURMOUNT-1.

7. Please provide a scenario analysis that assumes a proportion of people have type 2 diabetes at baseline, as might be expected within primary care, suitably adjusting baseline comorbidities for those with type 2 diabetes.

8. Please provide further scenarios to demonstrate the potential impact treatment effect waning of tirzepatide may have on the cost effectiveness estimates.
    - At a minimum this should apply a constant absolute annual percentage reduction from 72 weeks (or the start of the 2nd year if this is the closest that can be implemented within the model structure) in the net gain in terms of weight, prediabetes reversal, SBP, HDL and total cholesterol of the active treatment arms over the diet and exercise arm at 72 weeks (or the start of year 2). This should reduce the net gain linearly such that if the annual absolute percentage loss is 2% of the difference at 72 weeks those on active treatment will have the same values for weight, prediabetes reversal, SBP, HDL and total cholesterol at 50 year (plus 72 weeks or 2 years) as those in the diet and exercise arm. From this point active treatment values should remain equal to those of the diet and exercise arm, with scenarios of active treatment costs being retained thereafter and not retained thereafter. The starting point for this linear waning of net effects and the annual percentage loss should be explored through reversible dropdowns. Please implement this through a reversible drop down within the model.

9. Please provide scenarios varying the rate of discontinuation for people on tirzepatide.

10. Please provide the percentages of participants in SURMOUNT-1 achieving a 5% weight loss at 48-weeks separately by arm, implementing this through a reversible drop down within the model.

11. To the extent possible, please provide a more detailed breakdown of the direct drug costs and the microvascular complication costs taken from Capehorn et al. to estimate type 2 diabetes costs.

12. Please provide subgroup analyses for:
    - people with BMI 30 to 34.9 mg/kg^2 plus 1 weight related comorbidity

- people with BMI ≥35 mg/kg^2 plus 1 weight related comorbidity.

These analyses should allow other scenario analyses to be run within them, including all those requested in this document. Please make these implementable through a reversible drop down.

13. Please implement the analyses of multi-year risk for events reported in table 6 of the stakeholder comments form (23 Feb 2024) within a reversible dropdown in the model.

For information, the EAG has provided additional analysis on the annualisation of risk functions used in the model. This has been uploaded to NICEdocs for your attention.

Appendix

Table 2: NHS England proposed clinical services and costs of obesity management

Visit	Purpose	Duration	Assumed Resource for costing	Activity / Skill	Assumptions
Stage 1: Patient Assessment, Counselling and Training					
1	HCA Review	10	HCA	Blood Pressure, Height & Weight	
1	Initial consult	45	GP/Consultant	Alternative to GP could be used, for example: - ANP (LTC management) / other health care professionals with LTC management experience. - Senior practice nurses (diabetes specialist) However, GP will be ultimate accountability for patient care. 45 mins to include psychological support assesment.	The screening & eligibility process for the clinical trial is not appropriate in routine setting. Alternative screening and eligibility activity is based on NHSE. clinical input.
1	Blood Test + thyroid test	N/A	N/A		
2	Patient Training	30	Nurse	Checklist review + patient education (could be group sessions)	
2	Patient Education & Dietary/exercise advice	30	Dietician	Dietetic advice and guidance	
2	Clinical Review and prescription validation	15	GP/Consultant	Prescription check	
3	Week 0 - Treatment initiation (2.5mg)	15	Nurse	Patient education could be in video format for some patients.	As per SURMOUNT-1 trial
Stage 2: Titration & Weight Management Support					
4	Week 4 - dose titration (5 mg)	20	GP/Consultant	Same as above - different skills can do this, needs to be a prescriber. Contra-inidcation considerations (polypharmacy) drives requirement for senior oversight. Recognition that this could change as more long term data becomes available.	As per SURMOUNT-1 trial
5	Week 8 - dose titration (7.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 dose titration (10mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
7	Week 16 dose titration (12.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
8	Week 20 dose titration (15mg)	20	GP/Consultant		As per SURMOUNT-1 trial
9	Week 24 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
10	Week 26 - Medicines Review	20	GP		Activity based on clinical input
Stage 3: Maintenance (Every 12 weeks thereafter)					
10,11	Week 36 + 48 (Year 1) - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
12-16	Week 60, 72, 84, 96 (Year 2) - Dietary/exercise advise	30	Dietician		As per SURMOUNT-1 trial
17-21	Week 108, 120, 132, 144 (Year 3) - Dietary/exercuse advise	30	Dietician		As per SURMOUNT-1 trial
Additional Costs					
N/A	Multi Disciplinary Team (MDT) Patient Review	15	GP/Consultant + Nurse + Clinical Pharmacist+ Psychologist	Costing will assume minimum 2 MDT discussions per patient per year. To start from week 26	Activity based on clinical input
N/A	Psychological Support	30	Psychologist / Psychiatrist	Costing will assume 1 in 3 patients will require psychologist support. Where psychologist support is required assume 5 appointments in year 1 (as per DHSC/NHS obesity prescribing pilots).	Activity based on clinical input
N/A	Sharps & disposal	N/A	N/A		Activity based on clinical input

Table 3: NHSE proposed breakdown of appointments over 3 years

Number of appointments by profession		Year 1	Year 2	Year 3	Coverage	Cost per slot (£)	Year 1	Year 2	Year 3
GP	10 min slots	21	3	3	-	£ 41.00	£ 861.00	£ 123.00	£ 123.00
Nurse	10 min slots	4.5	3	3	-	£ 18.55	£ 83.47	£ 55.64	£ 55.64
HCA	10 min slots	1	0	0	-	£ 7.14	£ 7.14	£ -	£ -
Nurse group	10 min slots	3	0	0	-	£ 18.55	£ 55.64	£ -	£ -
Clinical pharmacist	10 min slots	3	3	3	-	£ 11.29	£ 33.88	£ 33.88	£ 33.88
Dietician	30 min slots	5	4	4	-	£ 27.19	£ 135.97	£ 108.77	£ 108.77
Psychologist	30 min slots	5.5	3	3	0.33	£ 33.88	£ 62.11	£ 33.88	£ 33.88
Total per patient cost (GP Led)							**£1,239.21**	**£ 355.18**	**£ 355.18**
Total per patient cost (Consultant Led)						**£ 23.33**	**£ 868.21**	**£ 302.18**	**£ 302.18**

Introduction

Thank you for the opportunity to respond to the questions to ensure that the Committee has the best evidence on which to base its guidance.

To provide context to the responses (and as outlined in our Part 1 response to NHSE feedback on service delivery), Lilly would like to reiterate that for the majority of patients with obesity, it is expected that an MDT-led approach akin to that provided in primary care for patients with other chronic diseases would be adequate and in line with the SURMOUNT-1 protocol. This MDT-led approach in primary care aligns with what is currently available to people with obesity in primary care (as per CG189). In particular, the target population are already being seen within primary care for the management of their comorbidities.

Recent market research conducted in March 2024 by Lilly and Sermo (an independent market research firm) in a representative sample (n=381) of primary care GPs in England and Wales should alleviate any concerns NICE has around the implementation of new and effective anti-obesity medications within primary care. Respondents were provided with the hypothetical situation of managing a patient with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity. Out of the 381 GP respondents:

- 90% were aware of CG189. Of these, a further 73% followed these guidelines always or very frequently.
- In terms of what GPs currently offer these patients, 78% already offer specific diet and exercise advice, and 94% has access to a dietician or qualified healthcare professional to provide diet and exercise support.
- To verify existing weight management services in primary care and the community are already being utilised for people with obesity, 88% of GPs confirmed that they use community-based diet and exercise services.
- 100% said that offering patients additional effective treatments in primary care would add value to their patients.
- Furthermore, 93% of GPs said that this would add value to their practice. When asked further on whether this perceived value of additional effective anti-obesity medications would help tackle capacity constraints, only 3% of GPs responded with “not at all”.
- Lastly, even with the immense pressure that primary care is currently under, 80% of surveyed GPs stated it was either “extremely important”, “very important”, or “important” that their practice was able to initiate effective anti-obesity medications.

For the full report and methodology, please see the Lilly Market Research Report – shared alongside our Part 1 response.

Finally, the multiple data analyses below demonstrate that irrespective of the analysis undertaken, all doses of tirzepatide remain a cost-effective use of NHSE resources in the target population within a primary care setting.

Evidence request for the company

1. Please present scenario analyses listed in table 1 to demonstrate the cost effectiveness of tirzepatide in the context of various assumptions around obesity management services. Feel free to provide any additional scenarios that you believe would be useful for committee decision making.

Table 1: requested scenarios to demonstrate various assumptions around obesity management services

No.	Intervention arm (all include GP assessment)	Comparator arm (all include GP assessment)
1	NHSE proposed resource use for obesity services while on tirzepatide*, then no resource use after stopping tirzepatide	No resource use for obesity services (reflecting current standard of care = no diet and exercise intervention for majority)
2	NHSE proposed resource use for obesity services while on tirzepatide, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model	NHSE proposed resource use for obesity services minus GP titration appointments for 2 years, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model
3	NHSE proposed resource use for obesity services while on tirzepatide, then 1 GP visit per year until 2, 4 or 6 years in model	1 GP visits per year until 2, 4 or 6 years in model
4	Company proposed resource use for obesity services while on tirzepatide: First 3 months: 1 GP visit, then nurse every 4 weeks 4-16 months: 1 GP visit, then nurse every 3 months	Company proposed resource use for obesity services for 2 years in model

	>16 months: 1 GP visit annually	
5	Company proposed resource use for obesity services while on tirzepatide, then 1 GP visit per year until 2, 4 or 6 years in model	1 GP visits per year until 2, 4 or 6 years in model
6	SWMS NHSE consultant led costs** for 2 years, then company proposed resource use from year 2 while on tirzepatide: First 3 months: 1 GP visit, then nurse every 4 weeks 4-16 months: 1 GP visit, then nurse every 3 months >16 months: 1 GP visit annually	SWMS NHSE consultant led costs** (+ semaglutide) for 2 years, then no resource use for obesity services
7	SWMS NHSE consultant led costs** for 2 years, then NHSE proposed resource use while on tirzepatide minus GP titration appointments, then 1 GP visit per year until 2, 4 or 6 years in model	SWMS NHSE consultant led costs** (+ semaglutide) for 2 years, then 1 GP visit per year until 2, 4 or 6 years in model

* See NHSE proposed clinical services and costs and breakdown of appointments below (appendix, tables 2 and 3)

**NHSE consultant led costs set out in appendix, table 3

Lilly wishes to note that several of these scenarios have already been presented in responses to NHSE's proposed resource use for obesity services while on tirzepatide (submitted: 22nd March 2024; NHSE Lilly Responses_Final_22March24), hereby referred to as Lilly Response Part 1). However, for ease of review, Lilly have replicated these scenarios below.

For all scenarios including the "Company proposed resource use for obesity services", a detailed breakdown of the number, duration and assumed required resource of appointments is provided in Lilly Response Part 1, alongside justifications of any changes from NHSE's proposed costs. It should also be noted that all scenarios presented in response to this question are in the **target population** (BMI ≥30 kg/m^2) with at least one weight-related comorbidity.

In all the following scenarios, the analysis finds that tirzepatide is a highly cost-effective use of NHS England resources.

Scenario 1

Table 1 presents a scenario analysis in which:

- NHSE's proposed resource use has been applied to the tirzepatide arm whilst patients remain on treatment, and then once patients discontinue treatment no resource use is applied
- No resource use has been applied for the diet and exercise arm for the entire time horizon in the model

Although this scenario is considered unrealistic for the reasons outlined in Lilly Response Part 1, and the fact that individuals with obesity would still incur some costs, this scenario analysis finds that tirzepatide remains a highly cost-effective use of NHS England resources.

Table 1. Cost effectiveness results for Scenario 1 (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,184	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,496	16.641	£10,312	0.644	£16,011
Tirzepatide (10.0 mg)	£29,889	16.576	£9,705	0.579	£16,758
Tirzepatide (15.0 mg)	£31,772	16.682	£11,588	0.685	£16,910

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 2

Table 2, Table 3 and Table 4 present the cost effectiveness results for Scenario 2, in which:

- NHSE's proposed resource use has been applied to the tirzepatide arm whilst patients remain on treatment, and then once patients discontinue treatment, dietician appointments and psychological support for 1/3 of patients are applied for 2, 4 and 6 further years, respectively
- NHSE's proposed resource use has been applied for the diet and exercise arms for 2 years, and then dietician appointments and psychological support for 1/3 of patients are applied for 2, 4 and 6 further years, respectively

While this scenario is more realistic than Scenario 1, given that individuals with obesity are still assumed to incur some costs if they do not choose to initiate tirzepatide, this scenario is still overly conservative (see Lilly Response Part 1, Table 1). Nevertheless, this scenario analysis finds that tirzepatide remains a highly cost-effective use of NHS England resources.

Table 2: Cost effectiveness results for Scenario 2 – dietician and psychological support (after NHSE proposed resource use) for 2 further years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,667	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,550	16.641	£9,883	0.644	£15,344
Tirzepatide (10.0 mg)	£29,937	16.576	£9,270	0.579	£16,007
Tirzepatide (15.0 mg)	£31,819	16.682	£11,153	0.685	£16,274

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 3: Cost effectiveness results for Scenario 2 – dietician and psychological support (after NHSE proposed resource use) for 4 further years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,964	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,631	16.641	£9,667	0.644	£15,008
Tirzepatide (10.0 mg)	£30,024	16.576	£9,060	0.579	£15,644
Tirzepatide (15.0 mg)	£31,908	16.682	£10,944	0.685	£15,970

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 4: Cost effectiveness results for Scenario 2 – dietician and psychological support (after NHSE proposed resource use) for 6 further years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,238	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,718	16.641	£9,480	0.644	£14,718
Tirzepatide (10.0 mg)	£30,124	16.576	£8,886	0.579	£15,344
Tirzepatide (15.0 mg)	£32,006	16.682	£10,768	0.685	£15,713

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 3

Table 5, Table 6 and Table 7 present the cost effectiveness results for Scenario 3, in which:

- NHSE's proposed resource use has been applied to the tirzepatide arm whilst patients remain on treatment, and then once patients discontinue treatment, a single GP appointment is applied for 2, 4 and 6 further years, respectively
- One GP appointment has been applied at 2, 4 and 6 in the diet and exercise arm, respectively, and then no resource use is provided for the rest of the modelled time horizon

Despite similar limitations as the previous scenarios, tirzepatide remains a highly cost-effective use of NHS England resources.

Table 5: Cost effectiveness results for Scenario 3 – one GP appointment per year for 2 years (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,262	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,510	16.641	£10,247	0.644	£15,909
Tirzepatide (10.0 mg)	£29,901	16.576	£9,638	0.579	£16,642
Tirzepatide (15.0 mg)	£31,784	16.682	£11,521	0.685	£16,812

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 6: Cost effectiveness results for Scenario 3 – one GP appointment per year for 4 years (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,336	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,530	16.641	£10,193	0.644	£15,826
Tirzepatide (10.0 mg)	£29,922	16.576	£9,586	0.579	£16,553
Tirzepatide (15.0 mg)	£31,806	16.682	£11,469	0.685	£16,737

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 7: Cost effectiveness results for Scenario 3 – one GP appointment per year for 6 years (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,404	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,551	16.641	£10,147	0.644	£15,754
Tirzepatide (10.0 mg)	£29,947	16.576	£9,543	0.579	£16,478
Tirzepatide (15.0 mg)	£31,830	16.682	£11,426	0.685	£16,673

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 4

Table 8 presents the cost effectiveness results for Scenario 4, in which:

- The resource use outlined in Table 1, Lilly Response Part 1 (also copied into the Appendix) has been applied to the tirzepatide arm for the duration of the modelled time horizon
- The resource use outlined in Table 1, Lilly Response Part 1 has been applied to the diet and exercise arm where appropriate (as detailed in Lilly Response Part 1) for 2 years, and then no resource use has been applied for the rest of the modelled time horizon

As noted in Lilly Response Part 1, these results are considered to model a realistic scenario that reflects NHSE clinical practice in primary care and that aligns with the SURMOUNT-1 protocol. When this resource use is applied, tirzepatide represents a highly cost-effective use of NHSE resource, with ICERs <£13,000 for all three doses of tirzepatide.

Table 8: Cost effectiveness results for Scenario 4 (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,515	15.997	-	-	-
Tirzepatide (5.0 mg)	£28,058	16.641	£7,543	0.644	£11,711
Tirzepatide (10.0 mg)	£27,635	16.576	£7,120	0.579	£12,294
Tirzepatide (15.0 mg)	£29,330	16.682	£8,815	0.685	£12,863

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 5

Table 9 presents the cost effectiveness results for Scenario 5, in which:

- The resource use outlined in Table 1, Lilly Response Part 1 has been applied to the tirzepatide arm for the duration of the modelled time horizon, but the nurse visits in Weeks 8/12/16 and 20 have been removed and replaced with one appointment at Week 24 (i.e. aligned with Scenario 1 presented in Lilly Response Part 1)
- The resource use outlined in Table 1, Lilly Response Part 1 has been applied to the diet and exercise arm where appropriate (as detailed in Lilly Response Part 1) for the entire duration of the modelled time horizon.

This scenario analysis finds that tirzepatide remains highly cost-effective, with ICERs that are largely consistent with Scenario 4.

Table 9: Cost effectiveness results for Scenario 5 (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,515	15.997	-	-	-
Tirzepatide (5.0 mg)	£28,102	16.641	£7,587	0.644	£11,779
Tirzepatide (10.0 mg)	£27,633	16.576	£7,119	0.579	£12,292
Tirzepatide (15.0 mg)	£29,275	16.682	£8,760	0.685	£12,783

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 6

Table 10 and Table 11 present the cost effectiveness results for Scenario 6 vs diet and exercise and vs semaglutide, respectively, in which:

- SWMS NHSE consultant led costs have been applied to the tirzepatide arm for 2 years, and then once patients discontinue treatment, the resource use outlined in Table 1, Lilly Response Part 1 has been applied to the tirzepatide arm for the rest of the modelled time horizon
- SWMS NHSE consultant led costs have been applied to the diet and exercise and semaglutide arms for 2 years, and then no resource use has been applied for this arm the rest of modelled time horizon

Although Lilly would reiterate that the majority of patients on tirzepatide would not require the same level of diet and exercise support that is provided in SWMS, this scenario finds that tirzepatide represents a highly cost-effective use of NHSE resources versus both comparators.

Table 10: Cost effectiveness results for Scenario 6 (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,321	15.997	-	-	-
Tirzepatide (5.0 mg)	£28,647	16.641	£7,326	0.644	£11,374
Tirzepatide (10.0 mg)	£28,198	16.576	£6,877	0.579	£11,875
Tirzepatide (15.0 mg)	£29,850	16.682	£8,529	0.685	£12,446

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 11: Cost effectiveness results for Scenario 6 (vs semaglutide)

Treatment	Total Costs	Total QALYs	vs. semaglutide		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Semaglutide	£23,775	16.159	-	-	-
Tirzepatide (5.0 mg)	£28,647	16.641	£4,872	0.482	£10,102
Tirzepatide (10.0 mg)	£28,198	16.576	£4,423	0.417	£10,598
Tirzepatide (15.0 mg)	£29,850	16.682	£6,075	0.523	£11,605

Abbreviations: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Scenario 7

Table 12 and Table 13, Table 14 and Table 15, and Table 16 and Table 17 present the cost-effectiveness results for Scenario 7 vs diet and exercise and vs semaglutide, in which:

- SWMS NHSE consultant led costs have been applied to the tirzepatide arm for 2 years, and then once patients discontinue treatment, NHSE's proposed resource use (excluding GP titration appointments) has been applied for 2, 4 and 6 further years, respectively
- SWMS NHSE consultant led costs have been applied to the diet and exercise and semaglutide arms for 2 years, and then one GP visit has been applied per year until 2, 4 and 6 further years, respectively

Despite the inclusion of SWMS costs, which would be excessive for the majority of patients, this scenario finds that tirzepatide represents a cost-effective use of NHSE resource, consistent with previous scenarios.

Table 12: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 2 years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,321	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,405	16.641	£9,085	0.644	£14,105
Tirzepatide (10.0 mg)	£29,622	16.576	£8,301	0.579	£14,334
Tirzepatide (15.0 mg)	£31,360	16.682	£10,039	0.685	£14,649

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 13: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 2 years in the model (vs semaglutide)

Treatment	Total Costs	Total QALYs	vs. Semaglutide		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Semaglutide	£23,775	16.159	-	-	-
Tirzepatide (5.0 mg)	£30,405	16.641	£6,630	0.482	£13,748
Tirzepatide (10.0 mg)	£29,622	16.576	£5,847	0.417	£14,010
Tirzepatide (15.0 mg)	£31,360	16.682	£7,584	0.523	£14,489

Abbreviations: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 14: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 4 years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,394	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,425	16.641	£9,031	0.644	£14,021
Tirzepatide (10.0 mg)	£29,643	16.576	£8,249	0.579	£14,244
Tirzepatide (15.0 mg)	£31,381	16.682	£9,987	0.685	£14,573

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 15: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 4 years in the model (vs semaglutide)

Treatment	Total Costs	Total QALYs	vs. Semaglutide		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Semaglutide	£23,849	16.159	-	-	-
Tirzepatide (5.0 mg)	£30,425	16.641	£6,576	0.482	£13,636
Tirzepatide (10.0 mg)	£29,643	16.576	£5,794	0.417	£13,885
Tirzepatide (15.0 mg)	£31,381	16.682	£7,532	0.523	£14,389

Abbreviations: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 16: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 6 years in the model (vs diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£21,462	15.997	-	-	-
Tirzepatide (5.0 mg)	£30,447	16.641	£8,985	0.644	£13,950
Tirzepatide (10.0 mg)	£29,668	16.576	£8,206	0.579	£14,169
Tirzepatide (15.0 mg)	£31,406	16.682	£9,943	0.685	£14,510

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 17: Cost effectiveness results for Scenario 7 – one GP visit per year (after SWMS) for 6 years in the model (vs semaglutide)

Treatment	Total Costs	Total QALYs	vs. Semaglutide		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Semaglutide	£23,918	16.159	-	-	-
Tirzepatide (5.0 mg)	£30,447	16.641	£6,530	0.482	£13,539
Tirzepatide (10.0 mg)	£29,668	16.576	£5,751	0.417	£13,781
Tirzepatide (15.0 mg)	£31,406	16.682	£7,488	0.523	£14,305

Abbreviations: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Summary

Overall, consistent with analyses presented in Lilly's Response Part 1, these results demonstrate that tirzepatide is a highly cost-effective use of NHSE resources, even when overly conservative and unrealistic assumptions surrounding the level of MDT support provided alongside tirzepatide treatment are used in a primary care setting. Compared to the ICERs when the costliest MDT support in SWMS is provided (Scenario 7), the ICERs for Lilly's proposed MDT costs in primary care (Scenario 4) only vary by ~£2,000 for all tirzepatide doses versus diet and exercise, driven by an additional ~£2,000 tirzepatide cost versus a smaller ~£1,000 increase in diet and exercise costs in the extreme SWMS scenario. These scenario analyses therefore further exemplify the significant costs that are averted from tirzepatide treatment in the long-term due to the avoidance of costly comorbidities, which greatly outweigh any variation in the level of diet and exercise support provided alongside tirzepatide.

2. Please amend the economic model so that resource associated with ongoing obesity management services (e.g. dietician appointments) can be included in all treatment arms with a prespecified duration.

Lilly can confirm that the economic model has now been modified such that the resource use associated with ongoing obesity management services can be included for a prespecified duration. This has been implemented such that when one of the above scenarios is selected, the relevant costs for that scenario are automatically set to the specified timepoint. After this specified point, all NHSE resource use costs are set to 0 in the traces. By selecting alternative user-definable time points (in years) for the relevant costs, the Committee may therefore easily explore variations of the above scenarios.

When using this functionality, it should be noted that conservative cost assumptions have been used throughout. For example, for appointments where diet and exercise advice is provided, the cost of a dietician is applied in the model. However, in clinical practice it is anticipated that these appointments could be carried out by a suitably qualified healthcare assistant (as per the SURMOUNT-1 protocol where a qualified health delegate was used), which would incur lower costs.

3. Please provide the following baseline demographic information for the population in SURMOUNT-1:
    - Baseline comorbidities which made a participant eligible to be included within the target population

An exhaustive list of the baseline weight-related comorbidities that made a participant eligible to be included in the target population are provided below (alongside all the relevant preferred terms/system organ class definitions for each of these comorbidities):

- **Hypertension** [Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive cardiomyopathy, Hypertensive crisis, Hypertensive heart disease, Hypertensive nephropathy, Hypertensive urgency, Retinopathy hypertensive, Systolic hypertension]
- **Dyslipidaemia** [Blood cholesterol increased, Blood triglycerides increased, Diabetic dyslipidaemia, Dyslipidaemia, High density lipoprotein decreased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Lipid metabolism disorder, Lipidosis, Lipids increased, Lipoprotein (a) increased, Lipoprotein deficiency, Lipoprotein increased, Low density lipoprotein increased, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type V hyperlipidaemia]
- **OSA** [Apnoea, Positive airway pressure therapy, Sleep apnoea syndrome]
- **ASCVD** [Acute coronary syndrome, Acute myocardial infarction, Angina pectoris, Angina unstable, Angioplasty, Aortic arteriosclerosis, Arterial stent insertion, Arteriosclerosis, Arteriosclerosis coronary artery, Arteriosclerotic retinopathy, Carotid arteriosclerosis, Carotid artery disease, Carotid artery occlusion, Carotid artery stenosis, Cerebral artery occlusion, Cerebral infarction, Cerebral ischaemia, Cerebrovascular accident, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery disease, Coronary artery occlusion, Coronary artery stenosis, Coronary revascularisation, Internal capsule infarction, Ischaemic cardiomyopathy, Ischaemic stroke, Myocardial infarction, Myocardial ischaemia, Percutaneous coronary intervention, Peripheral arterial occlusive

disease, Peripheral artery bypass, Peripheral artery occlusion, Peripheral artery stent insertion, Peripheral artery thrombosis, Peripheral vascular disorder, Renal artery arteriosclerosis, Renal artery stenosis, Renal artery stent placement, Retinal artery occlusion, Subclavian artery aneurysm, Transient ischaemic attack, Vascular calcification]

- **Prediabetes** [non-diabetic hyperglycaemia]
- **Hip or knee osteoarthritis** [Arthritis, Arthropathy, Articular calcification, Hip arthroplasty, Knee arthroplasty, Meniscal degeneration, Nodal osteoarthritis, Osteoarthritis, Periarthritis, Polyarthritis]
- **Asthma** [Allergic bronchitis, Allergic respiratory disease, Asthma, Asthma exercise induced, Bronchial hyperreactivity, Bronchitis, Bronchitis chronic, Bronchospasm, Childhood asthma, Chronic obstructive pulmonary disease, Cough variant asthma, Emphysema, Occupational asthma]
- **Liver disease (NASH or NAFLD)** [Hepatic steatosis, Non-alcoholic steatohepatitis, Nonalcoholic fatty liver disease, Steatohepatitis]
- **Cerebrovascular disease** [System Organ Class: 'Nervous system disorders']
- **Disorder of the reproductive system** [System Organ Class = 'Reproductive system and breast disorders']
- **Kidney disease** [System Organ Class = 'Renal and urinary disorders']
- **Gout** [including hyperuricaemia) [Gout, Gouty arthritis, Hyperuricaemia]

    - Distribution of comorbidities for:
        - people with a BMI of 30 to 34.9 mg/kg^2
        - people with a BMI of ≥35 mg/kg^2

Table 18 presents the distribution of weight-related comorbidities for patients with a BMI of 30–34.9 kg/m^2 and at least one weight-related comorbidity and patients with a BMI of ≥35 kg/m^2 with at least one weight-related comorbidity from the SURMOUNT-1 trial (i.e. subgroups of the target population).

Overall, these data demonstrate that the distribution of key comorbidities in these subpopulations were broadly aligned with each other as well as the overall target population.

Table 18. Summary of comorbidities for patients with BMI of 30–34.9 mg/kg^2 and ≥35 kg/kg^2 with at least one weight-related comorbidity

Comorbidity	n (%)	
	BMI of 30–34.9 mg/kg^2 with at least one weight-related comorbidity (N=605)	BMI of ≥35 mg/kg^2 with at least one weight-related comorbidity (N=1,110)
Hypertension	[redacted]	[redacted]
Dyslipidaemia	[redacted]	[redacted]
OSA	[redacted]	[redacted]
ASCVD	[redacted]	[redacted]
Prediabetes	[redacted]	[redacted]
Hip or knee osteoarthritis	[redacted]	[redacted]
Asthma	[redacted]	[redacted]

Liver disease	[redacted]	[redacted]
Cerebrovascular disease	[redacted]	[redacted]
Disorder of the reproductive system	[redacted]	[redacted]
Kidney disease	[redacted]	[redacted]
Gout	[redacted]	[redacted]

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; OSA: obstructive sleep apnoea

- Proportion of people who had a previous mental health condition for:

As detailed in Lilly Response Part 1, psychiatric disorders (including moderate to severe depression) were not an independent exclusion criteria in the SURMOUNT-1 trial. Therefore, the data presented below for each of the requested populations are for both historical or pre-existing conditions at baseline rather than 'previous' psychiatric disorders.

Overall, the proportion of patients with a historical or pre-existing psychiatric disorder was largely aligned across the target population, people with a BMI 30−34.9 kg/m^2 and people with a BMI ≥35 kg/m^2, indicating that the presence of psychiatric disorders in the target population is representative of both people with a BMI of 30–34.9 kg/m^2 and people with a BMI ≥35 kg/m^2.

- the total target population

A breakdown of the historical and pre-existing psychiatric disorders in the target population is provided in Table 19. Overall, 25.7% of the target population has a historical or pre-existing psychiatric condition.

Table 19. Summary of historical and pre-existing psychiatric disorders in the target population

System Organ Class Preferred Term	Placebo (N=435)		TZP 5mg (N=423)		TZP 10mg (N=433)		TZP 15mg (N=414)		Total (N=1,705)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	[redacted]									
Anxiety	[redacted]									
Depression	[redacted]									
Insomnia	[redacted]									
Attention deficit hyperactivity disorder	[redacted]									
Anxiety disorder	[redacted]									
Major depression	[redacted]									
Generalised anxiety disorder	[redacted]									

Post-traumatic stress disorder										
Sleep disorder										
Adjustment disorder with depressed mood										
Tobacco abuse										
Libido decreased										
Panic attack										
Panic disorder										
Perinatal depression[a]										
Nicotine dependence										
Bipolar disorder										
Drug abuse										
Middle insomnia										
Affective disorder										
Alcohol abuse										
Intentional self-injury										
Mood swings										
Obsessive-compulsive disorder										
Persistent depressive disorder										
Menopausal depression[a]										
Adjustment disorder										
Adjustment disorder with mixed anxiety and depressed mood										
Alcoholism										
Binge eating										
Bruxism										
Claustrophobia										
Disturbance in sexual arousal										
Drug dependence										

Grief reaction	[redacted]									
Hypnagogic hallucination	[redacted]									
Mania	[redacted]									
Mixed anxiety and depressive disorder	[redacted]									
Nightmare	[redacted]									
Poor quality sleep	[redacted]									
Stress	[redacted]									
Suicidal ideation[b]	[redacted]									
Suicide attempt[b]	[redacted]									
Trichotillomania	[redacted]									

Footnotes: [a]Denominator adjusted because sex-specific event for females: N = 289 (Placebo), N = 281 (TZP 5mg), N = 285 (TZP 10mg), N = 274 (TZP 15mg). [b]Protocol deviation: a patient met exclusion criterion regarding suicidal attempts but was included in the analysis population.

- people with a BMI of 30 to 34.9 mg/kg^2

A breakdown of the historical and pre-existing psychiatric disorders in people with a BMI of 30–34.9 kg/m^2 is provided in Table 20. Overall, 25.0% of this population had a historical or pre-existing psychiatric condition, which is largely aligned with the whole target population (Question 4).

Table 20. Summary of historical and pre-existing psychiatric disorders in people with a BMI of 30–34.9 kg/m^2

System Organ Class Preferred Term	Placebo (N=150)		TZP 5mg (N=171)		TZP 10mg (N=150)		TZP 15mg (N=134)		Total (N=605)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	[redacted]									
Anxiety	[redacted]									
Insomnia	[redacted]									
Depression	[redacted]									
Attention deficit hyperactivity disorder	[redacted]									
Anxiety disorder	[redacted]									
Generalised anxiety disorder	[redacted]									
Libido decreased	[redacted]									
Major depression	[redacted]									
Tobacco abuse	[redacted]									
Adjustment disorder with depressed mood	[redacted]									
Post-traumatic stress disorder	[redacted]									

Sleep disorder										
Nicotine dependence										
Mood swings										
Persistent depressive disorder										
Menopausal depression[a]										
Adjustment disorder										
Alcoholism										
Bipolar disorder										
Bruxism										
Disturbance in sexual arousal										
Drug abuse										
Mania										
Middle insomnia										
Obsessive-compulsive disorder										

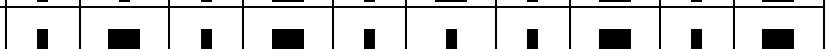
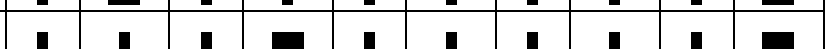
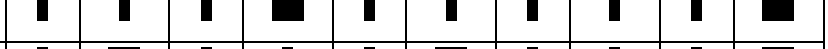
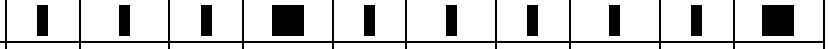
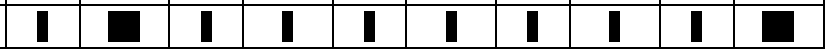
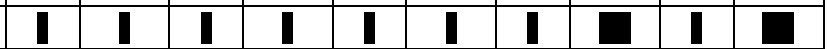
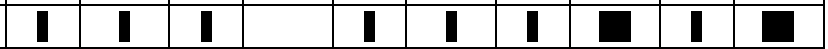
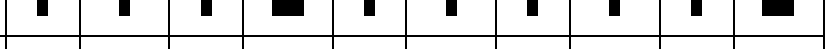
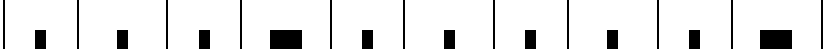
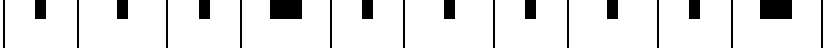
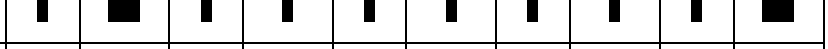
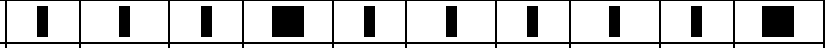
Footnotes: [a] Denominator adjusted because sex-specific event for females: N = 90 (Placebo), N = 107 (TZP 5mg), N = 106 (TZP 10mg), N = 92 (TZP 15mg)

- people with a BMI of ≥35 mg/kg^2

A breakdown of the historical and pre-existing psychiatric disorders in people with a BMI ≥25 kg/m^2 is provided in Table 21. Overall, 26.1% of the target population has a historical or pre-existing psychiatric condition, which is largely aligned with the whole target population.

Table 21. Summary of historical and pre-existing psychiatric disorders in people with a BMI of ≥35 kg/m^2

System Organ Class Preferred Term	Placebo (N=285)		TZP 5mg (N=252)		TZP 10mg (N=283)		TZP 15mg (N=280)		Total (N=1,100)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders										
Anxiety										
Depression										
Insomnia										
Attention deficit hyperactivity disorder										
Major depression										
Anxiety disorder										
Post-traumatic stress disorder										
Generalised anxiety disorder										
Sleep disorder										

Adjustment disorder with depressed mood										
Panic attack										
Panic disorder										
Perinatal depression[a]										
Tobacco abuse										
Affective disorder										
Alcohol abuse										
Bipolar disorder										
Drug abuse										
Intentional self-injury										
Libido decreased										
Middle insomnia										
Adjustment disorder with mixed anxiety and depressed mood										
Binge eating										
Claustrophobia										
Drug dependence										
Grief reaction										
Hypnagogic hallucination										
Mixed anxiety and depressive disorder										
Nicotine dependence										
Nightmare										
Obsessive-compulsive disorder										
Poor quality sleep										
Stress										
Suicidal ideation[b]										
Suicide attempt[b]										
Trichotillomania										

Footnotes: Denominator adjusted because sex-specific event for females: N = 199 (Placebo), N = 174 (TZP 5mg), N = 179 (TZP 10mg), N = 182 (TZP 15mg) [b]Protocol deviation: a patient met exclusion criterion regarding suicidal attempts but was included in the analysis population.

- Detailed gradation of the BMI distribution, providing the proportion who had BMI 30 to 30.9 mg/kg^2, 31 to 31.9 mg/kg^2

etc. Please comment on how this compares with the BMI distribution of the population in primary care in England.

Given that SURMOUNT-1 was a clinical trial, detailed gradation of the BMI distribution are available for the population. However, Lilly are not aware of equivalent data by BMI point for the population in England. Data published by HM Government gives a breakdown of the number of people in each BMI Class from primary care and community-led weight management services from April 2021–December 2022. Table 22 presents these data alongside the BMI classes in the SURMOUNT-1 trial population and target population.

Table 22. BMI distribution in SURMOUNT-1 trial population, target population and the primary care adult weight management services

BMI Class	SURMOUNT-1 whole trial population (n=2,539)	SURMOUNT-1 target population (n=1,705)	Primary Care Adult Weight Management Services (n=85,550)
Overweight (BMI 25–29.9 kg/m^2)	140 (5.5)	0 (0)	11,385 (13%)
Class I (BMI 30–34.9 kg/m^2)	876 (34.5)	605 (35.5)	29,390 (34%)
Class II (BMI 35–39.9 kg/m^2)	720 (28.4)	501 (29.4)	21,600 (25%)
Class III (BMI ≥40 kg/m^2)	803 (31.6)	599 (35.1)	21,905 (26%)

Abbreviations: BMI: body mass index
Source: HM Government, 2023 (Table 14a)[1]

4. Please provide evidence on the distribution of all relevant weight-related comorbidities in people with a BMI of ≥30mg/kg^2 in primary care and compare this with the baseline comorbidities in the target population in the SURMOUNT-1 trial.

Evidence sources

Given that the first point of contact for a patient with obesity is their GP or nurse within primary care, Lilly considers that the general population is synonymous with the 'primary care population in England'. Table 23 presents the proportion of people with key comorbidities from the target population in the SURMOUNT-1 trial, alongside relevant evidence for the distribution of these comorbidities in patients with obesity (BMI ≥30kg/m^2) from the general population.

To provide the most robust sources of evidence for the Committee's consideration, Lilly has focussed on presenting real-world data from studies that are likely to be representative of the general population. As such, the two main sources of evidence which Lilly has presented are:

- The cross-sectional RESOURCE survey (distributed May–June 2021) published by Evans *et al.* (2023)[2] which reported data on the prevalence of comorbidities in people with obesity in France, Germany, Italy, Spain, Sweden and the UK (n=1,850).

- The retrospective, longitudinal, observation cohort study published by Haase *et al*. (2021),[3] which used data from the Clinical Practice Research Datalink (CPRD) GOLD database to identify associations between BMI and obesity-related outcomes (n=2,924,952). As part of this study, data on the prevalence of comorbidities in BMI subgroups were collected and were reported in Figure 3; this Figure was subsequently used estimate the proportion of patients with a BMI ≥30kg/m^2 with the key comorbidities listed below.

Where evidence for specific comorbidities was not available from these sources, other sources were identified and are cited below in Table 23. It should also be noted that for certain comorbidities, it was not possible to locate relevant data in the general population in England so these have not been populated in the table.

Interpretation of results

Importantly, whilst these general population data may provide some reassurance to the Committee that the target population from the SURMOUNT-1 trial is generalisable to the primary care population, there are several key caveats which should be considered when interpreting the data:

- First, it is important to note that the cited studies may have used different definitions for the listed comorbidities when compared to the definitions that were used for the SURMOUNT-1 data (Question 3). This is particularly likely to have impacted comorbidities (such as ASCVD) which cover a variety of different conditions and where there is no clear consensus on the comorbidity definition.
- The data reported in these studies represents the *diagnosed population*, rather than the *true prevalence* of these conditions. As such, for specific conditions (particularly prediabetes, hypertension and dyslipidaemia) which are expected to be significantly underdiagnosed in clinical practice, the presented data should be interpreted with caution and should not be conflated with the true prevalence observed in SURMOUNT-1, where all patients had blood pressure, lipids and HbA1c measured as part of the trial protocol.
    - Using prediabetes as an example: unlike in SURMOUNT-1 where all participants were tested for their blood glucose level (allowing the prevalence of prediabetes to be estimated in this population), in clinical practice it is well-established that a large proportion of patients remain undiagnosed for both prediabetes and T2DM.[4] As such, there is likely to be a substantial difference in the proportion of patients with diagnosed prediabetes versus the true prevalence of prediabetes in people living with obesity in clinical practice.

Table 23. Comparison of baseline comorbidities in target population from SURMOUNT-1 trial versus general population (BMI ≥30kg/m^2)

Comorbidities	%		
	Target population (SURMOUNT-1; N=1,705)	General population (BMI ≥30kg/m^2)	General population sources
Prediabetes	[redacted]	4.5	Evans *et al.*[2]
Hypertension	[redacted]	39.3	Evans *et al.*[2]
		~33	Haase *et al.*[3]

Dyslipidaemia	[redacted]	22.8	Evans *et al.*[2]
		~16	Haase *et al.*[3]
Cerebrovascular disease	[redacted]		
Hip or knee osteoarthritis	[redacted]	16.1	Evans *et al.*[2]
		~12	Haase *et al.*[3]
Disorder of the reproductive system	[redacted]		
Asthma	[redacted]	12.1	Evans *et al.*[2]
		~15	Haase *et al.*[3]
OSA	[redacted]	8.6	Evans *et al.*[2]
Kidney disease	[redacted]		
ASCVD	[redacted]	3.8	Evans *et al.*[2]
Liver disease (NAFLD/NASH)	[redacted]		
Gout	[redacted]	2.68	Cea Soriano *et al.*[5]

Footnotes: grey shading denoted comorbidities where relevant sources could not be located
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; OSA: obstructive sleep apnoea.

Summary

Despite the limitations outlined above, the distribution of comorbidities in the general population (i.e. the population who would be presenting with obesity in primary care) was broadly aligned with that of the SURMOUNT-1 target population. The clinical and cost-effectiveness findings presented throughout this appraisal should be considered generalisable to primary care in England.

5. Please provide evidence on the prevalence of type 2 diabetes amongst people with a BMI of ≥30 mg/kg^2 and ≥35 mg/kg^2 in England.

Lilly does not have any data on file that directly addresses this request. Lilly suggests that the best source of available evidence for the prevalence of T2DM amongst people in specific BMI groups is data from the National Diabetes Audit (NDA) that is published annually by NHSE. However, Lilly notes that the NDA data **covers both England and Wales**. Additionally, as the NDA has not reported the number of people with T2DM according to BMI class in recent years, the most recent data available is for 2017–2018; these data are presented below in Table 24.[6]

Table 24. Total number of people with T2DM according to BMI class (2017–2018)

BMI class	Prevalence
<18.5 (underweight)	0.58%
18.5–24.9 (healthy weight)	14.95%
25–29.9 (overweight)	33.21%
30–35 kg/m^2 (obesity class I)	28.07%
35–39.9 kg/m^2 (obesity class II)	14.02%

40+ kg/m^2 (obesity class III)	9.17%

Abbreviations: BMI: body mass index; T2DM: type 2 diabetes mellitus
Source: NHSE, 2017–2018[6]

6. Please update the model so that people entering the model reflect the SURMOUNT-1 baseline comorbidities with respect to all the complications within the model. Where these baseline comorbidities were not recorded in SURMOUNT-1, adopt the same approach as for the other baseline comorbidities not recorded during SURMOUNT-1.

Table 25 presents the results of a scenario analysis in which a proportion of patients entering the model are assumed to have had a prior MI, OSA and NAFLD, in line with the baseline comorbidities reported in the target population in SURMOUNT-1. No changes have been implemented with regards to prediabetes, as a proportion of patients were already assumed to have prediabetes at baseline. In addition, Lilly has not assumed a proportion of patients have T2DM at baseline, as this would result in undue bias against tirzepatide (see response to Question 7) and would therefore compromise the validity of the results. For simplicity and due to time constraints, all prior CVD events were assumed to be MI (opposed to a combination of MI, stroke or angina). Varying this assumption (by assuming all prior events were strokes) had a limited impact on results.

Based on this scenario analysis, tirzepatide remains a highly cost-effective use of NHSE resources versus diet and exercise, with ICERs <£13,000 across all three doses.

Table 25: Scenario analysis with baseline characteristics reflecting SURMOUNT-1 population with respect to all complications in the model

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,542	15.951	-	-	-
Tirzepatide (5.0 mg)	£31,838	16.653	£7,296	0.702	£10,389
Tirzepatide (10.0 mg)	£31,191	16.544	£6,649	0.593	£11,210
Tirzepatide (15.0 mg)	£33,861	16.722	£9,318	0.771	£12,084

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

7. Please provide a scenario analysis that assumes a proportion of people have type 2 diabetes at baseline, as might be expected within primary care, suitably adjusting baseline comorbidities for those with type 2 diabetes.

Lilly understands the desire to see this request met and agrees that some proportion of patients presenting for weight management in primary care will also have T2DM. However, the economic model for this appraisal contains a number of fundamental structural assumptions that make it difficult to fulfil this request, as any results would be profoundly biased. Lilly is providing further detail on the restrictions to this analysis, as

well as relevant evidence from the SURMOUNT-2 trial that might help reassure the Committee that this issue should not be a barrier to recommendation in diabetic patients presenting for weight management in primary care.

Economic model assumptions that preclude this scenario

With respect to the requested scenario analysis, the economic model makes the following assumptions:

- HbA1c is not modelled as a continuous variable, instead simulated patients have a categorical variable comprising one of {"non-diabetic", "pre-diabetic", "diabetic"}. ***Within each category patients are assumed to have a fixed HbA1c, irrespective of which treatment they received***.

- Patients who are non-diabetic and pre-diabetic carry a risk of developing diabetes. A proportion of patients who are pre-diabetic at baseline revert to normoglycaemia using treatment-specific efficacy data. **Prediabetes reversion is the only glycaemic benefit of treatment modelled**.

- As noted in the CS Page 162, it is assumed that once patients develop T2DM, their HbA1c remains constant at 7.5%, in line with TA875 and TA664.[7, 8] This is a simplifying assumption since HbA1c would be expected to increase over time as beta-cell function deteriorates, but be maintained (at a minimum) due to patients receiving medication for T2DM. This was considered to be a reasonable simplification, because the model focuses on the progression of obesity, not T2DM.

- Likewise, with respect to costs, patients who develop diabetes in the model are modelled to incur a fixed disease cost, including antidiabetic medication costs, to avoid assumptions around where in the treatment pathway for diabetes they are and which specific anti-diabetic medications they are receiving and how these would develop and change over time in order to maintain a clinically acceptable HbA1c.

- As a consequence of these assumptions, **if patients were to be modelled to start the obesity model already diabetic, the model would ascribe no glycaemic benefit to use of tirzepatide to treat obesity** – yet the SURMOUNT-2 trial (in obesity, of patients with comorbid T2DM) and the SURPASS trial programme (in T2DM, in patients irrespective of obesity but all of whom were at a minimum overweight) have shown that tirzepatide has profound effects on HbA1c in patients with T2DM and obesity. Consequently, undertaking the requested scenario analysis would significantly underestimate the QALY gain from tirzepatide treatment, by not improving HbA1c (leading to more modelled events and deaths), while also overestimating the cost of tirzepatide treatment by applying the full anti-diabetic medication costs on top of tirzepatide (which is itself a potent anti-diabetic medication), as well as overestimating the costs by overpredicting modelled events that depend on HbA1c.

- For these reasons, the requested analysis would be profoundly biased against tirzepatide as a consequence of the simplified approach to modelling diabetes in the obesity model, as was also the case in TA875.

SURMOUNT-2: Quantifying the missing glycaemic benefits in the requested scenario

The SURMOUNT-2 trial, which was similar in design to the SURMOUNT-1 trial but included only patients with T2DM, found that tirzepatide as an adjunct to diet and exercise plus usual diabetic management led to significant reductions in HbA1c versus diet and exercise alone plus usual diabetic management. Details of SURMOUNT-2 were presented in Appendix M of the CS; the key glycaemic outcomes are represented below.

SURMOUNT-2: Mean change from baseline in HbA1c at Week 72 – *tirzepatide 10 mg and 15 mg each superior to placebo*

Mean change in HbA1c was investigated as a key secondary endpoint. Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for mean reductions in HbA1c from baseline compared with placebo at Week 72. A summary of mean change in HbA1c from baseline to Week 72 is presented in Table 26.

Table 26. Mean percent change from baseline HbA1c at Week 72; EAS

Parameters	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Baseline (%)	7.95	8.02	8.07
Percent change from baseline at 72 weeks (%)	−0.16*	−2.14†††	−2.22†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	−1.97*** (−2.15, −1.8)	−2.06*** (−2.24, −1.88)

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; HbA1c: glycosylated haemoglobin A1c; MMRM: mixed model repeated measures; N: number of participants randomly assigned and received at least 1 dose of study drug; TZP: tirzepatide.
Footnotes: MMRM analysis. Data shown are least-squares means.
*p-value <0.1; ** p-value <0.01; ***p-value <0.001 versus placebo.
†††p-value <0.001 versus baseline.
Source: Garvey, 2023; SURMOUNT-2 CSR.[9, 10]

SURMOUNT-2: Percentage of participants who achieve HbA1c <7%, ≤6.5%, or <5.7% – *tirzepatide 10 mg and 15 mg each superior to placebo*

The percentage of participants who achieve HbA1c <7%, ≤6.5%, or <5.7 was investigated as a key secondary endpoint. Tirzepatide 10 mg and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving HbA1c <7%, ≤6.5%, and <5.7% at 72 weeks. A summary of the percentage of participants achieving HbA1c targets at Week 72 is presented in Table 27.

Table 27. Percentage of participants achieving HbA1c targets at Week 72; EAS*

Parameters	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Participants achieving HbA1c <7% (%)	29.31	90.03***	90.67***
Participants achieving HbA1c ≤6.5% (%)	15.52	84.05***	86.67***
Participants achieving HbA1c <5.7% (%)	2.76	50.17***	55.33***

Abbreviations: CI: confidence interval; EAS: efficacy analysis set; HbA1c: haemoglobin A1c; MMRM: mixed model repeated measures; N/A: not applicable; SE: standard error; TZP: tirzepatide.
Footnotes: ***p-value <0.001 versus placebo.
Source: Garvey, 2023; SURMOUNT-2 CSR.[9, 10]

The base case ICERs are overestimated without the requested scenario

From the SURMOUNT-2 data it can be seen that the base case model ICERs are already biased against tirzepatide due to patients who are modelled to develop T2DM while on treatment, as the profound glycaemic efficacy of tirzepatide is not modelled. Lilly accepted this overestimation in the base case as a trade-off based on NICE's previous acceptance of the TA875 model structure and assumptions. Lilly cannot, however, accept the increased degree of overestimation that would be present in the requested scenario given that SURMOUNT-2 shows that more than half of diabetic patients treated with tirzepatide achieved an HbA1c *lower* than that modelled for non-diabetic patients in the economic model (5.7%), while more than 90% had HbA1c <7%.

Lilly notes that these fundamental structural assumptions were aligned to the model appraised and accepted by NICE in TA875, where the same issue arose but was not ultimately considered a barrier to recommendation.

Patients with T2DM in TA875

In TA875 this issue was discussed in paragraph 3.7:

a. *"… They also explained that, based on their experience, they would expect people with type 2 diabetes to have less weight loss with semaglutide than seen in STEP 1. This was also supported by data from the STEP 2 trial, a randomised controlled trial of semaglutide compared with placebo in people with overweight or obesity and type 2 diabetes. They noted that people with type 2 diabetes would be likely to have less weight loss than people without type 2 diabetes. But they commented that a small amount of weight loss is associated with greater health gain in a higher risk population such as this. The committee concluded that STEP 1 did not include people with type 2 diabetes, so did not cover the whole population who would potentially be offered semaglutide in the NHS. The committee agreed that this introduced some uncertainty about the generalisability of the clinical effectiveness results, and may have affected the reliability of the cost-effectiveness results."*

The situation faced in this appraisal is identical to that which the Committee found acceptable in TA875: the SURMOUNT-1 trial, upon which the model is based, excluded patients with T2DM at screening. As expected, people with T2DM exhibited somewhat less weight loss with tirzepatide in the SURMOUNT-2 trial, a randomised controlled trial of tirzepatide compared with placebo in people with overweight or obesity and T2DM than seen in patients without T2DM in SURMOUNT-1. Nevertheless, weight loss in SURMOUNT-2 occurred early and continued throughout the trial. At end of treatment (week 72, as in SURMOUNT-1), the weight loss was superior and clinically meaningful compared with placebo: average weight loss 13.4% (10mg TZP) and 15.7% (15mg TZP). Body weight reduction of 5% or more was observed in 81.6% (10mg TZP) and 86.4% (15mg TZP) of patients. As noted by the experts in TA875, even a small amount of weight loss is associated with greater health gain in a higher risk population with T2DM. Thus, while SURMOUNT-1 did not include people with T2D, and so did not cover the whole population who would potentially be offered tirzepatide in the NHS, the benefit of weight loss in the T2D population (demonstrated by tirzepatide in SURMOUNT-2) is known to be of greater value than in those without T2DM.

Conclusion

Since the economic model is already underestimating the glycaemic benefits of tirzepatide, and consequently all ICERs for tirzepatide are overestimated, Lilly requests that the Committee remains consistent to cover both diabetic and non-diabetic patients.

8. Please provide further scenarios to demonstrate the potential impact treatment effect waning of tirzepatide may have on the cost effectiveness estimates.
    - At a minimum this should apply a constant absolute annual percentage reduction from 72 weeks or the start of the 2nd year if this is the closest that can be implemented within the model structure) in the net gain in terms of weight, prediabetes reversal, SBP, HDL and total cholesterol of the active treatment arms over the diet and exercise arm at 72 weeks or the start of year 2). This should reduce the net gain linearly such that if the annual absolute percentage loss is 2% of the difference at 72 weeks those on active treatment will have the same values for weight, prediabetes reversal, SBP, HDL and total cholesterol at 50 year plus 72 weeks or 2 years) as those in the diet and exercise arm. From this point active treatment values should remain equal to those of the diet and exercise arm, with scenarios of active treatment costs being retained thereafter and not retained thereafter. The starting point for this linear waning of net effects and the annual percentage loss should be explored through reversible dropdowns. Please implement this through a reversible drop down within the model.

It was not possible for Lilly to implement these scenarios exactly as requested due to the significant complexity of directly fulfilling this request. However, as a pragmatic scenario, the effect of treatment waning on patient weight/BMI was explored by assuming an annual weight increase corresponding to 5% or 10% of the difference in initial change from baseline between diet and exercise and the respective tirzepatide regimen (applied to the baseline weight in order to determine the absolute incremental weight gain); this was applied to all patients on treatment after an initial period of either five or ten years, so that across the provided scenarios tirzepatide-treated patients arrived at the same weight levels as diet and exercise after 20–30 years.

Table 28, Table 29 and Table 30 present the results of different waning scenarios in which the rate of waning and the time horizon over which waning occurs have been

varied. Whilst Lilly reiterates that these scenarios are arbitrary and lack any evidence base, even in the most extreme scenario (10% waning after ten years; Table 30), tirzepatide remains a highly cost-effective use of NHSE resources vs diet and exercise, with ICERs <£15,000 across all tirzepatide doses.

Table 28. Scenario analysis exploring the impact treatment effect waning on tirzepatide (5% waning after ten years on treatment)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,877	16.588	£7,279	0.591	£12,308
Tirzepatide (10.0 mg)	£31,339	16.514	£6,742	0.517	£13,029
Tirzepatide (15.0 mg)	£33,043	16.617	£8,445	0.620	£13,628

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 29. Scenario analysis exploring the impact treatment effect waning on tirzepatide (5% waning after five years on treatment)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,966	16.541	£7,368	0.544	£13,552
Tirzepatide (10.0 mg)	£31,461	16.489	£6,864	0.492	£13,939
Tirzepatide (15.0 mg)	£33,202	16.577	£8,605	0.581	£14,823

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 30. Scenario analysis exploring the impact treatment effect waning on tirzepatide (10% waning after ten years on treatment)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,976	16.542	£7,379	0.545	£13,534
Tirzepatide (10.0 mg)	£31,405	16.488	£6,808	0.491	£13,858
Tirzepatide (15.0 mg)	£33,153	16.576	£8,556	0.579	£14,786

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

9. Please provide scenarios varying the rate of discontinuation for people on tirzepatide.

To explore the impact of varying the rate of discontinuation for people receiving tirzepatide on the cost-effectiveness results, Lilly have explored two scenarios in which the rate of discontinuation has been increased and decreased by a relative proportion of 5% vs the base case (presented in Table 31) – cost effectiveness results for these

scenarios are presented in Table 32 and Table 33, respectively. Should the Committee wish to explore further variations of this base case discontinuation rate, they may do so using the relevant dropdown in the EAG tab.

Overall, when the discontinuation rate is varied by a relative proportion of 5% vs the base case, there is minimal impact on the ICER, with <£200 changes in the ICER in either direction across all tirzepatide doses. Lilly also directs the EAG and Committee to the one-way sensitivity analysis function in the model, which varies the discontinuation inputs based on their calculated standard errors; the impact on the ICER is likewise immaterial, but is based on a statistical measure of uncertainty, rather than the arbitrary application of a relative proportion of 5% vs the base case input.

Table 31: Base case AE discontinuation rate results (based on Jastreboff *et al.* 2022)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,757	16.641	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£31,331	16.576	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£32,970	16.682	£8,373	0.685	£12,218

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 32: Scenario analysis for 5% relative increase in AE discontinuation rates from base case

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,545	16.620	£6,948	0.623	£11,144
Tirzepatide (10.0 mg)	£31,040	16.550	£6,443	0.553	£11,653
Tirzepatide (15.0 mg)	£32,737	16.670	£8,140	0.674	£12,084

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 33: Scenario analysis for 5% relative decrease in AE discontinuation rates from base case

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£31,899	16.655	£7,302	0.658	£11,101
Tirzepatide (10.0 mg)	£31,518	16.591	£6,920	0.594	£11,656
Tirzepatide (15.0 mg)	£33,264	16.694	£8,667	0.697	£12,432

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

10. Please provide the percentages of participants in SURMOUNT-1 achieving a 5% weight loss at 48-weeks separately by arm, implementing this through a reversible drop down within the model.

Table 34 presents a scenario analysis in which the primary discontinuation rate has been adjusted to align with the proportion of patients who did not achieve ≥5% weight loss at 48 weeks. Given that the proportions of patients achieving ≥5% weight loss at Week 48 (91%, 96%, and 96% for 5 mg, 10 mg and 15 mg, respectively) were not dramatically lower than in the Week 72 data (original company base case at the time of submission), implementation of this scenario has minimal impact on the ICER. As such, tirzepatide represents a highly cost-effective use of NHSE resources in this scenario compared with diet and exercise.

Table 34: Scenario analysis for application of 48-week 5% weight loss data in the model

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£24,597	15.997	-	-	-
Tirzepatide (5.0 mg)	£32,618	16.689	£8,021	0.692	£11,592
Tirzepatide (10.0 mg)	£32,453	16.658	£7,856	0.661	£11,891
Tirzepatide (15.0 mg)	£34,599	16.771	£10,001	0.774	£12,921

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

11. To the extent possible, please provide a more detailed breakdown of the direct drug costs and the microvascular complication costs taken from Capehorn et al. to estimate type 2 diabetes costs.

The annual costs for microvascular complications (£940.86) and insulin/oral treatments (£551.89) were taken from TA875, which were calculated by adding the relevant complication costs from Capehorn *et al.* and then dividing this total value by the undiscounted life expectancy (TA875 notes that these data were provided directly to the TA875 Manufacturer following direct communication with Capehorn). A full breakdown of these calculations is provided below, which were taken from TA875.

Microvascular complication costs

Annual microvascular complication costs = (a+b+c)/d

a) Lifetime ophthalmic complications: £6,460[11]

b) Lifetime ulcer, amputation, and neuropathy complications: £7,396[11]

c) Lifetime renal complications: £5,415[11]

d) Undiscounted life expectancy (years): 20.935 (TA875 notes that these data were provided directly to the TA875 Manufacturer following direct communication with Capehorn)

Costs of insulin and oral treatments

Direct complication costs = a/b

a) Total lifetime per patient, undiscounted T2DM pharmacy treatment cost (empagliflozin arm): £11,304 (TA875 notes that these data were provided directly to the TA875 Manufacturer following direct communication with Capehorn)
b) Undiscounted life expectancy (years): 20.935 (TA875 notes that these data were provided directly to the TA875 Manufacturer following direct communication with Capehorn)

For both microvascular complication and insulin/oral treatment costs, costs were then updated to 2020 costs using the PSSRU inflation indices.[12]

12. Please provide subgroup analyses for:
    - people with BMI 30 to 34.9 mg/kg^2 plus 1 weight related comorbidity
    - people with BMI ≥35 mg/kg^2 plus 1 weight related comorbidity.

    These analyses should allow other scenario analyses to be run within them, including all those requested in this document. Please make these implementable through a reversible drop down.

Considering the data available from the SURMOUNT-1 trial in the two subgroups requested, Lilly considers that a formal *post hoc* subgroup analysis of the efficacy outcomes for the trial would result in subgroup sizes that would be at significant risk of random variation due to low patient numbers as they comprise only approximately 24% and 43% of the trial population, respectively. Given this risk, Lilly has implemented the requested scenarios by applying the baseline characteristics from the two requested subgroups in the model, thus adjusting the baseline risk between the subgroups, but has applied the efficacy inputs from the base case target population (comprising the whole of the two requested subgroups, 67% of the trial population) to avoid the risk of bias in small *post hoc* subgroups.

Table 35 presents subgroup analyses for people with a BMI ≥35 kg/m^2 with at least one weight-related comorbidity. In this scenario, the baseline characteristics for the BMI ≥35 kg/m^2 with at least one comorbidity is used, but efficacy data from the target population (BMI ≥30 kg/m^2 with at least one weight-related comorbidity) is used. This subgroup analysis finds that tirzepatide remains a highly cost-effective use of NHSE resources versus diet and exercise, with ICERs <£11,500/QALY across all doses.

Table 35: BMI ≥35 kg/m^2 with at least one weight related comorbidity, with relevant baseline characteristics but target population efficacy data

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£26,583	15.807	-	-	-
Tirzepatide (5.0 mg)	£33,149	16.480	£6,567	0.673	£9,760

Tirzepatide (10.0 mg)	£32,867	16.445	£6,284	0.638	£9,847
Tirzepatide (15.0 mg)	£34,852	16.546	£8,269	0.739	£11,184

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Table 36 presents a subgroup analysis for the population with a BMI 30–34.9 kg/m^2 with at least one weight related comorbidity. As above, this subgroup analysis uses the baseline characteristics for the specific subgroup, but efficacy data from the target population.

As expected, given the lower baseline risk, the ICERs in this subgroup are higher than the population with a BMI ≥35 kg/m^2 with at least one weight related comorbidity. Nevertheless, tirzepatide remains a cost-effective use of NHSE resources versus diet and exercise.

Table 36: BMI 30–34.9 kg/m^2 with at least one weight related comorbidity, with relevant baseline characteristics and target population efficacy data

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Diet and Exercise	£20,354	16.376	-	-	-
Tirzepatide (5.0 mg)	£28,549	16.953	£8,195	0.577	£14,195
Tirzepatide (10.0 mg)	£28,263	16.878	£7,909	0.502	£15,761
Tirzepatide (15.0 mg)	£29,891	16.915	£9,537	0.539	£17,697

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Consistent with the implementation of all other request scenarios, these subgroup analyses are implementable through a reversible drop down.

13. Please implement the analyses of multi-year risk for events reported in table 6 of the stakeholder comments form (23 Feb 2024) within a reversible dropdown in the model.

For information, the EAG has provided additional analysis on the annualisation of risk functions used in the model. This has been uploaded to NICEdocs for your attention.

This request has not been implemented in the model, as Lilly is concerned that there are several limitations with the EAG analysis on the annualisation of risk functions used in the model:

a) Lilly notes that the values provided by the EAG are based on patient characteristics that are aligned with the cohort average at baseline, rather than an individual sampled patient (at baseline and/or reflective of any changes to these characteristics through the simulated patient's lifetime). Any observed changes in the ICERs in this scenario may therefore simply be a product of any differences between the cohort average and the individual sampled patient data – as such, Lilly does not consider

that these data would suitably address any concerns around this issue and would introduce more, not less, uncertainty.

b) In addition, categorical variables have not been incorporated fully – for example, the cohort used for the purposes of the provided calculations are assumed to always be White, moderate smokers and have hypertension but not have any other comorbidities (including assuming that no patients have treated hypertension), which does not represent the distribution of the sampled patients. Further, the calculations assume no patients have prediabetes.
c) The calculations also do not account for any potential reduction in BMI from when a patient enters the model (or any other changes to baseline characteristics, however BMI is expected to have the greatest impact on results), which means any difference between treatment arms is substantially reduced. In other words, a patient on tirzepatide and a patient on diet and exercise are assumed to have identical patient characteristics (including key surrogate endpoints in the model such as weight, SBP, etc.) despite the calculations being applied throughout the modelled time horizon.
d) In addition, Lilly has noted that the calculations assume that patients are already in the period where BMI is increasing in line with natural weight gain. As such, these data are not appropriate in scenarios where patients are still in the 72-week trial period (and experiencing a reduction in BMI) or if a patient is older than 68 years (after which point natural weight gain is no longer modelled and BMI is constant).
e) Finally, Lilly would highlight that the EAG's analyses have not been validated, so the utility of these data to reduce any uncertainty around this issue is likely to be limited.

Nevertheless, Lilly would highlight that the estimations suggested by the EAG do not vary significantly compared with the method that is currently used in the model. This is shown in Table 37. Please note for the purposes of this comparison, Lilly's "constant" values reported in the table have the same assumptions in terms of points (a) – (e) noted as limitations above. This has done so that the values are comparable with the EAG's annualisation spreadsheet.

Table 37. Comparison of EAG versus Company method of annualisation of risk functions

Risk equation	Company assumption	EAG analysis
QRisk3 - Males	0.004	0.004–0.015
QRisk3 - Females	0.002	0.002–0.01
QDiabetes - Males	0.018	0.018–0.025
QDiabetes - Females	0.011	0.011–0.015
OSA - Males	0.066	0.066–0.083
OSA - Females	0.023	0.023–0.03

In addition, to further alleviate any concerns around this issue, Lilly wishes to reiterate that even when extreme and unrealistic scenarios are explored, tirzepatide remains highly cost-effective. Specifically, in scenarios where the number of T2DM events occurring over the modelled time horizon is reduced by 25% and 50%, tirzepatide remains cost-effective versus diet and exercise, as presented in Table 38.

Lilly trusts that these extreme scenarios will help to remove any decision uncertainty surrounding this issue, as they clearly demonstrate that even if Lilly had dramatically overestimated the number of clinical events occurring in the model, tirzepatide would remain cost-effective.

Table 38. Scenario Analyses for Multi-Year Risk for Events

Intervention	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated Company Base Case: No adjustment to risk equation			
Tirzepatide (5.0 mg)	£7,160	0.644	£11,116
Tirzepatide (10.0 mg)	£6,734	0.579	£11,627
Tirzepatide (15.0 mg)	£8,373	0.685	£12,218
Scenario 1: Reduction of T2DM incidence in all arms by 25%			
Tirzepatide (5.0 mg)	£7,821	0.636	£12,295
Tirzepatide (10.0 mg)	£7,572	0.572	£13,235
Tirzepatide (15.0 mg)	£9,139	0.674	£13,566
Scenario 2: Reduction of T2DM incidence in all arms by 50%			
Tirzepatide (5.0 mg)	£8,578	0.618	£13,882
Tirzepatide (10.0 mg)	£8,329	0.562	£14,832
Tirzepatide (15.0 mg)	£10,092	0.655	£15,411

Abbreviations: ICER: incremental cost effectives ratio; Incr: incremental; QALY: quality-adjusted life year

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Appendix

Appendix Table 1. Proposed appointments for MDT support delivered in primary care for patients with obesity as per Lilly Response Part 1

Visit	Purpose	Duration (mins)	Assumed resource	Activity/Skill	Required for D&E, or specific to those on tirzepatide	Justification for amendment(s)
Stage 1: Patient Assessment Counselling and Training						
~~1~~	~~HCA Review~~	~~10~~	~~HCA~~	~~Blood Pressure, Height & Weight~~	N/A	• Lilly does not consider an Health Care Assistant (HCA) review as a treatment-specific requirement for tirzepatide; instead, an HCA review would be required for any intervention in any therapy area (As per CG189 and good clinical care for obesity management with or without pharmacotherapy)[13] • Lilly therefore proposes removing this cost.
1	Initial consult and assessment	10	GP/ Consultant	Alternative to GP could be used, for example: • ANP (LTC management) / other healthcare professionals with LTC management • Senior practice nurses (diabetes specialist) • However, GP will be ultimately accountable for patient care.	Relevant for both tirzepatide and diet and exercise	• This appointment would represent the starting point in the patient journey. It is expected that a 10-minute (rather than a 45-minute) consultation would be appropriate and realistic to enable a GP to assess their patient (including for psychological needs) as per CG189 and discuss treatment options, aligned with real-world primary care practice in the UK.[14] • For patients opting for tirzepatide treatment, this appointment would also be used to write-up an initial repeat prescription and schedule a second appointment for administration training by a nurse. In some surgeries, it may be possible for administration training to be carried out on the same day, enabling a patient to begin treatment immediately. • This consultation would be required for both patients opting to receiving tirzepatide, as well as those choosing

				• 10 mins to include psychological support assessment as per CG189.		diet and exercise intervention only, as both patient populations would require an initial consultation, an assessment for their obesity, and consequently a treatment decision.
~~1~~	~~Blood Test + thyroid test~~	~~N/A~~	~~N/A~~		N/A	• Blood and thyroid tests are not required for tirzepatide (not specified in the SmPC), so they should not be considered as a treatment-specific requirement. • Lilly therefore proposes removing this cost.
~~2~~	~~Patient Training~~	~~30~~	~~Nurse~~	~~Checklist review + patient education (could be group sessions)~~	N/A	• This is considered a duplicate of the 'Week 0 – treatment initiation (2.5mg)' cost in Week 3 as both comprise patient training/education. • Lilly therefore proposes removing this cost.
2	Patient education and dietary/exercise advice	30	Dietician or suitably qualified HCA	Diet advice and guidance	Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA.
~~2~~	~~Clinical Review and prescription validation~~	~~15~~	~~GP/Consultant~~	~~Prescription check~~	N/A	• Current prescribing practice in primary care does not require a separate prescription check. • Lilly therefore proposes removing this cost.

3	Week 0 - Treatment initiation (2.5mg)	20	Nurse	Patient education could be in video format for some patients.	Relevant for tirzepatide only	• Based on extensive patient and HCP feedback from Lilly's other injectable products, 40 minutes would be excessive for patients to receive training for the administration of tirzepatide. Lilly has therefore reduced this appointment duration to 20 minutes.[15, 16]
Stage 2: Titration & Weight Management Support						
4	Week 4 - dose titration (5 mg)	30	Nurse	Same as above - different skills can do this~~, needs to be a prescriber. Contra-indication considerations (polypharmacy) drives requirement for senior oversight. Recognition that this could change as more long term data becomes available.~~	Relevant for tirzepatide only	• To reflect the fact that some patients may experience adverse events during the dose titration phase, Lilly suggests that a 30-minute virtual appointment is provided when patients titrate from tirzepatide 2.5 mg to 5 mg so that patients can consult with the nurse about any issues they may be experiencing.
5	Week 8 - dose titration (7.5 mg)	15	Nurse			• Following the first dose titration from tirzepatide 2.5mg to 5mg (the first maintenance dose), Lilly has conservatively assumed that a 15-minute virtual consultation with a nurse would be the most that is required to check that the patient needs to proceed to the next titration step. • Consistent with the use of GLP-1 RAs in T2DM, it is assumed that titration would be carried out unless a patient experiences any issues (i.e. to achieve a patient's maximum tolerated dose). As such, Lilly consider that these appointments could be carried out virtually by a nurse, with the purpose of ensuring that the patient is not experiencing any issues (adverse events or otherwise) before dose escalation. • Although dose titration appointments are expected to vary by patient based on a patient-centred shared management plan that is aligned to both the patient's goals and the summary of product characteristics (SmPC), Lilly have presented a more realistic scenario that is more aligned with the use of GLP-RAs in T2DM where no nurse consultation is provided at Weeks 8, 12, 16 and 20 and is instead replaced with a single 15-minute
6	Week 12 dose titration (10 mg)	15	Nurse			

						nurse consultation at Week 26.
6	Week 12 - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA
7	Week 16 dose titration (12.5 mg)	15	Nurse		Relevant for tirzepatide only	• As per visit 4–6 above
8	Week 20 dose titration (15 mg)	15	Nurse			
9	Week 24 - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• To reflect the SURMOUNT-1 protocol, where diet and exercise support was provided by a dietician or other qualified delegate, patient education and dietary/exercise advice could be provided in primary care by a suitably qualified HCA
~~10~~	~~Week 26 - Medicines Review~~		~~GP~~		N/A	• This is considered a duplicate of the 'Muti Disciplinary Team (MDT) Patient Review' in the Additional Cost section below as both comprise an MDT review. • Lilly therefore proposes removing this cost.
Stage 3: Maintenance (every 12 weeks thereafter)						
10,11	Week 36 + 48 (Year 1) - Dietary/exercise advice	30	Dietician or suitably qualified HCA		N/A	As per the SURMOUNT-1 protocol, it expected that dietary and exercise advice could be provided by a suitably qualified HCA

12-16	Week 60, 72, 84, 96 (Year 2) - Dietary/exercise advice	30	Dietician or suitably qualified HCA		Relevant for both tirzepatide and diet and exercise	• As per the SURMOUNT-1 protocol, it expected that dietary and exercise advice could be provided by a suitably qualified HCA
17-21	~~Week 108, 120, 132, 144 (Year 3) - Dietary/exercise advise~~		~~Dietician~~		N/A	• It is expected that patients would have achieved their target weight loss by the end of Year 2 in the Maintenance Phase, and would be well-equipped to manage their diet and exercise, following NHS Live Well Guidance, without further intervention. Therefore, it is not anticipated that additional dietary and exercise advice would be required beyond Year 2 in the Maintenance Phase • Lilly therefore proposes removing this cost.
Additional Costs						
N/A	MDT patient review	10	GP/Consultant ~~+ Nurse + Clinical Pharmacist + Psychologist~~	Costing will assume ~~minimum~~ 1 MDT ~~discussions~~ per patient per year. To start from week 52	Relevant for tirzepatide only	• In primary care, an MDT patient review would likely involve a GP independently reviewing patient notes from supporting nurse(s), dietician(s) or other HCAs, rather than requiring an in-person meeting with all three professionals present. • Lilly therefore proposes removing nurse, clinical pharmacist and psychologist costs. • Consistent with annual reviews performed in primary care for other chronic diseases, it is also expected that such a review would occur on an annual basis from the end of Year 1, rather than from Week 26 where the maintenance phase has not yet been reached.

N/A	~~Psychological support~~		~~Psychologist / Psychiatrist~~	~~Costing will assume 1 in 3 patients will require psychologist support. Where psychologist support is required assume 5 appointments in year 1 (as per DHSC/NHS obesity prescribing pilots)~~	N/A	• Patients requiring psychological support would be provided it (as per CG189 and good standards of clinical care), regardless of whether they receive tirzepatide treatment or not. It is not a cost that is specifically attributed to the use of tirzepatide (and would apply equally to diet and exercise, or even no intervention). • Lilly therefore proposes the removal of this cost as it is not relevant to consider in the economic analysis for tirzepatide.
N/A	Sharps & disposal	N/A	N/A		N/A	N/A – no amendments proposed

Table 2. NHS England proposed clinical services and costs of obesity management

Visit	Purpose	Duration	Assumed Resource for costing	Activity / Skill	Assumptions
Stage 1: Patient Assessment, Counselling and Training					
1	HCA Review	10	HCA	Blood Pressure, Height & Weight	
1	Initial consult	45	GP/Consultant	Alternative to GP could be used, for example: - ANP (LTC management) / other health care professionals with LTC management experience. - Senior practice nurses (diabetes specialist) However, GP will be ultimate accountability for patient care. 45 mins to include psychological support assesment.	The screening & eligibility process for the clinical trial is not appropriate in routine setting. Alternative screening and eligibility activity is based on NHSE. clinical input.
1	Blood Test + thyroid test	N/A	N/A		
2	Patient Training	30	Nurse	Checklist review + patient education (could be group sessions)	
2	Patient Education & Dietary/exercise advice	30	Dietician	Dietetic advice and guidance	
2	Clinical Review and prescription validation	15	GP/Consultant	Prescription check	
3	Week 0 - Treatment initiation (2.5mg)	15	Nurse	Patient education could be in video format for some patients.	As per SURMOUNT-1 trial
Stage 2: Titration & Weight Management Support					
4	Week 4 - dose titration (5 mg)	20	GP/Consultant	Same as above - different skills can do this, needs to be a prescriber. Contra-inidcation considerations (polypharmacy) drives requirement for senior oversight. Recognition that this could change as more long term data becomes available.	As per SURMOUNT-1 trial
5	Week 8 - dose titration (7.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 dose titration (10mg)	20	GP/Consultant		As per SURMOUNT-1 trial
6	Week 12 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
7	Week 16 dose titration (12.5mg)	20	GP/Consultant		As per SURMOUNT-1 trial
8	Week 20 dose titration (15mg)	20	GP/Consultant		As per SURMOUNT-1 trial
9	Week 24 - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
10	Week 26 - Medicines Review	20	GP		Activity based on clinical input
Stage 3: Maintenance (Every 12 weeks thereafter)					
10,11	Week 36 + 48 (Year 1) - Dietary/exercise advice	30	Dietician		As per SURMOUNT-1 trial
12-16	Week 60, 72, 84, 96 (Year 2) - Dietary/exercise advise	30	Dietician		As per SURMOUNT-1 trial
17-21	Week 108, 120, 132, 144 (Year 3) - Dietary/exercuse advise	30	Dietician		As per SURMOUNT-1 trial
Additional Costs					
N/A	Multi Disciplinary Team (MDT) Patient Review	15	GP/Consultant + Nurse + Clinical Pharmacist+ Psychologist	Costing will assume minimum 2 MDT discussions per patient per year. To start from week 26	Activity based on clinical input
N/A	Psychological Support	30	Psychologist / Psychiatrist	Costing will assume 1 in 3 patients will require psychologist support. Where psychologist support is required assume 5 appointments in year 1 (as per DHSC/NHS obesity prescribing pilots).	Activity based on clinical input
N/A	Sharps & disposal	N/A	N/A		Activity based on clinical input

Appendix Table 3: NHSE proposed breakdown of appointments over 3 years

Number of appointments by profession		Year 1	Year 2	Year 3	Coverage	Cost per slot (£)	Year 1	Year 2	Year 3
GP	10 min slots	21	3	3	-	£ 41.00	£ 861.00	£ 123.00	£ 123.00
Nurse	10 min slots	4.5	3	3	-	£ 18.55	£ 83.47	£ 55.64	£ 55.64
HCA	10 min slots	1	0	0	-	£ 7.14	£ 7.14	£ -	£ -
Nurse group	10 min slots	3	0	0	-	£ 18.55	£ 55.64	£ -	£ -
Clinical pharmacist	10 min slots	3	3	3	-	£ 11.29	£ 33.88	£ 33.88	£ 33.88
Dietician	30 min slots	5	4	4	-	£ 27.19	£ 135.97	£ 108.77	£ 108.77
Psychologist	30 min slots	5.5	3	3	0.33	£ 33.88	£ 62.11	£ 33.88	£ 33.88
Total per patient cost (GP Led)							**£1,239.21**	**£ 355.18**	**£ 355.18**
Total per patient cost (Consultant Led)						**£ 23.33**	**£ 868.21**	**£ 302.18**	**£ 302.18**

Interpretation of Q1

The scenarios listed in Question 1 have been addressed, interpreting the requests in distinct sections depending on treatment discontinuation and selectable cost endpoints as per the requests. To illustrate the approach taken, a description of the interpretation of Scenario 2 has been provided:

Scenario 2 request	
Intervention arm (all include GP assessment)	**Comparator arm (all include GP assessment)**
NHSE proposed resource use for obesity services while on tirzepatide, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model	NHSE proposed resource use for obesity services minus GP titration appointments for 2 years, then dietician visit 4 times per year + psychological support for 1/3 (5 appts per year) until 2, 4 or 6 years in model
Scenario 2 interpretation	
Intervention arm (all include GP assessment)	**Comparator arm (all include GP assessment)**

Patients receiving tirzepatide:
• NHSE proposed resource use for patients on treatment
Patients after discontinuing tirzepatide:
• Prior to the selectable 2/4/6-year endpoint, for patients who have discontinued:
  ○ Dietician visits 4 times a year
  ○ Psychological support 5 times a year (for 1/3 of patients only)
• After the selectable 2/4/6-year endpoint:
  ○ No resource use for obesity services
	Patients receiving diet and exercise:
	• For the first 2 years:
	  ○ NHSE proposed resource use, excluding GP titration appointments
	• From 2 years until the selectable 2/4/6-year endpoint:
	  ○ Dietician visits 4 times a year
	  ○ Psychological support 5 times a year (for 1/3 of patients only)
	• After the selectable 2/4/6-year endpoint:
	  ○ No resource use for obesity services

Abbreviations: GP: general practitioner; NHSE: National Health Service England.

Implementation of Q1 in Economic Model

The per cycle costs for each requested scenario has been added into tables in the 'NHSE Resource Use' tab in the model. The tab incorporates cost inputs and time inputs (in minutes) per resource type for each scenarioto determine the total cost per patient. The

total costs per patients are recorded in interim ‘live’ tables, which update depending on the user scenario selection, and subsequently feed into the respective treatment arm traces. Notably, Scenarios 6 and 7, instead use cost inputs directly, which is more appropriate for the annual consultant led costs.

For simplicity, the minute and total cost tables in the ‘NHSE Resource Use’ tab are split into ‘All Patients’, ‘Total Cost per Patient on Treatment’ (per treatment arm) and ‘Total Cost per Patient off Treatment’ (per treatment arm); the former relates to costs accrued in each treatment arm equally, whereas the latter two relate to treatment-specific resource use requests (for pre- and post-discontinuation respectively). This distinction is not required in the Diet and Exercise arm as patients do not discontinue from Diet and Exercise. The distinction is also not relevant to the requests which include semaglutide, so a single ‘Total Cost per Patient’ column table is used instead.

The interim ‘live’ tables in the ‘NHSE Resource Use’ tab subsequently feed into the respective treatment arm traces. If none of the NHSE resource utilisation scenarios are selected, the original ‘BMI related HCRU’ costs in each treatment trace are used instead.

Interpretation of Results

In some cases, such as Scenario 2, a selectable 2-, 4- or 6-year endpoint has been requested for some of the resources. As per the interpretation in the table above, this endpoint only affects patients who have discontinued treatment in the tirzepatide arm. Therefore, adjusting this time point results in changes to the ‘Total Cost per Patient off Treatment’ tables in the tirzepatide arms and the ‘Total Cost per Patient’ table in the Diet and Exercise arm.

Increasing the selectable 2-, 4- or 6-year endpoint for a given scenario results in lower ICERs. This is because while total costs increase in each arm, they increase by a smaller amount in the tirzepatide arm as fewer patients (i.e. only those who have discontinued) accrue these costs.

In all scenarios tirzepatide remains a highly cost-effective use of NHS resources, and inputs are user-adjustable should other scenarios be of interest.

External Assessment Group's report post AC1

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

Produced by	*Warwick Evidence*
Authors	*Dr. Ewen Cummins, McMDC Ltd.* *Dr. Rhona Johnston, McMDC Ltd.* *Rachel Court, Information Specialist, Warwick Evidence* *Mubarak Patel, Research Fellow, Warwick Evidence* *Dr. Lena Al-Khudairy, Associate Professor, Warwick Evidence*
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Date completed	*05 April 2024*

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Ewen Cummins critiqued the cost-effectiveness evidence, Rhona Johnston reviewed and revised the VBA model implementation. Both implemented the revised EAG economic modelling. Mubarak Patel critiqued statistical aspects of the Company submission and provided statistical input to this report. Rachel Court critiqued the conducted additional EAG searches. Lena Al-Khudairy supported the critique of the clinical effectiveness evidence and coordinated the project.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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1 Executive summary

When reading this report it should be borne in mind that the EAG received the Company amended model at midday on the 2nd of April 2024. The EAG has had effectively 2 days to review the Company modelling, revise the model and undertake its own modelling*. In these circumstances the likelihood of EAG modelling error is not trivial. Committee may already view this assessment as having a high decision risk for the NHS. The possibility of EAG modelling errors increases this decision risk.

All issues identified represent the EAG's view and are not the opinion of NICE.

* Being an individual patient simulation model each run takes around 5 minutes.

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID 6179	Summary of issue	Section
Issue 1	Does the assumed gamma distribution of BMI accurately reflect the SURMOUNT-1 trial? Does the SURMOUNT-1 trial BMI distribution reflect the primary care population that will receive tirzepatide? What BMI distribution should be assumed?	2.1.3
Issue 2	Is it reasonable to assume that patients who have been living with obesity for some time prior to weight loss and their new healthier weight have the same risks of obesity related complications as those who have always been at that healthier weight? Does prior obesity have long term effects?	2.1.4
Issue 3	Are the company scenarios of a 5% loss and a 10% loss of net effect at 5 and 10 years with indefinite benefit thereafter while on treatment sufficient? How should treatment effect waning be considered?	2.1.5
Issue 4	Does the annualization of 10-year and 5-year risks and their annual updating lead to bias due to the risk factors changing over the 10-year and 5-year period? Results may not be sensitive to this but it increases the uncertainty around the assessment.	2.1.6
Issue 5	What MDT costs should be applied to tirzepatide and to diet and exercise for primary care patients, and for how long?	2.1.7

ID 6179	Summary of issue	Section
Issue 6	What are the most reasonable costs to apply for T2DM? Are the EAG direct drug cost estimates or the Company sourced direct drug costs preferable? Should the base case include some or all of the Company sourced costs for microvascular complications?	2.1.8
Issue 7	The model structure and clinical effect estimates are for those without T2DM. Key model drivers are the cost offsets and quality of life gains from avoiding T2DM. The current modelling provides no guide to the cost effectiveness of tirzepatide among those with T2DM. The company has not presented a cost effectiveness estimate for those with T2DM. Does it need to do so, and if so how? TA924 has assessed and approved tirzepatide for those with T2DM subject to some conditions. Does the current assessment need to make a recommendation for those with T2DM?	2.1.9
Issue 8	The estimated cost effectiveness of tirzepatide is worse among those with a lower BMI. Should BMI subsets of the Company target group be considered?	2.1.3 2.2

1.2 *Committee concerns*

NICE summarised the concerns around the economics expressed by Committee during its first meeting as follows.

- The primary comparison is between tirzepatide 15mg and diet and exercise delivered by an MDT in primary care. Further information on the costs of the MDT team has been requested from NHSE by NICE.
- Tirzepatide use will be ongoing, while semaglutide is limited to a two year duration.
- The responder proportions with 5% weight loss should be based upon 48 week data.
- Not including the observed baseline comorbidities in the model does not necessarily reflect the patient population.
- Patients in all arms are likely to experience the natural increase in weight over time.
- The EAG UKPDS T2DM costs are preferred to the original Company estimate based upon hospitalisation costs.

NICE and the Chair requested that the Company provide additional data and analyses.

1.3 *Modelled cost effectiveness: Company base case and scenarios*

The Company approach has been to retain its original base case and to submit one way scenario analyses around this. This is in line with the NICE request but is of limited usefulness for decision making as it does not revise the model to what seem likely to be the Committee's preferred set of assumptions.

The Company has made two revisions to its base case:

- Correcting a minor error in the calculation of QALYs.
- Applying the EAG inferred 48-week 5% weight loss responder rates.

It is unclear why the Company has applied the EAG inferred 48-week 5% weight loss responder rates rather than the actual SURMOUNT-1 responder rates.

The EAG presents the Company results for the comparison of tirzepatide 15mg with diet and exercise (D&E) in Table 2 below.

Table 2: Company base case with scenarios

Analysis	ICER
Company base case	£12,218
Resource use scenarios	
NHSE estimates while on tirzepatide, none for D&E	£16,910
NHSE estimates while on tirzepatide and D&E, subs. FU 2yr	£16,274
NHSE estimates while on tirzepatide and D&E, subs. FU 4yr	£15,970
NHSE estimates while on tirzepatide and D&E, subs. FU 6yr	£15,713
NHSE estimates while on tirzepatide and D&E, subs. GP 2yr	£16,812
NHSE estimates while on tirzepatide and D&E, subs. GP 4yr	£16,737
NHSE estimates while on tirzepatide and D&E, subs. GP 6yr	£16,673
Company resource use	£12,863
Company proposed, subsequent GP	£12,783
NHSE SWMS while on tirzepatide and D&E, subs. GP tirzepatide	£12,446
NHSE SWMS while on tirzepatide and D&E, subs. GP 2yr	£14,649
NHSE SWMS while on tirzepatide and D&E, subs. GP 4yr	£14,573
NHSE SWMS while on tirzepatide and D&E, subs. GP 6yr	£14,510
Baseline MI, OSA and NAFLD as per SURMOUNT-1 target pop.	£12,084
5% loss of effect at 5 years	£14,823
10% loss of effect at 5 years†	£17,160
20% loss of effect at 5 years	£20,151
5% loss of effect at 10 years	£13,628
10% loss of effect at 10 years	£14,786
20% loss of effect at 10 years	£15,770
5% relative increase in discontinuations	£12,084
5% relative decrease in discontinuations	£12,432
Natural weight gain in all arms	£14,268
SURMOUNT-1 target group 48 week responder data	£12,921
BMI ≥ 35 kgm^{-2} + 1 comorbidity baseline char.	£11,184

† Calculated by the EAG using the Company 02 April 2024 model. This also applies to the 20% treatment waning scenarios and the natural weight gain in all arms scenario.

BMI 30 – 35 kgm^{-2} + 1 comorbidity baseline char.	£17,697
T2DM risk reduced by 25% T2DM risk reduced by 50%	£13,566 £15,411

1.4 *Cost effectiveness: EAG's key issues*

Time constraints mean that the effect upon the tirzepatide 15mg compared to diet and exercise ICER is typically only presented for either the Company base case ICER of £12,218 per QALY or the EAG ICERs of:

1. £24,735 per QALY for the Company target group
2. £21,450 per QALY when applying the BMI ≥ 35 kgm^{-2} baseline characteristics
3. £30,533 per QALY when applying the BMI 30 – 35 kgm^{-2} baseline characteristics
4. £19,719 per QALY when applying the BMI ≥ 35 kgm^{-2}, prediabetic and high CVD risk baseline characteristics and clinical effect estimates
5. £27,682 per QALY for those with a BMI 30 - 35 kgm^{-2} or no prediabetes or no high CVD risk, inferred from (1) and (4) above.

Issue 1: Is the assumed gamma distribution for BMI reasonable

Report section	2.1.3
Why important	The Company model assumes that BMI follows a gamma distribution. For the target population this samples very few patients at the bottom end of the distribution. Their cost effectiveness is somewhat worse. The gamma distribution may not be a reasonable assumption and may bias the analysis. The method of truncating the gamma distribution for the BMI 30 – 35 kgm^{-2} increases this bias. The BMI distribution of the primary care population may be to the left of the SURMOUNT-1 distribution. It may be more reasonable to model it as a truncated normal distribution with a lower bound of a BMI ≥ 30 kgm^{-2}, and an upper bound of 35 kgm^{-2} where relevant.
EAG alternative approach	Applying the actual SURMOUNT-1 target population distribution. Applying the general population distribution and assuming a truncated normal.
Effect on ICER	The effect of the actual SURMOUNT-1 target population distribution is unknown. Applying the general population distribution and assuming a truncated normal worsens the EAG ICER for the target population from £24,735 to £29,176 per QALY.
Additional evidence or analyses.	SURMOUNT-1 BMI distribution by BMI point for the target group. This was requested by NICE but was not supplied. Correcting the truncated gamma distribution within the model.

Issue 2: Does prior obesity have long term effects?

Report section	2.1.4
Why important	The model assumes that someone who, say, has had a BMI of 37 kgm^{-2} for twenty years who loses weight to a BMI of 32 kgm^{-2} has the same risks of events as someone who has always had a BMI of 32km^{-2}. Some of the damage of obesity may not be fully reversed; e.g. joint damage may be permanent. There is some evidence in the literature that the assumption is unreasonable, particularly for the subset of those with a BMI 30 – 35 kgm^{-2}. The model may overestimate the effect of weight loss upon obesity related complications and mortality.
EAG alternative approach	Exploring this through ad hoc adjustments to the direct effects of obesity related complications upon costs and quality of life and upon mortality, based upon the estimates of a Novo Nordisk sponsored study of UK CPRD/HES data. This is only available grouped by BMI 30 – 35 kgm^{-2} and BMI ≥ 35 kgm^{-2}.
Effect on ICER	The largest adjustments made by the EAG to explore this, including mortality effects, worsen the ICER for the BMI 30 – 35 kgm^{-2} baseline characteristics modelling from £30,533 to £40,591 per QALY. The ICER for the BMI ≥ 35 kgm^{-2} baseline characteristics modelling, excluding mortality effects as these are less obviously reasonable to explore for this subset, worsens from £21,450 to £22,862 per QALY.
Additional evidence or analyses.	A review of the literature for further evidence.

Issue 3: What waning of treatment effect is reasonable to explore?

Report section	2.1.5
Why important	Results are sensitive to whether the net effect of tirzepatide wanes over time. The company provides limited treatment waning scenarios of a stepped loss in the net treatment effect at 5 years and at 10 years of 5% and 10%, after which the remaining 95% and 90% net effects are retained indefinitely while on treatment. The EAG augments these with scenarios of a 20% loss of effect. Even a small constant annual loss of effect, e.g. 1% annually, will worsen the ICER more than the stepped 5% change at 5 years.
EAG alternative approach	NICE asked the company to provide a scenario that applied a constant annual loss of net effect. The Company states that this cannot be easily implemented. The EAG finds this surprising given the Company ability to change the rate of pre-diabetes loss and to apply constant annual BMI changes to the active treatment arms.
Effect on ICER	The company base case ICER of £12,218 per QALY with a loss of effect at 5 years and subsequent retention of the remaining effect to: • £14,823 per QALY for a 5% loss of effect • £17,160 per QALY for a 10% loss of effect • £20,151 per QALY for a 20% loss of effect If the loss of effect is at 10 years the ICER worsens to £13,628, £14,786 and £15,770 per QALY respectively.
Additional evidence or analyses.	The NICE requested scenarios.

Issue 4: Does the annualization of 10-year and 5-year risks result in bias?

Report section	2.1.6
Why important	The model uses risk functions that estimate the risks of events over 10 years and over 5 years, and then annualises these to align with the annual model cycle. These risks are updated each model cycle over the subsequent 10 or 5 years, when conceptually a more correct approach would be to retain the initial annualised risk over the subsequent 10 or 5 years.
EAG alternative approach	What seems conceptually reasonable cannot be implemented within the model structure. Exploratory analyses that apply ad hoc adjustments to the 10-year risk functions, informed by EAG work on the range of possible biases.
Effect on ICER	The EAG exploratory analyses suggest that at central values the effects may be limited, the EAG ICER for the Company target group worsening from £24,735 to £25,319 per QALY. The bias seems likely to be larger for younger patients in their thirties. The overall effect is unknown. It increases the uncertainty about the ICERs.
Additional evidence or analyses.	None for present purposes.

Issue 5: What MDT costs apply to tirzepatide and diet and exercise in primary care?

Report section	2.1.8
Why important	The primary care administration and monitoring costs for tirzepatide and diet and exercise are model drivers.
EAG alternative approach	The EAG bases its estimates for tirzepatide on the NHSE estimates. The EAG provides a scenario that applies these costs for a maximum of two years for the diet and exercise, excluding the tirzepatide titration costs. The two year duration is aligned with the Company modelling assumptions and NHSE opinion, though the NHSE notes that these services are not currently generally provided.
Effect on ICER	The NHSE estimates are not much affect by whether the service is GP led or consultant led. The EAG ICER for the Company target group improves from £24,735 to £24,434 per QALY. Applying MDT costs for diet and exercise improves it from £24,735 to £24,257 per QALY, and if consultant led to £23,987 per QALY.
Additional evidence or analyses.	Data from the NHSE pilots.

Issue 6: What is the most reasonable annual cost to assume for T2DM?

Report section	2.1.8
Why important	Cost offsets from the avoidance or delay of T2DM are a key model driver.
EAG alternative approach	The EAG estimates the possible direct drug costs of T2DM and adds these to the UKPDS sourced costs. The EAG provides scenarios that include the company preferred T2DM costs of microvascular events, noting their possible limitations. The EAG notes that the model requires the net additional cost of T2DM over that of routine patient management. The EAG applies the net cost estimate.
Effect on ICER	Applying the company preferred T2DM drug costs improves the EAG ICER for the company target group from £24,735 to £24,046 per QALY. Applying half and all of the company sourced T2DM costs of microvascular complications improves the EAG ICER for the company target group from £24,735 to £23,543 and £22,351 per QALY respectively. Applying the company preferred T2DM drug costs and all of the company sourced T2DM costs of microvascular complications improves the EAG ICER for the company target group from £24,735 to £21,662 per QALY.
Additional evidence or analyses.	None for present purposes.

Issue 7: Modelling of those with T2DM at baseline

Report section	2.1.9
Why important	The scope does not restrict the patient population to reflect the SURMOUNT-1 trial; i.e. those without T2DM at baseline.
EAG alternative approach	None. The EAG notes that the inputs to the modelling and the model structure are specific to those without T2DM at baseline. The ICERs are driven in large part by the avoidance of T2DM and so are not relevant to those with T2DM at baseline. They provide no information about the probable cost effectiveness of tirzepatide among those with T2DM at baseline. The company has presented no cost effectiveness estimates for those with T2DM at baseline. The EAG also notes that this was presented during TA924 and given this is unclear why the current assessment has to make any recommendations about those with T2DM at baseline.
Effect on ICER	Cannot be stated.
Additional evidence or analyses.	Full T2DM modelling using clinical effectiveness estimates specific to those with T2DM at baseline, as presented during TA924.

Issue 8: Consideration of subsets of the Company target group

Report section	2.1.3, 2.2
Why important	The ICER for those with a lower BMI is somewhat worse.
EAG alternative approach	Consideration of subsets of the Company target population.
Effect on ICER	Applying the baseline characteristics for those with a BMI 30 - 35 kgm^{-2} worsens the EAG ICER from £24,735 to £30,533 per QALY. Applying the baseline characteristics for those with a BMI 30 - 35 kgm^{-2} improves the EAG ICER from £24,735 to £21,450 per QALY.
Additional evidence or analyses.	None for present purposes

1.5 *Cost Effectiveness: EAG lesser issues*

Issue 9: Target group subset specific clinical effectiveness estimates

Report section	2.1.10
Why important	NICE asked the Company to provide cost effectiveness scenarios for the target group subsets of those with a BMI 30 – 35 kgm^{-2} and those with a BMI ≥ 35 kgm^{-2}. The Company only changed the baseline characteristics due to the target group subsets possibly being too small. The clinical effect estimates were not made subset specific.
EAG alternative approach	Applying subset specific clinical effect estimates. The Company in its original submission provided subset specific clinical effect estimates for subsets smaller than those currently being requested by NICE.
Effect on ICER	For the target group subset with a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk applying only the subset specific baseline characteristics improves the EAG ICER from £24,735 to £20,093 per QALY. Applying both the baseline characteristics and the subset specific clinical effectiveness estimates improves it to £19,719 per QALY. This change appears relatively minor. The effect for the subsets of those with a BMI 30 – 35 kgm^{-2} and those with a BMI ≥ 35 kgm^{-2} is unknown.
Additional evidence or analyses.	Target group subset specific clinical effect estimates, including the 5% weight loss responder percentages.

Issue 10: Speed of loss of effect after treatment cessation

Report section	2.1.11
Why important	While not a model driver the first Committee meeting did not come to an opinion about the most reasonable assumption.
EAG alternative approach	Based upon the STEP-2 semaglutide trial data the EAG thinks that a 2 year loss of effect is more reasonable to assume than a 3 year loss of effect.
Effect on ICER	A 3 year loss of effect improves the EAG ICER for the company target group of £24,735 to £24,533 per QALY.
Additional evidence or analyses.	Tirzepatide specific loss of effect data.

1.6 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG largely retains its preferred set of assumptions and model inputs of its original report. For the current report the EAG makes the following changes to its exploratory base case.

- Applies the constant annual natural increase in BMI
- Assumes a 2 year loss of effect after treatment cessation
- Applies the 72 week 5% weight loss proportions due to 48 week trial data not having been supplied
- Attempts to include the baseline prevalences of MI, OSA and NAFLD
- Changes the SWMS costs to be the NHSE MDT costs as per Table 10 below.
- Applies an annual T2DM cost of £780, this including medication costs but excluding £234 routine management costs that the patient incurs both prior to and during T2DM to yield a net cost estimate.

This results in ICERs of:

1. £24,735 per QALY for the Company target group
2. £21,450 per QALY when applying the BMI ≥ 35 kgm^{-2} baseline characteristics
3. £30,533 per QALY when applying the BMI 30 – 35 kgm^{-2} baseline characteristics
4. £19,719 per QALY when applying the BMI ≥ 35 kgm^{-2}, prediabetic and high CVD risk baseline characteristics and clinical effect estimates
5. £27,682 per QALY for those with a BMI 30 - 35 kgm^{-2} or no prediabetes or not with a high CVD risk, inferred from (1) and (4) above.

The EAG scenario analyses are presented in Section 2.2 below. Results are particularly sensitive to:

- The baseline BMI distribution that is assumed
- Whether prior obesity has long term effects upon the risk of complication and mortality
- The costs of T2DM

2 COST EFFECTIVENESS

2.1 *EAG comment on Company's post AC1 submissions*

2.1.1 Company results and scenario analyses approach

The Company approach has been to retain its base case and to submit one way scenario analyses around this. This is in line with the NICE request but is of limited usefulness for decision making as it does not attempt to revise the model to reflect what seem likely to be the Committee's set of preferred assumptions.

The Company has made two revisions to its base case:

- Correcting a minor error in the calculation of QALYs.
- Applying the EAG inferred 48 week 5% weight loss responder rates.

It is unclear why the Company has applied the EAG inferred 48 week 5% weight loss responder rates rather than the SURMOUNT-1 responder rates.

The EAG briefly summarises the Company results for the comparison of tirzepatide 15mg with diet and exercise (D&E) in Table 3 below.

Table 3: Company base case with scenarios

Analysis	ICER
Company base case	£12,218
Resource use scenarios	
NHSE estimates while on tirzepatide, none for D&E	£16,910
NHSE estimates while on tirzepatide and D&E, subs. FU 2yr	£16,274
NHSE estimates while on tirzepatide and D&E, subs. FU 4yr	£15,970
NHSE estimates while on tirzepatide and D&E, subs. FU 6yr	£15,713
NHSE estimates while on tirzepatide and D&E, subs. GP 2yr	£16,812
NHSE estimates while on tirzepatide and D&E, subs. GP 4yr	£16,737
NHSE estimates while on tirzepatide and D&E, subs. GP 6yr	£16,673
Company resource use	£12,863
Company proposed, subsequent GP	£12,783
NHSE SWMS while on tirzepatide and D&E, subs. GP tirzepatide	£12,446

NHSE SWMS while on tirzepatide and D&E, subs. GP 2yr	£14,649
NHSE SWMS while on tirzepatide and D&E, subs. GP 4yr	£14,573
NHSE SWMS while on tirzepatide and D&E, subs. GP 6yr	£14,510
Baseline MI, OSA and NAFLD as per SURMOUNT-1 target pop.	£12,084
5% loss of effect at 5 years	£14,823
10% loss of effect at 5 years‡	£17,160
20% loss of effect at 5 years	£20,151
5% loss of effect at 10 years	£13,628
10% loss of effect at 10 years	£14,786
20% loss of effect at 10 years	£15,770
5% relative increase in discontinuations	£12,084
5% relative decrease in discontinuations	£12,432
Natural weight gain in all arms	£14,268
SURMOUNT-1 target group 48 week responder data	£12,921
BMI ≥ 35 kgm^{-2} + 1 comorbidity baseline char.	£11,184
BMI 30 – 35 kgm^{-2} + 1 comorbidity baseline char.	£17,697
T2DM risk reduced by 25%	£13,566
T2DM risk reduced by 50%	£15,411

2.1.2 EAG modelling correspondence with company modelling

The Company states that EAG revisions to the model caused the *Data_Store* functionality to stop working. The post FAC model that the EAG used to generate all result for the first Committee meeting was supplied to the Company. The EAG recollection is that it was only upon receiving this back from the Company and prior to any further EAG revisions that type mismatch errors occurred. The loss of the *Data_Store* functionality in the Company 2 April 2024 model means that the EAG has had to revert to the post FAC EAG amended model that was used to generate the results for the EAG 02 Nov 2024 report.

Time constraints mean that the EAG revised model does not address all the Company resource use scenarios. Time constraints also mean that the EAG has not

‡ Calculated by the EAG using the Company 02 April 2024 model. This also applies to the 20% treatment waning scenarios and the natural weight gain in all arms scenario.

been able to address the treatment waning scenarios. For the other analyses the correspondence between the 2 April 2024 Company submitted model and the EAG revised model that attempts to implement the Company analyses is presented in Table 4 below.

Table 4: Company modelling vs EAG modelling of Company analyses

Model	Company	EAG
Company base case	£12,218	£12,315
Baseline comorbidities as per SURMOUNT-1 target pop.	£12,084	£12,130
5% relative increase in discontinuations	£12,084	£12,183
5% relative decrease in discontinuations	£12,432	£12,416
SURMOUNT-1 target group 48 week responder data[§]	£12,921	£12,685
BMI ≥ 35 kgm^{-2} + 1 comorbidity baseline char.	£11,184	£10,930
BMI 30 – 35 kgm^{-2} + 1 comorbidity baseline char.	£17,697	£17,395
T2DM 10-year risk reduced by 25%	£13,566	£13,151
T2DM 10-year risk reduced by 50%	£15,411	£16,128

The minor discrepancy in the Company base case of £12,315 per QALY rather than £21,218 is due to the EAG expanding the list of baseline characteristics from 45 to 48 to encompass the baseline prevalences of CVD, OSA and NAFLD, whereas the company only does this within the relevant scenario analysis. This alters the sampling of random numbers in the model.

The minor discrepancy when baseline of CVD, OSA and NAFLD comorbidities are included may be due to the EAG not being able to identify where in the VBA or whether the Company applied the baseline OSA and NAFLD comorbidities. The EAG is also not 100% confident that its implementation does so either.

There are some differences in results when the BMI subset baseline characteristics are applied, around a £2-300 difference in the ICERs or around 2%. This seems unlikely to affect decision making, but is a modelling concern.

[§] The EAG assumes this scenario is returning the 5% weight loss percentages to those of the original company base case 72 week values but this may be incorrect. It is the closest available scenario that the EAG can get the company model to approach to £12,291 per QALY.

The Company 02 April 2024 model does not include the T2DM risk reduction scenarios so the EAG cannot identify why there is a discrepancy here..

2.1.3 BMI Distribution

NICE asked the Company to provide the SURMOUNT-1 target group distribution by BMI point. This has not been provided. This means that the EAG cannot judge how well the assumed gamma distribution of the model matches the actual distribution within SURMOUNT-1. The assumed gamma distribution can be compared with UK HSE general population survey data[**], restricted to those with a BMI ≥ 30 kgm^{-2} and assuming BMI to be normally distributed.

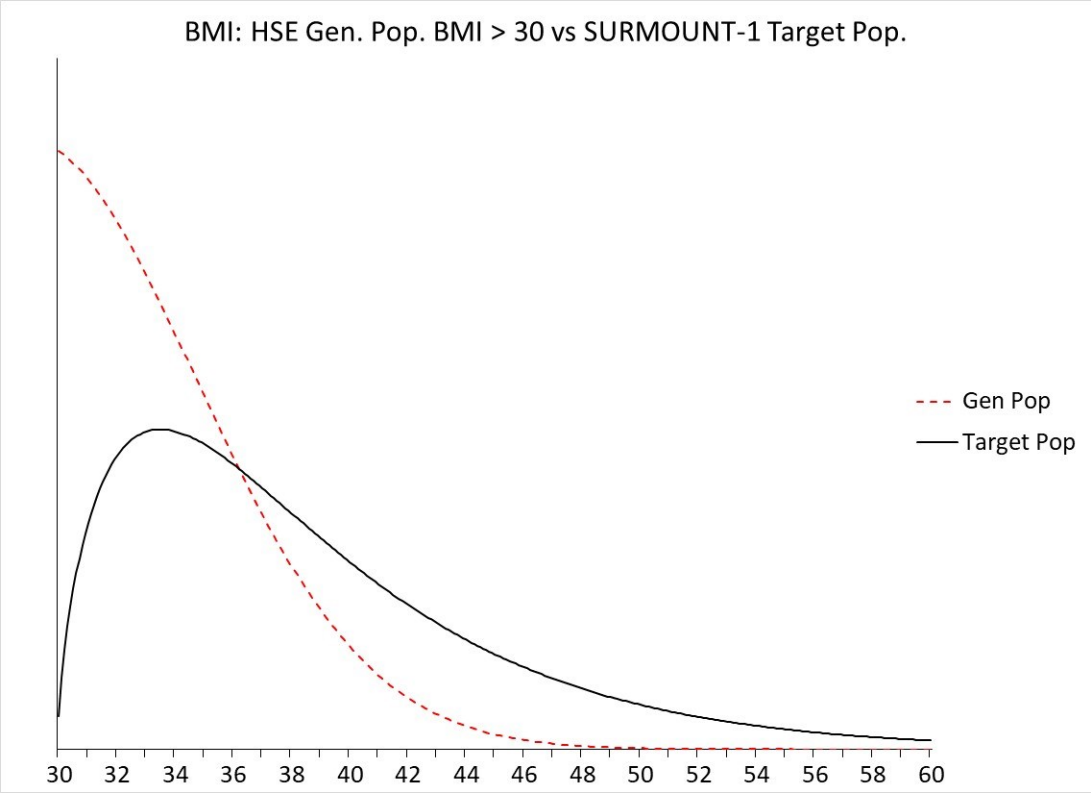

Figure 1: BMI: HSE survey vs assumed gamma for target population

Note that for its analysis that applies the patient characteristics of the BMI 30 - 35 kgm^{-2} subset the company samples from the above gamma distribution and then revises any values sampled above 35 kgm^{-2} to 35 kgm^{-2}. Given the mean (s.d.) for this subset of 32.6 (1.4) kgm^{-2} this means that around 6% of the sampled patients

[**] Health Survey for England: Overweight and obesity in adults, Excel Tables, Table 1, Publication 15 Dec 2022. Standard deviation taken from standard error of the mean and unweighted bases. Means and s.d.s similar across adult groups, values for those 45-54 applied: Mean 28.4, s.d. 5.96.

are reallocated to have a BMI of 35 kgm^{-2}, with the remaining distribution between 30 and 35 kgm^{-2} also probably also having a degree of unwarranted rightwards shift. In the light Figure 2 below this seems likely to bias the analysis in favour of tirzepatide.

The Company provides BMI distributions in 5 kgm^{-2} bands for SURMOUNT-1 and the target population subgroup. The Company compares this with the BMI distribution of those in community led weight management services (ComWMS) between April 2021 and December 2022. This data appears to relate to all local authorities in receipt of a grant from the adult weight services grant 31/5440, with all local authorities in receipt of a grant being required to ensure that all commissioned service providers collect and submit the minimum data set. The EAG augments this with the HSE general population survey distribution, restricted to those with a BMI ≥ 30 kgm^{-2} and assuming BMI to be normally distributed and the modelled gamma distribution.

Table 5: BMI distributions by 5 kgm^{-2} bands

BMI	SURMOUNT	Target	Model	ComWMS	Gen.Pop.
30.0 – 34.9	37%	35%	35%	40%	66%
35.0 – 39.9	30%	29%	32%	30%	27%
40 +	33%	35%	33%	30%	7%

The restriction of the SURMOUNT-1 subgroup with a BMI ≥ 30 kgm^{-2} to those with a weight related comorbidity only very slightly shifts the distribution rightward. Weight related comorbidities do not appear to much affect the BMI distribution.

The assumed gamma distribution for the model appears to conform closely to the distribution of the target population, but this is in the context of 5 kgm^{-2} bands which provide relatively little distributional information and should be viewed in the light of Figure 1 above. How realistic is the left hand end of the assumed gamma distribution?

The community led weight management services BMI distribution among those with a BMI ≥ 30 kgm^{-2} is a reasonable amount to the left of the SURMOUNT-1 target group. The general population BMI distribution among those with a BMI ≥ 30 kgm^{-2} is considerably to the left of the SURMOUNT-1 target group. It also broadly corresponds with the figures cited in the Novo-Nordisk consultation report of 64% of

people living with obesity in England having a BMI of 30 - 35 kgm^{-2} and 24% having a BMI of 35 - 40 kgm^{-2}, apparently sourced from the draft NICE overweight and obesity management guidance.

The Company argument for presenting the BMI distribution of those in community led weight management services between April 2021 and December 2022 rather than that of the primary care population may be that it better reflects the probable distribution of patients who will receive tirzepatide in primary care. This may not be the case. Based upon NHSE comments, the EAG thinks that demand for tirzepatide in primary care is likely to somewhat outstrip the current provision of community led weight management services. But capacity constraints may initially limit this, causing the initial distribution to be more akin to that of the community led weight management services. This might best be judged by comparing the projected ongoing steady state patient numbers of the Company budget implication modelling with the 73,000 patients in community led weight management services with a BMI ≥ 30 kgm^{-2} during the 22 months between April 2021 and December 2022.

Note that in response to the NICE request to provide evidence on the distribution of weight related comorbidities in the primary care population the Company states that "*Given that the first point of contact for a patient with obesity is their GP or nurse within primary care, Lilly considers that the general population is synonymous with the 'primary care population in England'*". This may be an argument for applying the HSE BMI distribution.

The estimated cost effectiveness[††] for the BMI values that are sampled within the target group varies quite substantially by BMI. Time constraints mean that the EAG illustration[‡‡] is limited to BMI increments of 2.5 kgm^{-2}, going from a baseline of 30 kgm^{-2} up to 55 kgm^{-2} which provides a reasonable span around the target group mean of 38.75 kgm^{-2}. Note that these cost effectiveness estimates all apply the pooled clinical effectiveness estimates, the clinical effectiveness estimates are not BMI specific.

[††] Note that these estimates are based upon the original company model and base case with an ICER for tirzepatide 15mg compared to diet and exercise of £12,792 per QALY rather than the revised company base case with an ICER of £12,218. But the same pattern will apply.
[‡‡] Implemented by revising *Subgroup Data* O18:P19 to e.g. 30.04 and 0.01 respectively. Note that the 0.04 was applied to avoid sampling values under 30. It was also inadvertently retained for some other simulations but applying the stated values for O18 should result in very similar if not identical estimates.

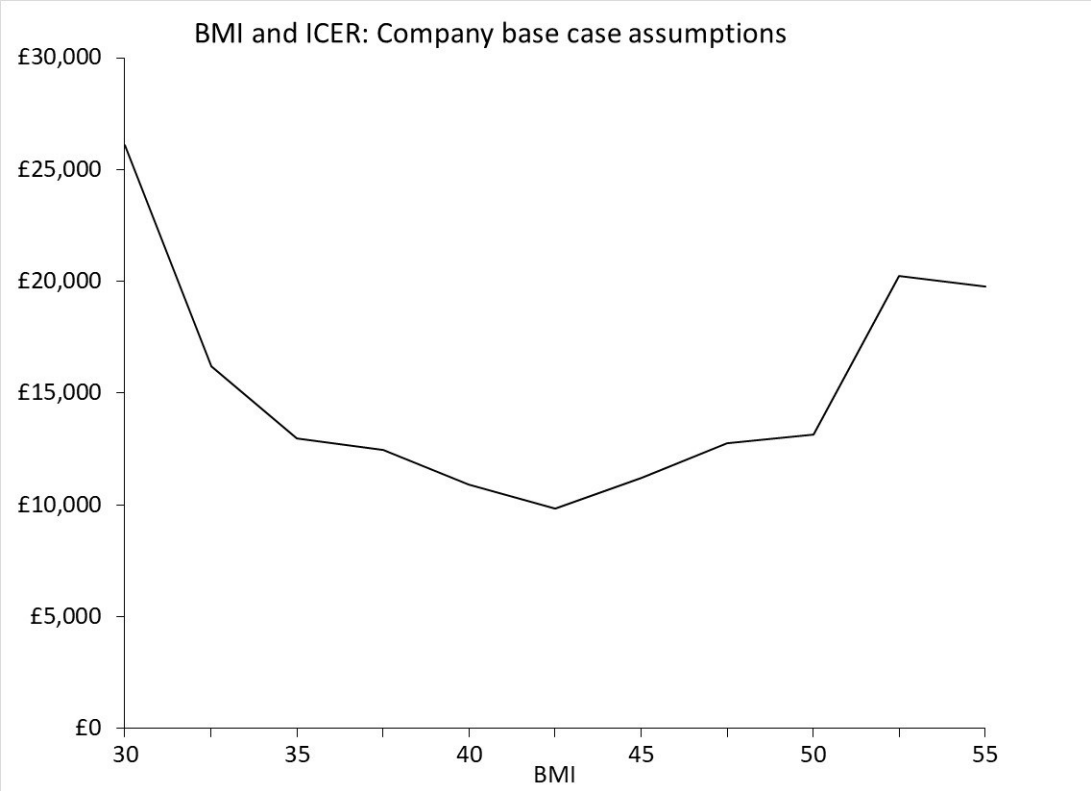

Figure 2: BMI and Company base case ICERs

The estimated cost effectiveness is reasonably constant for those with a BMI between 35 and 50 kgm^{-2}. The cost effectiveness for those with a BMI of 30.0 kgm^{-2} is somewhat worse, but the assumed gamma distribution gives these estimates little to no weight. The same holds true to a lesser degree for those with a BMI of 32.5 kgm^{-2}. At the other end of the scale, cost effectiveness begins to worsen as the BMI rises above 50 kgm^{-2}.

The EAG is concerned that the assumed gamma distribution may not be realistic for the lower end of the BMI scale. It may give too little weight to these patients and their relatively poor cost effectiveness, biasing the analysis.

The entry criteria for SURMOUNT-1 were either (1) a BMI ≥ 30 kgm^{-2}, or (2) a BMI ≥ 27 kgm^{-2} with at least one weight related comorbidity. The assumed gamma distribution may somewhat bias the analysis if it does not reflect the actual SURMOUNT-1 distribution. The Company notes that "*Given that SURMOUNT-1 was a clinical trial, detailed gradation of the BMI distribution are available for the*

population". The provision of this data is the only reliable means of assessing the extent of this bias.

A judgement also has to be made about how well the BMI distribution in the SURMOUNT-1 target population matches that likely in primary care. Will those who will receive tirzepatide in primary care most likely match the BMI distribution of (1) those currently receiving community led weight management services, (2) the general primary care population, or (3) something between (1) and (2). As outlined in Table 5 above, both (1) and (2) lie to the left of the assumed gamma distribution.

In the absence of the actual SURMOUNT-1 target group BMI distribution the EAG will retain the Company assumed gamma distribution for its base case. It will apply the HSE general population distribution as scenario analyses, assuming a truncated normal distribution.

2.1.4 Steady state versus rapid weight loss

An issue not previously raised by the EAG is that the Company model in effect assumes that a patient who has, say, had a BMI of 37kgm^{-2} for 20 years but then reduces this to a BMI of 30kgm^{-2} has the same risks of developing T2DM, CVD, OSA, NAFLD, TKR and death as a patient who has always had a BMI of 30kgm^{-2}. This was also noted as an issue in the FADs of TA664 and TA875. It is a strong assumption which may not be reasonable for some or all events within the model.

The question is what BMI related damage is long lasting or permanent and what BMI related damage is transitory and reversible?

EAG expert opinion is that if someone has been obese and insulin resistant for decades there will be an impact on future CVD risk. They would have accelerated atherosclerosis over that time and this is largely irreversible. Someone who has been obese who reverts to normal weight will have a higher CVD risk than someone who has been of normal weight throughout. A similar process occurs around diabetes where there is glycaemic legacy. A patient with poor glycaemic control for many years carries forward that glycaemic legacy, it being the area under the curve when glycaemia is plotted against time that confers their glycaemic risk.

The EAG thinks that the most obvious area where BMI related damage may not be reversed by weight loss is damage to the knee joint. A BMI of 37kgm^{-2} for 20 years

may damage the knee. If the patient then loses weight to a BMI of 30 kgm^{-2} this damage may not be reversed. The patient will accrue knee damage at a slower rate but it seems likely that their knee will remain more damaged than that of someone who has always had a BMI of 30 kgm^{-2}. If so, the risk of total knee replacement will fall but not to that of someone who has always had a BMI of 30 kgm^{-2}.

Intuitively, this may not apply to OSA if a high BMI results in pressure on the airways but no lasting damage. Weight loss and pressure reduction may largely or fully reverse the risk of OSA.

Novo Nordisk, presumably to support the launch of semaglutide for obesity, sponsored the 2021 Haase et al[§§] study of UK CPRD and HES data bases that estimates the effect of weight loss on the risks of various weight related complications. The study contains a number of arbitrary data cuts and subgroup definitions. It also lacks much exploration of alternative assumptions and functional forms. The selective reporting of outcomes and analyses cannot be discounted.

Haase et al define the baseline period as the first 4 years of data. Those maintaining their weight ±5% from start to end of the baseline period were defined as stable. Those losing between 10% and 25% of their weight from start to end of the baseline period were defined as weight loss. Those with weight loss were also required to have evidence of dietary advice, and those with cancer or thyroid disorder were excluded. For inclusion in the follow-up period patients were required to have a BMI of 25 to 50 kgm^{-2} at the end of the baseline period.

Haase et al explored the risks of 10 BMI related comorbidities over the subsequent 10-year period: T2DM, OSA, hip or knee osteoarthritis, hypertension, dyslipidaemia, unstable angina or MI, asthma, AF, heart failure and CKD. Separate models were developed for each of the 10 outcomes, individuals with the outcome at start of the follow-up period being excluded. 902,341 met the inclusion criteria, with 523,138 (58%) being of stable weight, 76,110 (8.4%) has lost weight and 48,823 (5.4%) had lost weight with evidence of an intention to lose weight. The median BMI in the weight loss group was 35.3 kgm^{-2} and 30.4 kgm^{-2} representing a median weight loss

[§§] All authors are Novo Nordisk employees other than Phil McEwan. The EAG assumption is that Phil McEwan undertook the actual statistical analyses. The paper states that Phil McEwan did not receive any funding for the collaboration but that his company, HEOR Ltd, has received funding from Novo Nordisk for previous studies. The EAG does not know if it has received subsequent funding from Novo Nordisk.

of 13%. At start of follow-up the median (IQR) age was 55 (45, 63) years, with 49% being male. Median follow-up during the 10-year follow-up period was 6.3 years.

Among those with weight loss the weight loss interventions were patient initiated diet (53%), dietary advice (58%) weight loss medication (27%) and bariatric surgery (1%). The same weight loss interventions were also recorded for those of stable weight, 36%, 29%, 8% and <0.0% respectively.

Two further definitions are required: for an individual with weight loss (1) a patient with stable weight at their initial baseline weight, stable upper weight, and (2) a patient with stable weight at their weight loss end of baseline weight, stable lower weight. Haase et al classified their results into four statistical categories.

1. No significant difference between those with weight loss and those with stable upper weight. Effect: None.
2. A significant improvement for those with weight loss compared to those with stable upper weight, but a significantly higher risk compared to those with stable lower weight. Effect: Residual risk.
3. A significant improvement for those with weight loss compared to those with stable upper weight, but not significantly difference compared to those with stable lower weight. Effect: No residual risk.
4. A significant improvement for those with weight loss compared to those with stable upper weight and stable lower weight. Effect. Superior.

The current modelling assumption is akin to assuming Effect with no residual risk applies to all event risks. But within Haase et al it can be noted that since these are statistically based some categorisations are more likely if the confidence intervals are tight, while others may be further if the confidence intervals are wide; e.g. provided that a statistical improvement is found between those with weight loss and those with stable upper weight, high uncertainty around the risk for those with weight loss and/or those with stable lower weight increases the likelihood of falling into this classification. For this reason, Residual Risk and Superior may in a sense be stronger statistical results as they require full separation of the three 95% confidence limits. Similarly, it would have been between if for None Haase et al distinguished between (1) None where the weight loss distribution was significantly worse that

those with a stable lower weight, and (2) None where the weight loss distribution was not significantly worse that those with a stable lower weight

Cox proportional hazard models were estimated with time as an underlying variable, the main covariates were BMI at end of baseline period, a quadratic term for the BMI and an interaction term for the BMI and cohort. All models were adjusted for age, sex and smoking. It appears that ethnicity was not adjusted for despite this being in both the QDiabetes algorithms and QRisk3 algorithm.

The supplementary figure 1 appears to show that the median 13% weight loss in the weight loss cohort reversed over the next two year to a weight loss of around 10%, this this following a general upward drift roughly paralleling the weight of those in the stable weight cohort, Haase et al noting that "*there remained a stable difference of ≈10% between the cohorts*".

Given the event hazard ratios as functions of BMI for those with stable weight and weight loss estimated relative to a patient with a stable BMI of 30 kgm^{-2}, Haase et al estimate the effect for the median 13% weight loss among three bands of baseline BMI.

Table 6: Haase et al effects summary

Baseline BMI	30.5 – 35.0 kgm^{-2}				34.8 – 40.0 kgm^{-2}				39.2 – 45.0 kgm^{-2}			
Effect	None	Residual risk	No residual risk	Superior	None	Residual risk	No residual risk	Superior	None	Residual risk	No residual risk	Superior
T2DM		X						X				X
Dyslipidaemia				X				X				X
Hypertension			X					X				X
CKD			X					X				X
Asthma			X				X		X			
OSA		X				X				X		
Hip/Knee Osteo.		X				X			X			
AF	X				X				X			

Heart Failure	X				X				X			
Unst. Angina / MI	X				X				X			

Haase et al do not present the median weight loss by BMI category. It is unclear why the BMI category specific median weight losses were not used when calculating the results of Table 6. If those with in the weight loss cohort with a lower BMI at baseline had a smaller median BMI reduction than those with a higher BMI at baseline Table 6 may tend to overstate the effect of weight loss upon results for those with a lower BMI at baseline, but understate it for those with a higher BMI at baseline.

For current purposes that above suggests that during the 10 years subsequent to weight loss of 10-13% among those with an initial BMI of 30 – 35 kgm^{-2} the risk of T2DM improved but not to the full extent implied by the Company modelling assumption: the three confidence intervals are separate.

Perhaps surprisingly, the above also suggests that among those with an initial BMI of more than 35 kgm^{-2} and a weight loss of 10-13% their risk of developing T2DM during the next 10 years at their new BMI is actually less than that of patients who have been stable at that BMI during the 4-year baseline period. This may be due to those with weight loss also making other lifestyle changes, such as taking exercise, which those with stable weight do not make. Whether this means that the Company model assumption is too pessimistic for these patients is more difficult to gauge, as the source of these lifestyle changes may be the dietary advice rather than any weight loss medication.

In general, the above suggests that there is residual risk for OSA and total knee replacement, the three confidence intervals being separate for these. Again, the Company modelling assumption may be too optimistic.

Haase et al suggest that the lack of a statistically significant effect for some event risks may have been due to the 10-year follow-up period being insufficient. The EAG interpretation of Figure 1 of Haase et al is that this is an unreasonable conclusion for AF and heart failure, with it being likely that None but with weight loss being significantly worse that those with a stable lower weight applies. It appears to be a more reasonable conclusion for unstable angina/MI.

As already noted, Haase et al do not explore mortality. For those with a baseline BMI of 30 – 35 kgm^{-2} unless the superior risk profile for dyslipidaemia over rides all other event risks the EAG think that the above implies that assuming a 10-13% weight loss will result in the same mortality risk as always having been at the lower weight is too optimistic. The picture is much less clear for those with a baseline BMI of more than 35 kgm^{-2}. The EAG still finds it curious that Haase et al did not explore mortality.

The above discussion has to be read alongside the weight loss in Haase et al being between 10% and 25% by construction, with a median weight loss of 10-13%, compared to a mean weight loss in SURMOUNT-1 for both the target group and for those with a BMI of more than 35 kgm^{-2} though not restricted to being in the target group of around [redacted]. The modelling assumption relates to a bigger weight loss and so is in a sense a bigger assumption, the reasonableness of which cannot be definitively answered by the work of Haase et al.

To explore the above the EAG will provide scenarios that assume where the Haase et al classed risk changes as:

- None, assume no effect
- Residual risk, assume 75% effect, and 50% effect as a further scenario
- No residual risk, assume 100% effect
- Superior, assume 125%, and 100% as a scenario

The reason for including the 100% scenario for the Superior risk change is that as previously discussed it is unclear what the source of the Superior risk change is. It may be related to lifestyle changes such as diet and exercise, with SURMOUNT-1 including diet and exercise in both arms.

Since Haase et al only provide these estimates classed by BMI subgroups the EAG will apply the Haase et al related effect modifiers for those with a BMI 30 – 35 kgm^{-2} to the subset analyses with a BMI 30 – 35 kgm^{-2}, and those for a BMI 35 – 40 kgm^{-2} to the subset analyses with a BMI ≥ 35 kgm^{-2}.

Given the overall Haase et al results for those with a BMI 30 – 35 kgm^{-2} the EAG will augment the scenarios for this subset with a scenario which assumes a BMI effect upon mortality of 75% of that of the base case.

Note that these scenarios do not explore a reduction in the direct BMI effect upon quality of life.

2.1.5 Treatment effect waning over time

NICE requested that the Company provide scenarios of a constant loss of net effect compared to diet and exercise. Part of the justification for requesting this may have been the longer term follow-up data for liraglutide during SCALE as reproduced from the EAG report below for ease of reference.

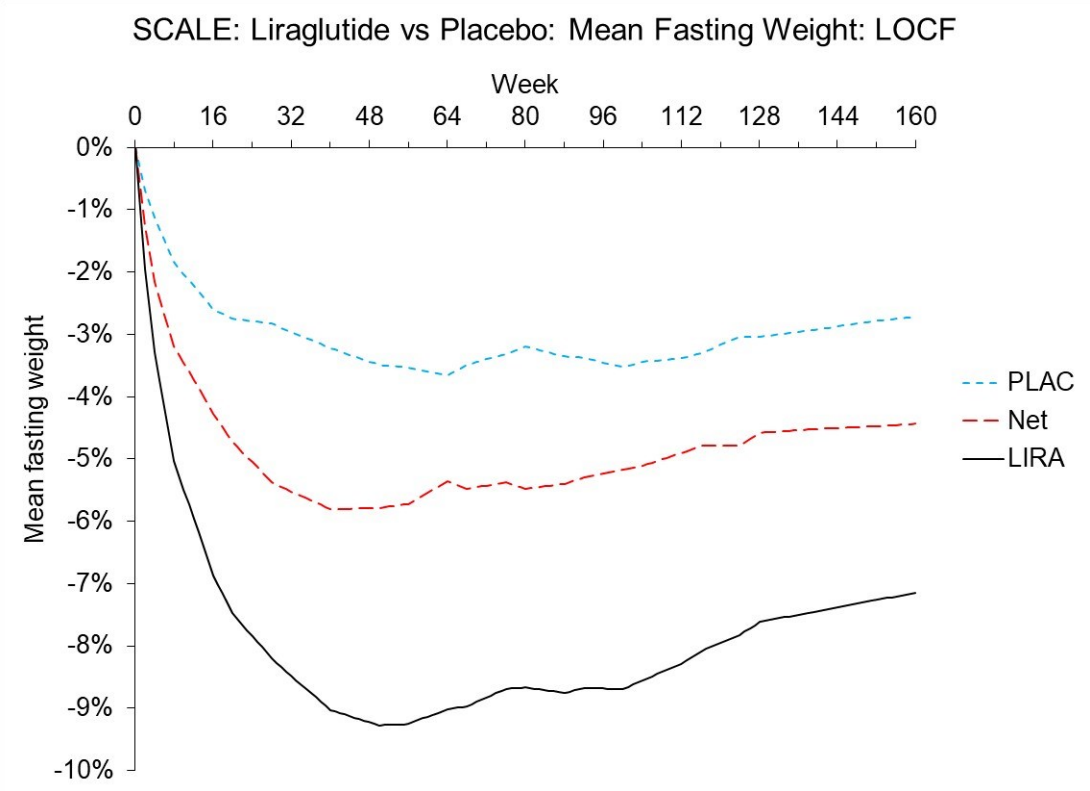

Figure 3: SCALE weight loss from baseline to 160 weeks: Prediabetes population

Table 7: SCALE prediabetes patient numbers to 160 weeks

Week	0	28	56	80	104	124	160
LIRA	1,467	1,223	1,100	971	885	833	747
PLAC	734	576	508	436	375	355	322

Between week 50 and week 160 the net effect falls from around -5.8% to -4.4%: a reduction in the net effect of 23% or an annual 11%. This is in the context of the

SCALE trial where both the weight loss in the active treatment arm and the net effect were somewhat less than in SURMOUNT-1.

NICE asked that the Company implement treatment waning scenarios that applied an constant annual loss of net effect for the various treatment effects modelled, BMI, SBP etc.. The Company states that "*It was not possible for Lilly to implement these scenarios exactly as requested due to the significant complexity of directly fulfilling this request*". Given the model structure, and that the Company has been able to implement net effect losses at 5 years and at 10 years while also previously exploring a more gradual loss of pre-diabetes reversal, the EAG cannot understand why the Company could not implement an annual loss of net effect as requested by NICE.

For the comparison of tirzepatide 15mg with diet and exercise the effects upon BMI at 72 weeks in the target group are reductions of [redacted] and [redacted] respectively, implying a net effect at 72 weeks of [redacted]. Note that cessation of diet and exercise at 2 years causes the model to return those on diet and exercise to their baseline value with this then increasing by the natural annual weight gain of 0.106 kgm^{-2}.

The Company provides three scenarios around treatment waning: reductions in the net effect of:

- 5% from [redacted] to [redacted] at 5 years
- 5% from [redacted] to [redacted] at 10 years
- 10% from [redacted] to [redacted] at 10 years

The remaining net effects of around [redacted] or [redacted] are assumed to applying for the duration of tirzepatide treatment.

The Company scenarios worsen the Company base case for the comparison of tirzepatide 15mg with diet and exercise from £12,218 per QALY to £14,823, £13,628 and £14,786 per QALY respectively.

Given the relatively small changes explored by the Company with no further treatment waning after the 5 year or 10 year cutoffs and the Company model revisions, the EAG further explores losses of 20% at 5 years and at 10 years; i.e. reducing the net effect from [redacted] to [redacted] at 5 years and at 10 years as presented in Table 3 above, with ICERs of £20,151 and £15,770 per QALY respectively.

Unfortunately, time constraints mean that the EAG has not been able to implement the treatment waning scenarios within the EAG revised model. But given the smaller cost offsets and quality of life gains for broadly similar treatment costs it thinks that the effect upon its ICERs would be proportionately greater than that upon the company ICERs.

Are these treatment waning scenarios sufficient?

2.1.6 Annualization of 10-year and 5-year risk equations: Lesser issue

While an issue that does somewhat increase the overall uncertainty around the reliability of the modelled ICERs, results are not particularly sensitive to the EAG explorations of this. Many readers may wish to skip forward to Section 2.1.7.

The EAG provided the Company with an excel implementation that estimated the overestimation of the 10-year risks of T2DM, CVD and OSA. The Company has reviewed this and notes that:

1. The patient characteristics are based upon the central estimates of SURMOUNT-1
2. Categorical variables have not been incorporated fully
3. The calculations do not take into account the effect of reductions in BMI
4. The calculations assume an ongoing natural gain in BMI
5. The EAG analyses have not been validated

Points 1 and 2 are incorrect. The EAG spreadsheet allows for both sampling, specification of the categorical variables and user specification of the patient characteristics.

With regards point 3 it does appear that the overstatement of 10-year risks when using the Company method is less among those with a higher risk so the bias will be greater among those losing weight. But the effects of annualization of the 10-year and 5-year risk functions apply from the time point that they are calculated. The concern remains.

Point 4 is the AC preferred base case.

Point 5 relates to why the EAG provided the Company with a copy of the spreadsheet, to give the Company time to check that the EAG implementation

matches its own. The EAG has independently validated the EAG estimates for the QRisk3 and the QDiabetesC algorithms against the online calculators for a range of hypothetical patients and gets a very good correspondence.

The Company presents ICERs that apply a 25% risk reduction and a 50% risk reduction in the risk of T2DM, CS 23 Feb 2024 page 14 Table 6 and CS 27 March 2024 page 32 Table 38. The ICER for tirzepatide 15mg compared to diet and exercise worsens from £12,218 per QALY to £13,566 per QALY and to £15,411 per QALY respectively. The Company does not explore the effects of the possible overstatement of CVD 10-year risks or the OSA 5-year risks.

The EAG implementation can provide illustrative examples of any overstatement or understatement of the 10-year risks. The obvious illustrative example is those at the central values of the base case patient characteristics: white, female, non-smoker with no comorbidities. It also seems sensible to augment this with a white, male, non-smoker with no comorbidities, around a third of the sample being male. To illustrate the effects of higher risks a Pakistani, male, moderate smoker with no comorbidities will also be presented.

The 10-year risk of CVD is based upon the QRisk3 algorithm. For the white female the Company method results in a 10-year CVD risk of 3.2% compared to an actual risk of 1.9%: a 68% overstatement. But this underestimates the degree of overestimation that will be applied within the modelling because it does not take into account that some patients will develop T2DM during the 10-year period. During the 10-year period the modelling significantly increases these patients' 10-year risk of CVD. But the 10-year risks of CVD when pooled across all patients should equal the original 1.9%.

Exploring this further, the 10-year CVD risk increases with age. The 10-year risk for the female patient at mean values and a baseline age of 30, 40, 50 and 60 years can be plotted. This can be further augmented by the degree of "overstatement" that the development of T2DM causes. This is not strictly correct in terms of terminology as the "overstatement" is relative to the original age specific baseline 10-year risk. The correct way of thinking about this is that the 10-year risks pooled across patients taking into account the development of T2DM should be equal to the original estimate of the QRisk3 algorithm.

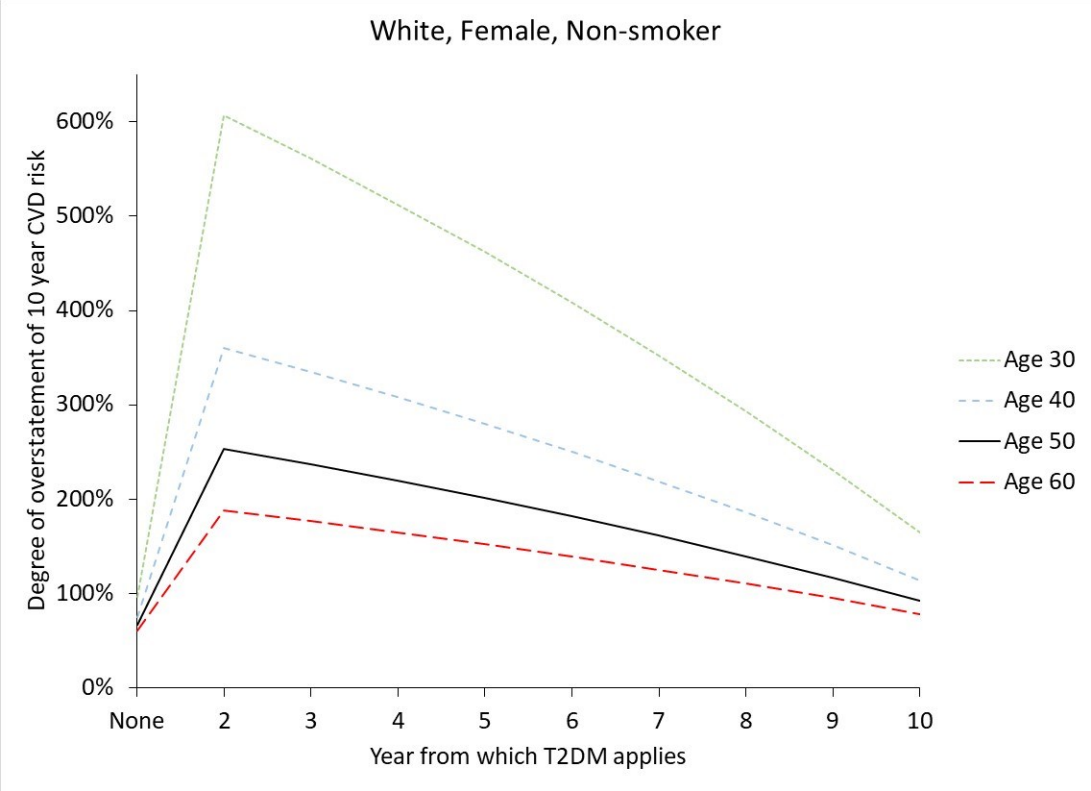

Figure 4: 10-year CVD risk overstatement: White, female, non-smoker

A similar exercise can be presented for the white, male, non-smoker and the Pakistani, male, moderate smoker.

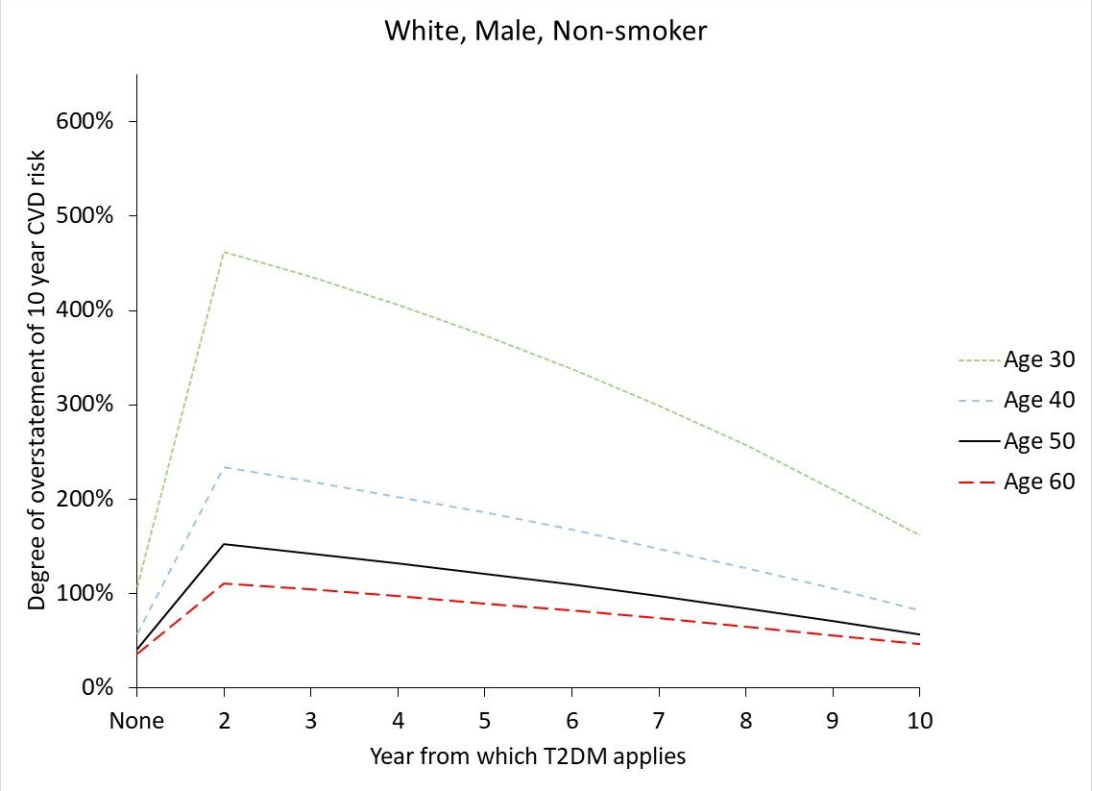

Figure 5: 10-year CVD risk overstatement: White, male, non-smoker

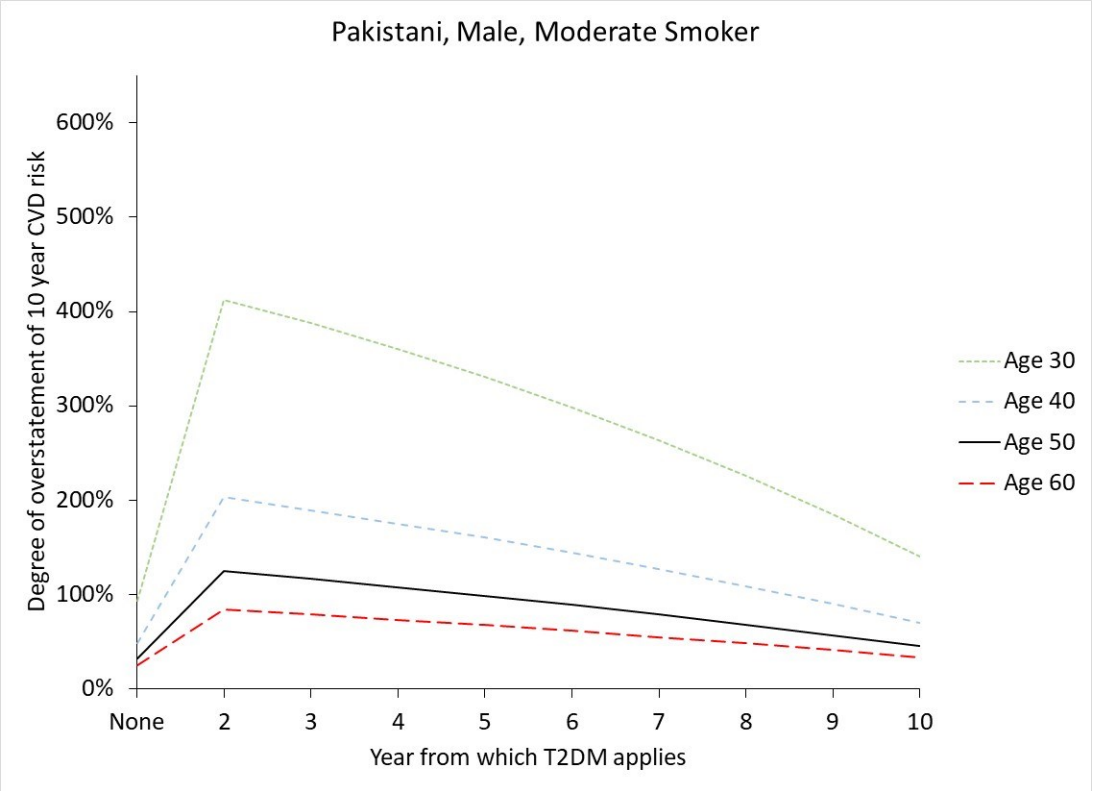

Figure 6: 10-year CVD risk overstatement: Pakistani, male, mod. smoker

The degree of overstatement of CVD risk varies by age. Ignoring the effects of T2DM the degree of overstatement for the illustrative examples is presented in Table 8 below.

Table 8: Overstatement of 10-year CVD risk ignoring T2DM effects

Sex	Female	Male	Male
Ethnicity	White	White	Pakistani
Smoking	None	None	Moderate
Age 30	96%	108%	94%
Age 40	75%	58%	49%
Age 50	67%	42%	33%
Age 60	61%	36%	25%

The development of T2DM is also a major driver if it occurs relatively early during the 10-year period. But the annual incidence of T2DM may not be that large and the EAG thinks that this aspect while important should not be the over-riding concern.

Given the preponderance of white ethnicity in the target population, 82%, the EAG will present scenarios that “corrects” the values for 40 year old, white non-smokers. 75%[***] and 58% for female and male respectively, and for 50 year old, white non-smokers, 67% and 42% respectively, noting the mean age in the target group of 47 years.

The EAG scenario will underestimate the bias for those less than 50 and overstate it for those over 50. But the EAG thinks that were this bias to be symmetric around that of a 50 year old for, say, a 40 year old and a 60 year old the overall bias on modelling outcomes would be to overestimate the CVD effect due to the effective time horizon for a 40 year old being somewhat longer than that of a 60 year old. The EAG scenario is likely to overestimate the bias compared to taking the effects of ethnicity, smoking (23%) and other comorbidities properly taken into account, but it will underestimate the bias compared to taking the effects of developing T2DM during the 10-year period properly taken into account. Correctly modelling these aspects would require considerable model revision.

[***] If the calculated annual risk is 10% the 75% adjustment reduces this to 2.5%

A similar exercise can be presented for the QDiabetesC algorithm that estimates the 10-year risk of developing diabetes. For the white, female, non-smoker the Company method results in a 10-year risk of diabetes of 11.2% compared to an actual risk of 10.3%: only a 9% overestimate.

But similar to the QRisk3 CVD risk algorithm being complicated by the development of diabetes, the QDiabetesC diabetes risk algorithm is complicated by the development of CVD. If the white, female, non-smoker has a CVD event in that applies from year 2 the Company method results in an 10-year diabetes risk of 12.9% which is a 25% overestimate, while a CVD event applying from the last year causes the Company method to estimate a 10-year risk of 11.4% which is an 11% over estimate.

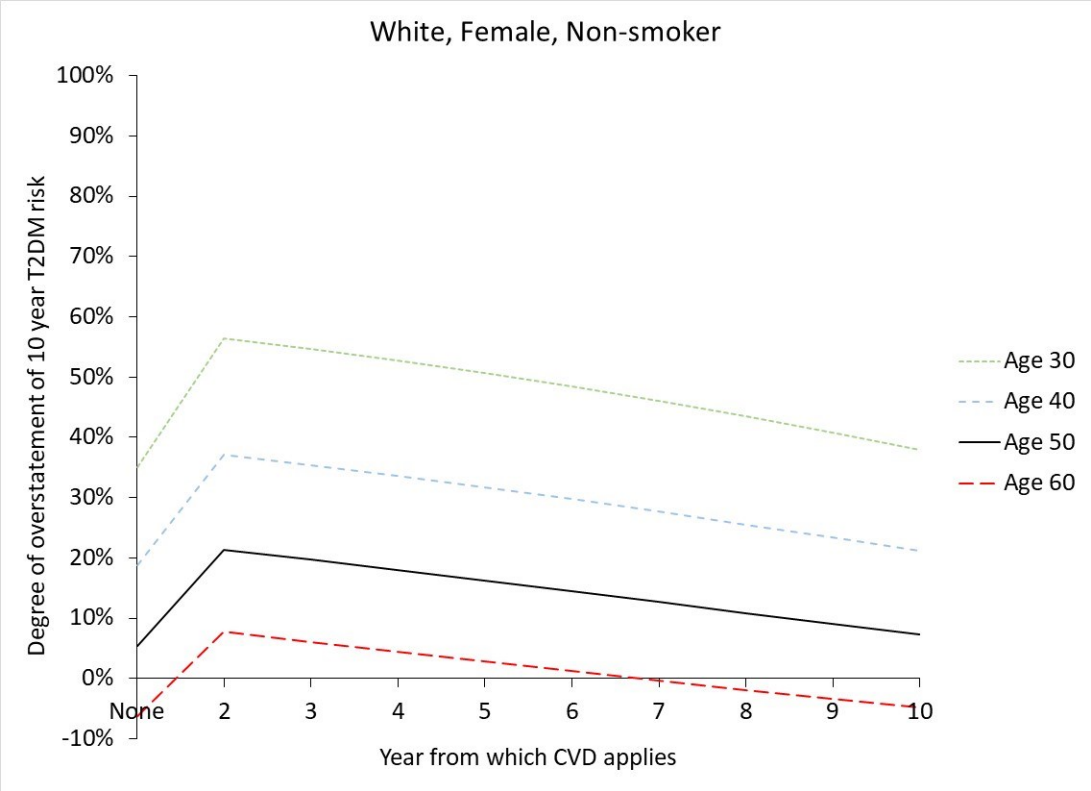

Figure 7: 10-year diabetes risk overstatement: White, female, non-smoker

The QDiabetesC algorithm estimates that, within the set of patient characteristics explored by the EAG, the risk of developing diabetes fall from around the age of 60 years. This seems likely to be due to a survivor effect in that those who have not developed it by 60 years are, possibly genetically, less likely to develop it thereafter than those who developed it before the age of 60 years. Whatever the explanation,

the falling 10-year risk causes the Company method to underestimate the 10 year risk.

For a white, male, non-smoker the corresponding estimates using the Company method are 18.4%, 20.7% and 18.7% compared to the QDiabetesC 10-year risk of 16.5%, overestimates of 11%, 26% and 13% respectively.

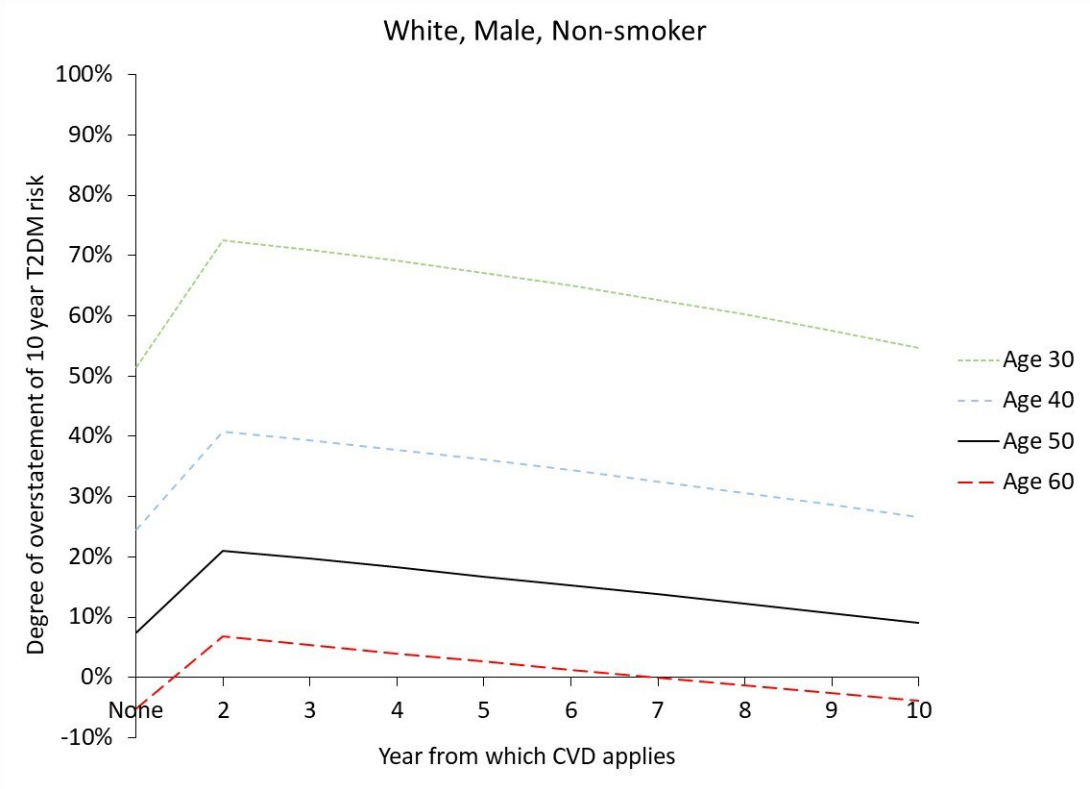

Figure 8: 10-year diabetes risk overstatement: White, male, non-smoker

Likewise, for a Pakistani, male, moderate smoker the corresponding estimates using the Company method are 40.6%, 44.8% and 41.1% compared to the QDiabetesC 10-year risk of 37.0%, overestimates of 10%, 21% and 11% respectively.

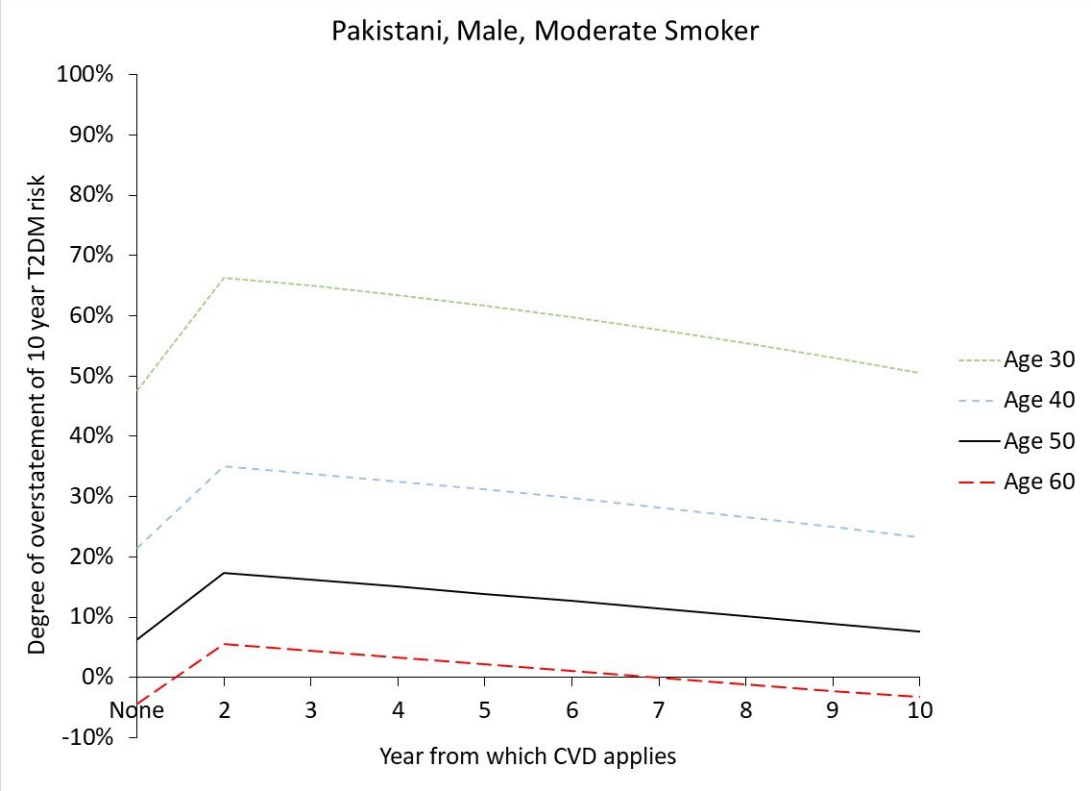

Figure 9: 10-year diabetes risk overstatement: Pakistani, male, mod. smoker

Ignoring the effects of CVD the overstatements of the 10-year risk of T2DM is presented in below.

Table 9: Overstatement of 10-year diabetes risk ignoring CVD effects

Sex	Female	Male	Male
Ethnicity	White	White	Pakistani
Smoking	None	None	Moderate
Age 30	35%	52%	48%
Age 40	19%	24%	21%
Age 50	5%	8%	6%
Age 60	-6%	-5%	-4%

In common with the approach to correcting the CVD 10-year risk estimates the EAG will present scenarios that “corrects” the values for 40 year old, white non-smokers. 19% and 24% for female and male respectively, and for 50 year old, white non-smokers, 5% and 8% respectively, again noting the mean age in the target group of 47 years.

Similar to the consideration of the overstatement of the 10-year CVD risk, the EAG thinks that if the overestimation bias for a 40 year old and the underestimation bias for a 60 year old were equally spread around the bias of a 50 year old, simply reducing the 10-year diabetes risk by the bias of the 50 year old will still tend to bias the analysis in favour of the more effective treatment. This is again due to the longer effective time horizon for the 40 year old compared to the 60 year old. This is also subject to the same considerations around ethnicity, smoking and comorbidities as the 10-year CVD risk.

Time constraint mean that the EAG has not been able to provide a similar analysis for the 5-year risk of OSA. This is also complicated by the OSA risk functions containing discontinuities in age. It can be noted that within the Company revised base case and a total net cost of £8,373 for tirzepatide 15mg compared to diet and exercise the net cost offsets from T2DM, CVD and OSA are £4,741, £233 and £307 respectively. Similarly, the total patient gain of 0.685 QALYs have contributions from reduced T2DM, CVD and OSA of 0.105, 0.008 and 0.039 QALYs respectively. So the effect of any possible overestimation of the 5-year risk of OSA is likely to be non-trivial.

It must be stressed that these EAG “corrections” to the 10-year risks of CVD and diabetes, which might more properly be called adjustments, are quite ad hoc. The Committee may prefer to not have these adjustments applied, to view the possible biases as unquantifiable within the Company model structure and to come to a more informal assessment of their likely effect upon the ICERs.

2.1.7 NHSE MDT and SWMS costs

The NHSE costings for primary care MDT resource use and hospital led community based MDT resource use, labelled as SWMS within this document, assume a cost per 9.22 minute GP block of £41 but a cost per equivalent consultant time of £33. This strikes the EAG as unreasonable, different costing methods having been used to arrive at this.

For consistency the costs of both of these within the 2022 PSSRU Unit Costs of Health and Social Care can be considered.

The hourly cost of GMS activity of a GP is £139 and £162 without and with qualification costs respectively. The hourly cost of a hospital based medical

consultant is £143 including capital costs. While it is unclear to the EAG if this includes the costs of qualifications, this is 102% and 88% of the GP hourly cost without and with qualification costs. Given the uncertainty whether consultant qualification costs are included within the PSSRU costs, the EAG will apply the NHSE GP based MDT costing for its base case. A scenario costing with a consultant at 88% of the cost of the GP will be provided.

The company has provided data on the proportion of SURMOUNT-1 patients with current or historic psychiatric problems: [redacted]. The EAG applies this proportion rather than the 33% sourced by NHSE from the bariatric surgery guidance.

This results in the following EAG MDT cost scenarios for those remaining on treatment. The EAG interpretation of the NHSE submission is that (1) tirzepatide use will require ongoing MDT services in part due to the need to monitor patients using a new treatment, and (2) if MDT diet and exercise services are provided on a stand alone basis they will be limited to a maximum of two years, in line with the original Company modelling assumptions.

Table 10: EAG MDT cost scenarios

	Tirzepatide			Diet and Exercise		
	0-6mth	6-12mth	Yr2+	0-6mth	6-12mth	Yr2
Base case: GP	£1,008	£179	£297	..	..	..
Cons. led	£909	£171	£282	..	..	..
MDT for D&E: GP	£1,008	£179	£297	£500	£179	£297
MDT for D&E: Cons.	£909	£171	£282	£462	£171	£282

2.1.8 The costs of T2DM

For its base case the Company retains its preference for some NHS reference costs that the Company has selected. All these costs have been incurred by T2DM patients, but this does not imply that all T2DM patients have incurred these costs.

The EAG is very strongly of the opinion that this data is not a reasonable estimate of the annual cost of T2DM. At the risk of patronising Committee, the situation is analogous to being asked to estimate the annual transport costs of the average British family and doing so by going to your local BMW dealer and asking them what

the average cost of the cars they sold last year was. The Company base case in effect assumes that every year all 3 million T2DM patients incur the Company selected NHS reference costs, when in fact only 74,000 of them did so. Only a small subset of British families buy a BMW each year, and only a small subset of T2DM patients incur the Company selected NHS reference costs each year. Neither provide a sensible estimate.

The Company cites Capehorn et al 2021 as a potential source of costs for T2DM: an annual average discounted drug cost of £552 and discounted cost of microvascular complications of £940. This is a Novo Nordisk sponsored modelling exercise that estimates the cost effectiveness of semaglutide compared to empagliflozin for the treatment of T2DM, using the iQVIA CDM.

An immediate concern is that patients were not newly diagnosed with T2DM which is what is required for the current modelling. The average duration of T2DM at baseline was 7 years. Their T2DM was somewhat further along than is required for the current modelling. This seems likely to result in the complications of diabetes being modelled as being sooner / greater than is required for the current modelling.

This also means that patients were somewhat further down the treatment pathway. All patients in the comparator arm were receiving empagliflozin 25mg at baseline, which at drug tariff prices costs £477 annually. HbA1c progression was then modelled using the UKPDS equation and when it rose above 7.5% it was assumed that empagliflozin was stopped with patients switching to basal insulin, which assuming a dose of 0.3IU/kg and a patient weight of 100kg would for glargine cost £254 annually. Lancets, needles and SMBG might increase this to £360 each year. The paper does not mention if a subsequent switch to biphasic or basal-bolus insulin was modelled, but it appears that it was not. EAG opinion is that most T2DM patients are controlled on basal insulin, in common with the apparent modelling assumptions of Capehorn et al.

For newly diagnosed T2DM patients diet and exercise is recommended as a first step[†††]. For the current patient population, given that they have already failed at least one attempt to lose weight this might be anticipated to be of short duration. But the

[†††] https://www.nice.org.uk/guidance/ng28/resources/visual-summary-full-version-choosing-medicines-for-firstline-and-further-treatment-pdf-10956472093

initial oral anti-diabetic drugs that would then be prescribed are extremely cheap. Metformin monotherapy at 1,500 mg daily has an annual drug cost of £26.59 at drug tariff prices. Similarly, dual therapy metformin plus sulfonylurea using glimepiride would only add an additional £10.95 annually, to give an annual dual therapy drug cost of £37.54.

NICE guidance recommends using an SGLT2 immediately alongside metformin if the patient has a QRisk2 score of more than 10% or established CVD. For these patients, using the lowest priced SGLT2 within the drug tariff, ertugliflozin 15mg daily yields an additional annual cost of £383. For the SGLT2s NICE notes that "*Costs may vary in different settings because of negotiated procurement discounts*" so this cost estimate may be an overestimate.

NICE guidance recommends considering switching to insulin once dual therapy has failed, but permits triple therapy.

The duration of treatment can be modelled using the UKPDS 68 equation for the evolution of HbA1c. The EAG thinks that this risk function evolution is also used by the iQVIA CDM T2DM model. Assuming an HbA1c at diagnosis of 7.5% and that patients will switch intensify therapy if their HbA1c rises above 7.5%, if the initial treatment results in a 1.0% fall in HbA1c the treatment lasts 6 years. If only a 0.5% fall in HbA1c occurs the treatment lasts 5 years. Assuming treatments last 5 years and a 1.5 mortality multiplier for T2DM‡‡‡, for those diagnosed at 50 and 60 years of age the mean annual discounted cost of metformin followed by metformin plus followed by additional basal insulin is £229 and £194 respectively. For those requiring an SGLT2 throughout these costs are £661 and £619 respectively.

Due to the BMI 35 ≥ kgm^{-2}, prediabetes and high CVD subset are 32% of the Company target group the EAG will apply an annual average T2DM drug cost of £340. For those with a BMI 30 – 35 kgm^{-2} the EAG will reduce this to £210. For those with a BMI 35 ≥ kgm^{-2}, prediabetes and high CVD the EAG will provide a scenario analysis increasing this to £630§§§.

‡‡‡ A rough midpoint of the 2.70 HR for those not achieving more than 1 risk factor targets and 1.16 HR for those achieving a maximum of 6-7 risk factor targets of the Wang et al UK study.
§§§ This may be the most reasonable base case assumption for this subset but the EAG does not adopt it for this subset so that the EAG inferred ICERs for the Company target group subset with a BMI 30 – 35 kgm^{-2} or no prediabetes or low CVD risk remain correct.

Turning to the costs of microvascular complications both the Company and the EAG are correct to note that these are not within the modelling and can be substantial, Capehorn et al modelling costs of £6,460 for ophthalmic complications, £7,396 for ulcer, amputation and neuropathy complications and £5,415 from renal complications. The EAG has not has time to cross check the Capehorn et al unit cost inputs in detail but notes that many of them are drawn from the UKPDS 68, the same source that the EAG uses for its estimate of the costs of T2DM in the absence of complications.

An initial objection to using the Capehorn et al modelled costs of microvascular complications is that it assumes that only those with T2DM have ophthalmic, ulcer, amputation, neuropathy and renal complications. While these will be higher for those with T2DM it is not obvious that among those who are overweight these costs are £0.

It can also be noted that Capehorn et al is an industry sponsored study with a clear interest in estimating the highest costs for these events. Many of these costs are taken from the UKPDS 84, the same source as used by the EAG to estimate the additional net cost of T2DM compared to obesity in the absence of complications. It appears likely that the unit costs of events within Capehorn et al are the gross cost of these events rather than their net cost. For instance, Capehorn et al apply an annual cost among those who have survived an MI of £2,008, This is similar to the UKPDS 84 gross cost of £2,080[****] for a 60 year old man, but the UKPDS 84 net cost compared to having no complications is only £951. Similarly, for being blind in one eye Capehorn et al apply an annual cost of £1,311 which is similar to the UKPDS gross cost of £1,190 but considerably in excess of the UKPDS 84 net cost of £227 compared to having no complications. The EAG does not have access to the iQVIA CDM code so cannot make a definitive judgement, but it appears that net costs may not have been applied among those developing complications. This may have seriously biased the Capehorn et al cost estimates.

The EAG will provide a scenario analysis that includes the Capehorn et al costs of microvascular complications, adjusting these for the 7 years mean duration of

[****] Inflated by 14% to concert 2013 prices to 2021 prices.

diabetes within Capehorn et al: a 78% discount factor resulting in an average annual cost of £734, together with a scenario that arbitrarily reduces them by 50% to £367.

Within the original EAG report there is an error in the implementation of the T2DM costs. Gross costs are applied. But only the costs in addition to the ongoing routine patient management costs should be applied, i.e. the net costs. The EAG will subtract the £234 ongoing routine patient management costs from the gross T2DM costs to yield the net increase in costs associated with T2DM management.

2.1.9 Modelling those with T2DM at baseline

NICE asked the Company to include a reasonable proportion of patients with T2DM in its modelling.

The Company argues that the model is not designed to assess the cost effectiveness of tirzepatide for those with T2DM and trying to use it for this would result in bias. The Company states that each category of non-diabetic, prediabetic and diabetic is assumed to have a constant HbA1c, but it can be noted that the proportion in each category is affected by the treatment effectiveness estimates so does differ by arm. But the Company is correct that if a proportion of patients are assumed to have T2DM at baseline the current model would estimate them to have no glycaemic benefit from weight loss.

The economic modelling is based upon data from the SURMOUNT-1 trial. This excluded those with T2DM. But as an illustration, if the model is set to assume that the probability of developing T2DM in the first cycle is 100%†††† the Company base case ICER for tirzepatide 15mg compared to diet and exercise of £12,218 per QALY worsens to £25,699 per QALY. The EAG does not think that this is a reasonable estimate of the cost effectiveness of tirzepatide for those with T2DM.

The EAG thinks that estimates of the cost effectiveness of tirzepatide among those with T2DM can only be made within a T2DM model such as the iQVIA CDM, which has been used for a number of previous NICE assessments. Any such modelling may need to keep a weather eye on possible overestimation of events given peer reviewed model validation work and the Mt. Hood challenges. This would preferably

†††† Implemented in the VBA by revising *If rand1 < p_event Then QDiabetes_C = 1 End If* to *QDiabetes_C = 1*.

apply T2DM specific clinical effect estimates. But it can be noted TA924 did just this. In October 2023 NICE approved tirzepatide for those with T2DM provided that:

1. Triple therapy metformin plus two other oral antidiabetic drugs is ineffective, not tolerated or contraindicated; and,
   a. They have a BMI ≥ 35 kgm^{-2} and specific psychological or other medical problems associated with obesity; or
   b. They have a BMI < 35 kgm^{-2}; and,
      i. Insulin therapy would have significant occupational implications; or
      ii. Weight loss would benefit other significant obesity related complications.

The current cost effectiveness modelling for tirzepatide relates those who do not have T2DM at baseline. Its results are driven in large part by the cost offsets and utility gains from avoiding T2DM. The Company modelling provides no information about the probable cost effectiveness of tirzepatide among those with T2DM. The Company has not submitted any cost effectiveness estimates for those with T2DM during the current assessment.

Given the recommendation of TA924, it is not obvious to the EAG why the current assessment needs to make any recommendation for those with T2DM.

2.1.10 Lesser Issue: Target group subset specific clinical effect estimates

The Company provides baseline characteristics for those with (1) a BMI 30 - 35 kgm^{-2} and at least 1 weight related comorbidity and (2) a BMI ≥ 35kgm^{-2} and at least 1 weight related comorbidity. But it does not supply subgroup specific treatment effect estimates for these two groups. This somewhat reduces the relevance of the resulting ICERs: CS 27 March 2024, page 29, tables 35 and 36. Despite only the baseline characteristics being varied the Company estimates that the ICER for tirzepatide against diet and exercise for group (1) is £17,697 per QALY, 58% worse than the ICER for group (2) of £11,184 per QALY and 45% worse than the overall pooled Company base case ICER of £12,218 per QALY.

The CS 27 March 2024 states "*Lilly considers that a formal post hoc subgroup analysis of the efficacy outcomes for the trial would result in subgroup sizes that would be at significant risk of random variation due to low patient numbers as they comprise only approximately 24% and 43% of the trial population, respectively*". The

EAG views this with some surprise given that the original Company submission contained subset specific clinical effectiveness estimates‡‡‡‡ for the SURMOUNT-1 subsets of those with:

- a BMI 30 – 35 kgm^{-2}
- a BMI ≥ 35 kgm^{-2}
- a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk.

The subset of the last bullet is a smaller subset of the target population than both the subsets of the target population requested by NICE. The only clinical effectiveness estimate that is not subset specific within original Company modelling was the proportion achieving a 5% weight loss at 72 weeks, on which more below.

The CSR provides subgroup analyses for the 72 week 5% weight loss proportions for the entire SURMOUNT-1 population for the subgroups with a BMI of (1) < 30kgm-2, (2) 30 - 35kgm-2, (3) 35 - 40kgm-2 and (4) ≥ 40kgm-2. For the mITT - Efficacy Analysis Set the CSR notes that

"[redacted]". The associated forest plot appears to show a smaller 5% weight loss proportion for tirzepatide 15mg and a smaller net effect compared to diet and exercise for those with a BMI between 30kgm^{-2} and 35 kgm^{-2}, compared to those with a BMI ≥ 35kgm^{-2}. During the most recent teleconference between the Company, NICE and the EAG the EAG thought that the Company argued the opposite to the above text, but this may have been a misinterpretation by the EAG or the EAG may have misinterpreted the above text. The EAG argued for a subset specific presentation of the 5% weight loss proportions.

If the proportion of patients achieving a 5% weight loss is less among those with a BMI 30 - 35 kgm^{-2} compared to those with a BMI ≥ 35kgm^{-2} the ICER for those with a

‡‡‡‡ Ignoring the proportion achieving at least a 5% weight loss at 72 weeks, adverse events, discontinuations

BMI 30 - 35 kgm^{-2} is too optimistic. The ICER for those with a BMI ≥ 35kgm^{-2} would be correspondingly too pessimistic.

If the EAG has correctly interpreted the above text it argues for applying subset specific 5% weight loss proportions. The said, for the target population the pooled 5% weight loss proportion at 72 weeks in the tirzepatide 15mg arm was [redacted] The EAG will explore this by assuming a 100% responder rate for those with a BMI ≥ 35 kgm^{-2}, implying responder rates of around ???% at 48 weeks and 89.5% at 72 weeks for those with a BMI 30 – 35 kgm^{-2}.

The Company has confirmed that pre-diabetes is one of the weight related comorbidities that defines the target group: those with a BMI ≥ 30kgm^{-2} and at least 1 weight related comorbidity. This means that the subset with a BMI ≥ 30kgm^{-2}, prediabetes and a high risk of CVD that the Company has presented clinical effectiveness estimates for is a subset of the target group.

2.1.11 Lesser Issue: Speed of loss of effect after treatment cessation

For ease of reference the EAG reproduces the rate of loss of effect from the STEP-1 trial of semaglutide.

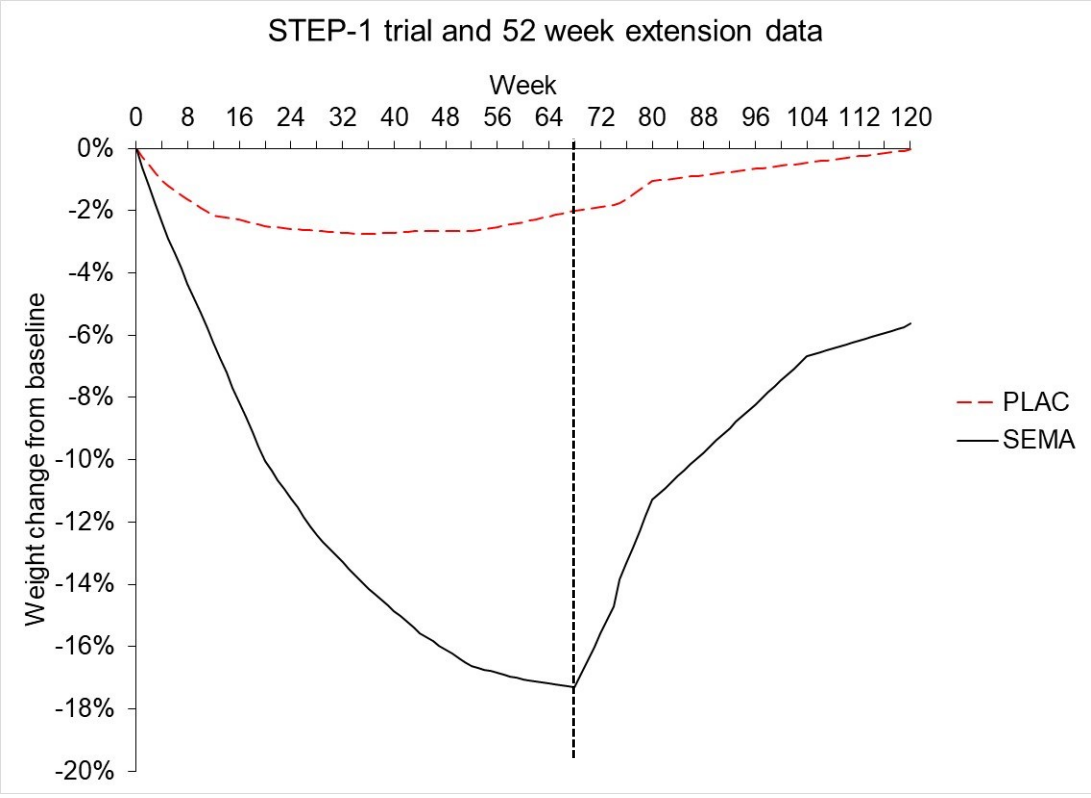

Figure 10: STEP-1 weight loss from baseline and 52 week treatment withdrawal

Committee did not express an opinion whether a 2 year loss of effect or a 3 year loss of effect is the most reasonable for the base case. Given the above, the EAG thinks that a 2 year loss of effect is the most reasonable to assume.

2.2 *EAG exploratory cost effectiveness modelling*

Given the Committee preferences and time constraints the EAG focusses upon the comparison of tirzepatide 15mg with diet and exercise in a primary care setting. The EAG largely retains the changes it made in its exploratory revised base case of Section ?? of its original report.

- No stopping rule for tirzepatide other than the 6 month 5% weight loss responder rule
- Only applying the BMI mortality multipliers
- Mainly applying the adverse event discontinuation rates in the first year, with a common 1% annual rate thereafter
- An annual NAFLD rate of 0.06/1,000 patient years
- A 5 year OSA risk of 2.85%
- Revising the quality of life function intercepts to align with SURMOUNT-1 quality of life data and align the two quality of life functions at 35 kgm^{-2}
- Only applying the QoL coefficients of the main BMI quality of life function
- Various minor revision detailed in the original EAG report Section 5.5.7

For the current report the EAG makes the following changes to its exploratory base case.

- Applies the constant annual natural increase in BMI
- Assumes a 2 year loss of effect after treatment cessation, though this has little effect: the EAG revised base case for the Company target group changes from £24,735 to £24,533 per QALY with a 3 year loss of effect

- Applies the 72 week 5% weight loss proportions due to 48 week trial data not having been supplied
- Attempts to include the baseline prevalences of MI, OSA and NAFLD
- Changes the SWMS costs to be the NHSE MDT costs as per Table 10 above.
- Applies an annual T2DM cost of £, this including medication costs but excluding £234 routine management costs that the patient incurs both prior to and during T2DM to yield a net cost estimate.

The EAG provides ICERs for:

1. The entire target group: those with a BMI ≥ 30kgm^{-2} and at least 1 weight related comorbidity: N=1,705 (100%) within SURMOUNT-1
2. The subset of the target group with a BMI ≥ 30kgm^{-2} but < 35 kgm^{-2}, noting that this only applies the subset specific baseline characteristics and not the subset specific clinical effect estimates: N=605 (35.5%)
3. The subset of the target group with a BMI ≥ 35kgm^{-2}, noting that this only applies the subset specific baseline characteristics and not the subset specific clinical effect estimates: N=1,100 (64.5%)
4. The subset of the target group with a BMI ≥ 35kgm^{-2}, prediabetes and a high CVD risk, noting that this applies the subset specific baseline characteristics and clinical effect estimates: N=545 (32.0%)
5. The subset of the target group with a BMI < 35kgm^{-2} or without prediabetes or without a high CVD risk, inferring this from the estimates of bullets (1) and (4) above: N=1,160 (68.0%).

Note that the mean BMI for those in the target group with a BMI ≥ 35kgm^{-2}, was 42.1 kgm^{-2} while for those in the target group with a BMI ≥ 35kgm^{-2}, prediabetes and a high CVD risk it was 42.6 kgm^{-2}. The difference in the cost effectiveness estimates between these two groups does not appear to be due to their BMI.

The EAG presents the following scenario analyses.

- SA01: Sampling assuming BMI is normally distributed, assuming the general population distribution truncated by the modelled BMI bounds; e.g. BMI ≥ 30 kgm^{-2} for the Company target group

- SA02: Assuming past obesity has long term effects, assuming lesser effects upon modelled events as taken from the Novo Nordisk Haase et al study, retaining high partial effects, low partial effects and low partial effects with additional reductions in the effects upon mortality
- SA03: Adjusting the risks of events to adjust for the possible overestimation due to annualization for a representative 40 year old and a representative 50 year old
- SA04: Applying MDT costs based upon being consultant led rather than GP led, applying GP led MDT costs to both tirzepatide and diet and exercise, and applying consultant led MDT costs to both tirzepatide and diet and exercise
- SA05: Applying the company drug costs for T2DM, 50% of the company microvascular complication costs for T2DM, 100% of the company microvascular complication costs for T2DM, the company drug costs for T2DM coupled with 100% of the company microvascular complication costs for T2DM, and the EAG subgroup specific T2DM drug costs

Table 11: EAG exploratory cost effectiveness modelling ICERs

Modelled population	Target group	BMI 30 – 35 kgm^{-2} base. characteristics	BMI ≥ 35 kgm^{-2} base characteristics	BMI 30 - 35 kgm^{-2}, or not prediabetic, or not high CVD risk	BMI ≥ 35 kgm^{-2}, prediabetic high CVD risk
Base case	£24,735	£30,533	£21,450	£27,682	£19,719
SA01: BMI Gen. Population normal distribution	£29,176	£32,228	£21,479	£36,375	£19,868
SA02a: Effects of weight loss on complications high	..	£33,057	£21,035	..	£18,955
SA02b: Effects of weight loss on complications low	..	£35,340	£22,862	..	£21,227
SA02c: SA02b and lesser effects on mortality	..	£40,591	..	..	..
SA03a: Annualization 40 year old adjustment	£25,319	£31,451	£22,039	£27,969	£20,738
SA03b: Annualization 50 year old adjustment	£24,959	£30,724	£21,598	£27,920	£19,914
SA04a: MDT consultant led	£24,434	£30,171	£21,186	£27,357	£19,460
SA04b: MDT for diet and exercise	£24,257	£29,956	£21,032	£27,166	£19,306
SA04c: SA04a and SA04c	£23,987	£29,632	£20,795	£26,875	£19,074
SA05a: Company T2DM drug costs	£24,046	£29,771	£20,804	£27,133	£18,792
SA05b: 50% of company T2DM complication costs	£23,543	£29,215	£20,333	£26,732	£18,116
SA05c: 100% of company T2DM complication costs	£22,351	£27,897	£19,216	£25,782	£16,513
SA05d: SA05a and SA05c	£21,662	£27,134	£18,570	£25,233	£15,586
SA05e: EAG subgroup T2DM specific drug costs	..	£31,001	..	..	£18,451

3 REFERENCES

National Institute for Health and Care Excellence. Overweight and obesity management (GID-NG10182) - Draft for consultation. 2023.

Haase, C.L. et al Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database, Int J Obes (Lond), 2021, Jun;45(6):1249-1258

Wang et al Assessing the impact of type 2 diabetes on mortality and life expectancy according to the number of risk factor targets achieved: an observational study, BMC Medicine 2024, 22

The EAG apologies if any references are missing due to time constraints. The numbered UKPDS references are easy to find. Should there be any other missing references please contact the EAG for details of these.

Committee's preferred assumptions (ACM2)

Before outlining the Committee's preferred assumptions, it should be acknowledged that there remains concern around the different versions of the model. The company has highlighted errors in the EAG model revision which need to be explained and resolved. At the same time, the EAG has noted that the version of the model supplied by the company for ACM2 does not allow it to implement its preferred assumptions in the way the original model did. We need to resolve these issues before returning to committee so that the ICERs are agreed to be robust by all parties. It is proposed that the company meet with NICE and the EAG to resolve these issues and share a version of a model that is suitable for both to provide further analyses.

The committee's preferred assumptions are principally aligned with the EAG base case as follows:

- including a proportion of people at baseline in the model reflective of the proportion with each comorbidity in SURMOUNT-1 with previous myocardial infarction, obstructive sleep apnoea and non-alcoholic fatty liver disease
- removing the net increase in tirzepatide treatment effect by applying the same natural progression increase in weight according to age to the tirzepatide arm after 72-weeks as in the diet and exercise arm
- assuming weight is regained over 2 years after stopping treatment
- using the costs for type 2 diabetes from UKPDS plus an estimate of drug costs associated with type 2 diabetes
- removing mortality modifiers applied in the company's model for history of angina, myocardial infarction and stroke as the increased risk of death from these events is covered by the BMI mortality modifier

- amending the adverse event-related treatment stopping rate from annually applying the stopping rate due to adverse events from SURMOUNT-1 at 72-weeks (the company's assumption), to mainly applying stopping due to adverse events in the first year of the model, followed by an annual 1% stopping rate

- halving the non-alcoholic fatty liver disease incidence rate to adjust for differences observed across the studies used by the company to estimate incidence rate and hazard ratios for the development of non-alcoholic fatty liver disease

- increasing the prevalence of obstructive sleep apnoea for people with a BMI between 30 kg/m^2 and 35 kg/m^2 (2.85% sourced from the UK Clinical Practice Research Datalink database) compared with the company's assumption that this population has equal risk of obstructive sleep apnoea to the general population

- amending the quality of life functions used by the company to compensate for effects of the function where quality of life starts to improve as BMI increases beyond 39.0 kg/m^2 for men and 46.5 kg/m^2 for women

- removing disutilities for obesity related complications which are already covered by the quality of life functions

- other minor model amendments outlined in section 5.5.7 of the EAG report

Committee's preferred assumptions also included:

- assuming tirzepatide stopping rates at 6 months due to non-response based on the proportion of non-responders at 48-weeks in the target population in SURMOUNT-1

- prediabetes reversal loss modelled so that it aligns with the approximate time in the model that baseline weight is regained in all arms

- an adjustment for BMI distribution in the model to reflect the population who would be potentially eligible to receive tirzepatide in the general population

- including the population specific efficacy results for each subgroup

The committee would like to see subgroup analyses including all its preferred assumptions for the following subgroups:

- People with a BMI of at least 30 kg/m^2 and at least 1 weight related comorbidity (the company's target population)

- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight related comorbidity

- **People with a BMI of at least 35 kg/m^2 and at least 1 weight related comorbidity**

- **People with a BMI of at least 35 kg/m^2, prediabetes and a high risk of cardiovascular disease**

- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight related comorbidity or with a BMI of at least 35 kg/m^2 without prediabetes and a high risk of cardiovascular disease.

In the first instance, the BMI of at least 35 kg/m^2 subgroups (in bold) should be prioritised.

Scenario analyses:

It is not within the committee's remit to agree what the obesity management services will include for people receiving or not receiving tirzepatide. Given the uncertainty around what these services will include, it requested to see a range of scenarios on a base case including all its other preferred assumptions. These scenarios should include:

- the EAG's preferred assumption (applying the resource use proposed by NHS England for obesity management services to the tirzepatide

arm for the duration of tirzepatide treatment and no resource use to the diet and exercise arm)

- the company's preferred assumptions for obesity management services in each arm

- other scenarios presented by the company in the submission to NICE on 22nd March 2024.

The committee would also like to see scenario analyses on a base case including all its other preferred assumptions on the long-term impact on outcomes from previously having had a higher BMI.

Please confirm how long would be required to implement and present ICERs for the committee's preferred assumptions as well as the listed scenario analyses the committee would like to see applied to a base case including the committee's preferred assumptions.

Company Response to Committee-Preferred Assumptions Post-ACM2

Lilly would like to thank NICE for sharing the Committee-preferred assumptions post-ACM2, and for providing the opportunity to provide them with a comprehensive set of ICERs aligned to these assumptions.

This response has two key sections and an accompanying appendix. First, Lilly will describe for each priority population identified by NICE (BMI ≥35 kg/m^2 with at least one weight-related comorbidity and BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD) how the Committee preferences have been implemented in the current model version, and will provide cost-effectiveness results for these populations when all the Committee-preferred inputs and assumptions are applied. Next, Lilly will present the Committee-requested scenarios.

A Technical Appendix to this response is also provided, wherein Lilly addresses the concerns that the Committee have raised with the model versions used prior to ACM2 and respond to the most recent EAG requests.

BMI ≥35 kg/m^2 with at least one weight-related comorbidity

Table 1 presents the cost-effectiveness results for tirzepatide vs. diet and exercise when each of the Committee-preferred assumptions is applied one at a time; for transparency, Lilly has also provided details of the model settings which have been updated for each assumption.

All results are aligned with what the Committee has requested and how the EAG have implemented these assumptions in their model. As detailed in Technical Appendix A, both the Company and Committee-preferred results presented in the table below include the subgroup-specific efficacy data – a minor update compared with the previous model version (as requested by the committee).

Overall, these results demonstrate that the Committee-preferred assumptions do not change the conclusion that tirzepatide is a cost-effective use of NHSE resources for patients with a BMI ≥35 kg/m^2 with at least one comorbidity, with ICERs well below the WTP threshold across all tirzepatide doses.

Table 1: Committee-preferred settings applied individually to the Company-preferred base case results for population with BMI ≥35 kg/m^2 with at least one weight-related comorbidity (vs. D&E)

Setting Applied to the Company-Preferred Base Case	Model Implementation	vs. D&E		
		Tirzepatide (5.0 mg)	Tirzepatide (10.0 mg)	Tirzepatide (15.0 mg)
Company-Preferred Base Case Settings (from pre-ACM2)		£9,842	£9,573	£10,679
Including a proportion of people at baseline in the model reflective of the proportion with each comorbidity in SURMOUNT-1 with previous myocardial infarction, obstructive sleep apnoea, and non-alcoholic fatty liver disease	B74 'EAG' tab: Change to 'TRUE'	£8,339	£9,546	£10,919
Removing the net increase in tirzepatide treatment effect by applying the same natural progression increase in weight according to age to the tirzepatide arm after 72-weeks as in the diet and exercise arm	B70 'EAG' tab: Change to 'TRUE' B71 'EAG' tab: Change to '=72/(365.25/7)'	£12,652	£11,115	£12,044
Assuming weight is regained over 2 years after stopping treatment	B67 'EAG' tab: Change to '2'	£10,629	£10,360	£11,444
Using the costs for type 2 diabetes from UKPDS plus an estimate of drug costs associated with type 2 diabetes	B39 'EAG' tab: Change to £1,226	£11,786	£11,688	£12,516
Removing mortality modifiers applied in the company's model for history of angina, myocardial infarction and stroke	B28 'EAG' tab: Change to 'FALSE' B97 'EAG' tab: Change to 'TRUE'	£9,770	£9,463	£10,568
Amending the adverse event-related treatment stopping rate from annually applying the stopping rate due to adverse events from SURMOUNT-1 at 72-weeks (the company's assumption), to mainly applying stopping due to adverse events in the first year of the model, followed by an annual 1% stopping rate	B31 'EAG' tab: Change to 'TRUE'	£10,536	£10,587	£11,790
Halving the non-alcoholic fatty liver disease incidence rate (12% to 6%)	B32 'EAG' tab: Change to '0.06'	£10,654	£9,772	£11,019
Increasing the prevalence of obstructive sleep apnoea for people with a BMI between 30 kg/m^2 and 35 kg/m^2 (2.85% sourced from the UK Clinical Practice Research Datalink database)	B33 'EAG' tab: Change to 'TRUE'	£10,028	£9,765	£10,755
Amending the quality of life functions used by the company to compensate for effects of the function where quality of life starts to improve as BMI increases beyond 39.0 kg/m2 for men and 46.5 kg/m2 for women	B34 and B63 'EAG' tab: Change to 'TRUE'	£9,057	£8,714	£9,757
Removing disutilities for obesity related complications which are already covered by the quality of life functions	B35 'EAG' tab: Change to 'TRUE'	£10,531	£9,644	£10,814

Other minor model amendments outlined in section 5.5.7 of the EAG report: • Apply an adjustment to NAFLD mortality of 1.71 • Apply the incidence of AEs once • Apply an annual cost to NAFLD of £952	B42 'EAG' tab: Change to 'TRUE' B44 and B65 'EAG' tab: Change to 'TRUE' B45 'EAG' tab: Change to '£952'	£9,985	£9,552	£10,724
Additional committee preferred assumptions				
Tirzepatide stopping rates at 6 months due to non-response based on the proportion of non-responders at 48-weeks	B90 'EAG' tab: Change to 'Yes, Use Inputs from the ACM3 Request-Stage (Subgroup-Specific)'	£10,065	£9,960	£11,057
Return to prediabetes when patients' weight equals their baseline weight (all treatment arms)	B91 and B92 'EAG' tab: Change to 'Yes'	£11,418	£11,538	£12,210
Adjustment for BMI distribution in the model to reflect the population who would be potentially eligible to receive tirzepatide in the general population	B77 'EAG' tab: Change to 'Normal'	£9,040	£8,910	£10,304
Committee-Preferred Base Case	All of the above settings applied	**£14,867**	**£13,800**	**£14,954**

Abbreviations: AE: adverse event; CVD: cardiovascular disease; D&E: diet and exercise; EAG: external assessment group; ICER: incremental cost effectiveness ratio; MDT: multidisciplinary team; NAFLD: non-alcoholic fatty liver disease; NHSE: National Health Service England; QALY: quality-adjusted life years; QC: quality check; SWMS: Specialist Weight Management Service; T2DM: type 2 diabetes mellitus.

BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD

Table 2 presents the cost-effectiveness results for tirzepatide vs. diet and exercise in the population with a BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD when all Committee-preferred inputs and assumptions are employed in the model. As above, all results are aligned with what the Committee has requested and how the EAG have implemented these assumptions in their model.

Overall, these results demonstrate that the Committee-preferred assumptions do not change the conclusion that tirzepatide is a cost-effective use of NHSE resources for patients with a BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD, with ICERs well below the WTP threshold across all tirzepatide doses.

Table 2: Committee-preferred settings applied individually to the Company-preferred base case results for population with BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD (vs. D&E)

Setting Applied to the Company-Preferred Base Case	Model Implementation	vs. D&E		
		Tirzepatide (5.0 mg)	Tirzepatide (10.0 mg)	Tirzepatide (15.0 mg)
Company-Preferred Base Case Settings (from pre-ACM2)		£6,043	£5,548	£7,181
Including a proportion of people at baseline in the model reflective of the proportion with each comorbidity in SURMOUNT-1 with previous myocardial infarction, obstructive sleep apnoea, and non-alcoholic fatty liver disease	B74 'EAG' tab: Change to 'TRUE'	£5,422	£5,770	£7,578
Removing the net increase in tirzepatide treatment effect by applying the same natural progression increase in weight according to age to the tirzepatide arm after 72-weeks as in the diet and exercise arm	B70 'EAG' tab: Change to 'TRUE' B71 'EAG' tab: Change to '=72/(365.25/7)'	£7,390	£6,283	£8,339
Assuming weight is regained over 2 years after stopping treatment	B67 'EAG' tab: Change to '2'	£6,674	£6,260	£7,821
Using the costs for type 2 diabetes from UKPDS plus an estimate of drug costs associated with type 2 diabetes	B39 'EAG' tab: Change to £1,226	£8,665	£8,184	£9,531
Removing mortality modifiers applied in the company's model for history of angina, myocardial infarction and stroke	B28 'EAG' tab: Change to 'FALSE' B97 'EAG' tab: Change to 'TRUE'	£5,994	£5,458	£7,098
Amending the adverse event-related treatment stopping rate from annually applying the stopping rate due to adverse events from SURMOUNT-1 at 72-weeks (the company's assumption), to mainly applying stopping due to adverse events in the first year of the model, followed by an annual 1% stopping rate	B31 'EAG' tab: Change to 'TRUE'	£6,897	£7,273	£8,794
Halving the non-alcoholic fatty liver disease incidence rate (12% to 6%)	B32 'EAG' tab: Change to '0.06'	£6,779	£5,927	£7,559
Increasing the prevalence of obstructive sleep apnoea for people with a BMI between 30 kg/m^2 and 35 kg/m^2 (2.85% sourced from the UK Clinical Practice Research Datalink database)	B33 'EAG' tab: Change to 'TRUE'	£6,030	£5,534	£7,164
Amending the quality of life functions used by the company to compensate for effects of the function where quality of life starts to improve as BMI increases beyond 39.0 kg/m2 for men and 46.5 kg/m2 for women	B34 and B63 'EAG' tab: Change to 'TRUE'	£5,651	£5,137	£6,678

Removing disutilities for obesity related complications which are already covered by the quality of life functions	B35 ‘EAG’ tab: Change to ‘TRUE’	£6,517	£5,661	£7,320
Other minor model amendments outlined in section 5.5.7 of the EAG report: • Apply an adjustment to NAFLD mortality of 1.71 • Apply the incidence of AEs once • Apply an annual cost to NAFLD of £952	B42 ‘EAG’ tab: Change to ‘TRUE’ B44 and B65 ‘EAG’ tab: Change to ‘TRUE’ B45 ‘EAG’ tab: Change to ‘£952’	£6,278	£5,654	£7,286
Tirzepatide stopping rates at 6 months due to non-response based on the proportion of non-responders at 48-weeks	B90 ‘EAG’ tab: Change to ‘Yes, Use Inputs from the ACM3 Request-Stage (Subgroup-Specific)’	£6,288	£6,161	£7,500
Return to prediabetes when patients' weight equals their baseline weight (all treatment arms)	B91 and B92 ‘EAG’ tab: Change to ‘Yes’	£8,640	£8,309	£9,577
Adjustment for BMI distribution in the model to reflect the population who would be potentially eligible to receive tirzepatide in the general population	B77 ‘EAG’ tab: Change to ‘Normal’	£5,660	£5,018	£6,985
Committee-Preferred Base Case	All of the above settings applied	**£12,985**	**£11,949**	**£13,574**

Abbreviations: AE: adverse event; CVD: cardiovascular disease; D&E: diet and exercise; EAG: external assessment group; ICER: incremental cost effectiveness ratio; MDT: multidisciplinary team; NAFLD: non-alcoholic fatty liver disease; NHSE: National Health Service England; QALY: quality-adjusted life years; QC: quality check; SWMS: Specialist Weight Management Service; T2DM: type 2 diabetes mellitus.

Committee-requested scenario analyses

Given that the BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD population represents a higher-risk subset of the BMI ≥35 kg/m^2 with at least one weight-related comorbidity population (and *a priori* will have similar or lower ICERs), Lilly has presented the scenario analyses for the BMI ≥35 kg/m^2 with at least one weight-related comorbidity population only in the following sections.

Resource use for obesity management services

In line with the Committee's request, various resource use scenarios have been explored on top of the Committee-preferred base case, as detailed in Table 3. A detailed cost breakdown of each of the appointments included in the model for these scenarios is provided in Technical Appendix B.

Table 3. Resource use scenarios

Scenario	Model Implementation
EAG-preferred resource use (as per "ID6179 Tirzepatide overweight and obesity_EAG critique pre ACM2 050424 [CON]" Section 2.1.7.)	B36 and B38 'EAG' tab: Change to 'TRUE' B37 and B62 'EAG' tab: Change to 'TRUE'
Company-preferred resource use (applying the revised resource use outlined in Table 1 in Lilly's NHSE Response on 22nd March)	Change B93 and B94 on the 'EAG' tab to 'Yes' and cell B95 on the 'EAG' tab to 'S2 Lilly Response Pt 1'
Other scenarios presented by Company in their submission to NICE on the 22nd March	
Company-preferred resource use scenario (with additional nurse touchpoints, as outlined in Table 1 in Lilly's NHSE Response on 22nd March)	Change B93 and B94 on the 'EAG' tab to 'Yes' and cell B95 on the 'EAG' tab to 'S1 Lilly Response Pt 1'
NHSE-proposed resource use (as per ID6179 Questions for NHSE 26Jan24 NHSE Submission FINAL v2.0 200224, Page 9/10) applied to both the tirzepatide and diet and exercise arms	Change B93 and B94 on the 'EAG' tab to 'Yes' and cell B95 on the 'S3 Lilly Response Pt 1'
NHSE-proposed resource use (as per ID6179 Questions for NHSE 26Jan24 NHSE Submission FINAL v2.0 200224, Page 9/10) applied to tirzepatide arm only	Change B93 and B94 on the 'EAG' tab to 'Yes' and cell B95 on the 'S4 Lilly Response Pt 1'

Results

Table 4 presents the cost-effectiveness results for the scenarios outlined above that explore different levels of obesity management support. Overall, these scenarios demonstrate that all three tirzepatide represent a cost-effective use of NHSE resources vs. diet and exercise regardless of the level of support that is provided alongside treatment, with ICERs below the WTP threshold across all tirzepatide doses.

Table 4. Scenario analyses for obesity management services resource use in the BMI ≥35 kg/m^2 with at least one weight-related comorbidity population (vs. diet and exercise)

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
EAG-preferred resource use					
Diet and Exercise	£20,982	15.77	-	-	-
Tirzepatide (5.0 mg)	£39,416	16.71	£18,434	0.94	£19,603
Tirzepatide (10.0 mg)	£43,118	17.03	£22,136	1.26	£17,542
Tirzepatide (15.0 mg)	£46,641	17.16	£25,659	1.39	£18,433
Company-preferred resource use					
Diet and Exercise	£16,843	15.77	-	-	-
Tirzepatide (5.0 mg)	£31,375	16.71	£14,532	0.94	£15,454
Tirzepatide (10.0 mg)	£34,812	17.03	£17,969	1.26	£14,240
Tirzepatide (15.0 mg)	£38,218	17.16	£21,375	1.39	£15,355
Company-preferred resource use scenario					
Diet and Exercise	£16,843	15.77	-	-	-
Tirzepatide (5.0 mg)	£31,328	16.71	£14,486	0.94	£15,404
Tirzepatide (10.0 mg)	£34,812	17.03	£17,970	1.26	£14,241
Tirzepatide (15.0 mg)	£38,273	17.16	£21,430	1.39	£15,395
NHSE-proposed resource use applied to both arms					
Diet and Exercise	£17,095	15.77	-	-	-
Tirzepatide (5.0 mg)	£34,890	16.71	£17,796	0.94	£18,924
Tirzepatide (10.0 mg)	£38,695	17.03	£21,601	1.26	£17,118
Tirzepatide (15.0 mg)	£42,346	17.16	£25,252	1.39	£18,140
NHSE-proposed resource use applied to tirzepatide arm only					
Diet and Exercise	£16,512	15.77	-	-	-
Tirzepatide (5.0 mg)	£34,890	16.71	£18,378	0.94	£19,544
Tirzepatide (10.0 mg)	£38,695	17.03	£22,183	1.26	£17,580
Tirzepatide (15.0 mg)	£42,346	17.16	£25,834	1.39	£18,559

Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Long-term impact on outcomes from previously having a higher BMI

The Committee has requested that the Company explore scenarios on the Committee-preferred base case exploring the impact on the cost-effectiveness results for tirzepatide when a potential long-term impact on outcomes of previously having a higher BMI is integrated into the model. These scenarios have been informed by Haase *et al*., and are implemented as follows:

- Hazard ratios (HRs) are included for each complication, with chronic kidney disease (CKD) used as a proxy for NAFLD (as per the EAGs implementation).
- For each complication in Figure 4 of Haase *et al*. where the 'risk after weight loss' is less than the 'reference', a 'superior' risk is applied, equivalent to a HR of 0.75. Similarly, for each complication where the 'risk after weight loss' is greater than the 'reference', a 'residual' risk is applied, equivalent to a HR of 1.25. It should be noted that the specific choice of the 0.75 and 1.25 adjustments are arbitrary, but aligned

with the EAG's initial implementation of the paper, with values corresponding to 75% and 125%. When the 'risk after weight loss' is similar to the 'reference', a HR of 1 is applied.
    - The HRs used for each outcome can be found in the model on the EAG tab in cells L110:L114
- For the subgroups presented in this response, data from 'Profile 2' of the figure have been used, equivalent to patients with a BMI of 35–40 kg/m^2.
- In contrast to the EAG's implementation, the Company has applied the HRs to the actual probability of developing the event, rather than just cost/utilities of the event.

Table 5. Company implementation of Haase et al. for population with BMI ≥35 kg/m^2 with at least one weight-related comorbidity (vs. diet and exercise)*

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
Committee-preferred base case results					
Diet and Exercise	£20,982	15.77			
Tirzepatide (5.0 mg)	£34,962	16.71	£13,980	0.94	£14,867
Tirzepatide (10.0 mg)	£38,396	17.03	£17,414	1.26	£13,800
Tirzepatide (15.0 mg)	£41,798	17.16	£20,816	1.39	£14,954
Company implementation of Haase et al.					
Diet and Exercise	£20,377	15.78			
Tirzepatide (5.0 mg)	£34,446	16.71	£14,069	0.93	£15,167
Tirzepatide (10.0 mg)	£37,946	17.03	£17,569	1.25	£14,085
Tirzepatide (15.0 mg)	£41,355	17.16	£20,978	1.38	£15,233

Footnote: *This setting is applied by changing B96 on the 'EAG' tab to 'Yes, Use Company Implementation of Haase et al. 2021'.
Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

Summary

In conclusion, Lilly has provided cost-effectiveness results for the Committee-preferred assumptions in the prioritised BMI ≥35 kg/m^2 populations as requested, and in doing so has demonstrated that all three tirzepatide doses represent a cost-effective use of NHSE resources in both populations (even though some assumptions/scenarios are extreme and/or implausible). In Lilly's response to the forthcoming draft guidance consultation, we look forward to providing analyses for additional populations and providing justification for further refinement of the Committee-preferred inputs and assumptions at ACM2 for consideration at ACM3.

References

1. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med 2023;389:2221-2232.
2. Gerstein HC CM, Dagenais GR, Diaz R, et al.,. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet 2019;394:121 - 130.
3. Aronne LJ SN, Horn DB, et al.,. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity; The SURMOUNT-4 Randomized Clinical Trial. JAMA 2024;331:38-48.
4. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide Semaglutide Once Weekly in Patients with Type 2 Diabetes. New England Journal of Medicine 2021;385:503-515.

Technical Appendix A

Model version

Following ACM2, the Committee indicated that there were concerns surrounding the most suitable version of the model to use going forwards, given that different versions of the model were used by the EAG and the Company prior to ACM2.

With this in the mind, the Company wish to reassure the EAG and Committee that the model version used to generate the results in this response is consistent with the earlier model version used by the EAG. A number of minor updates have been made to the model to allow for the implementation of the Committee preferences (detailed in the adaptation log); however, all of these updates are selectable in the model via a drop-down to ensure that nothing previously implemented by the EAG has been overridden. The model provided by the Company alongside this report is saved on the Committee-preferred assumptions in the BMI ≥ 35 kg/m^2 with at least one weight-related comorbidity population. Accordingly, Lilly has outlined in the following sections how the EAG's pre-ACM2 base case results can be reproduced within the model.

EAG requests

As well as detailing how the EAG base case results may be reproduced, Lilly has responded below to the EAG's most recent requests in "ID6179 Tirzepatide - post ACM2 EAG notes on model 250424 [NoCON]", and has incorporated any amendments resulting from these requests to the Committee-preferred results presented:

Question 1: Please clarify which implementation of OSA and NAFLD (EAG or Company) is correct:

- The EAG's implementation has been used for including baseline comorbidities for OSA, NAFLD and MI (Row 74 on the EAG tab). The Company has included subgroup-specific values for baseline comorbidities, in Cell 74:76 on the Baseline Characteristics tab.

Question 2:

A. *Please outline if there are any modelling issues with permitting a cohort larger than 5,000 by changing EAG B8 and Settings I25*: Without changing further aspects of the model programming, the model cannot currently simulate cohorts larger than 5,000 patients.

B. *Please outline if there are any modelling issues with permitting a larger random seed by revising Control Panel M23*: The model should be able to run on any random seed number. This should be changed by altering the random seed in Cell M23 on the Control Panel tab (the Company has removed the data validation).

C. *Please outline if there are any modelling issues with removing tirzepatide 5, semaglutide and liraglutide by setting Control Panel L30, L31, L33 and L34 to be equal to 2*: All treatments except for Tirzepatide 15.0 mg and Diet and Exercise can be excluded by changing the corresponding Yes/No drop-downs for treatment inclusion/exclusion on the Settings tab (e.g. I30). Changes should not be made directly on the Control Panel, as it would break this link in the model.

Question 3: Please provide an account of the differences in the N between the Week 48 responder data in Efficacy Q57 and the Company Submission:

- The Week 48 data included in the model prior to ACM2 did not include imputations for patients who had missing data. To align with other efficacy data used in the model, the Company has therefore amended this in its implementation of the Committee's preferred assumptions, so that the imputed N value is used for primary treatment failure. It should be noted that these N numbers still differ slightly compared with those presented in Table 22 in the Company Submission (as highlighted by the EAG). This is because the N numbers presented in Table 22 in the Company Submission correspond with the total randomised population in the target population, rather than the actual number of participants included in the efficacy estimand analyses at Week 48 (where participants were required to have a baseline and at least one post-baseline measurement).

Reversion to pre-ACM2 EAG base case

The EAG's pre-ACM2 base case results (ICER of £21,652 for tirzepatide 15.0 mg vs. diet and exercise in the BMI ≥35 kg/m^2 with at least one weight-related comorbidity population) can be reproduced by changing the settings outlined in Table 6 within the model shared alongside this response.

The EAG's pre-ACM2 base case results (ICER of £19,719 for tirzepatide 15.0 mg vs. diet and exercise in the BMI ≥35 kg/m^2 with prediabetes and a high risk of CVD) can be reproduced by changing the settings outlined in Table 7 within the model shared alongside this response.

Table 6. EAG-preferred settings applied individually to the committee-preferred base case results for population with BMI ≥35 kg/m² with at least one weight-related comorbidity (vs. D&E)

Setting Applied to the Committee Preferred Base Case	Model Implementation	ICER vs. D&E		
		Tirzepatide (5.0 mg)	Tirzepatide (10.0 mg)	Tirzepatide (15.0 mg)
Committee-Preferred Base Case		£14,867	£13,800	£14,954
Remove CVD event mortality	B29 'EAG' tab: Change to 'FALSE'	£16,196	£14,666	£15,617
Apply EAG preferred resource use	B36 and B38 'EAG' tab: Change to 'TRUE' B37 and B62 'EAG' tab: Change to 'TRUE'	£19,603	£17,542	£18,433
Change the T2DM cost to the EAG preference	B39 'EAG' tab: Change to £780.37	£16,164	£14,939	£16,041
Change the primary treatment failure inputs used	B50 'EAG' tab: Change to 'FALSE' B90 'EAG' tab: Change to 'No'	£14,878	£13,753	£14,948
Use a gamma distribution for sampling BMI	B77 'EAG' tab: Change to 'Gamma'	£17,681	£14,451	£15,176
Remove assumption on loss of prediabetes reversal in line with returning to baseline weight	B91 and B92 'EAG' tab: Change to 'No'	£13,900	£13,011	£14,262
Remove the Corrections Identified by Lilly Following their QC*				
Remove the NAFLD mortality multiplier include the additional EAG.SWMS.Year1 Cost Implementation from all scenarios Remove MDT/NHSE resource use to patients regardless of response status	B97 'EAG' tab: Change to 'FALSE' B98 'EAG' tab: Change to 'FALSE' B99 'EAG' tab: Change to 'FALSE'	£15,180	£14,325	£15,596
Do not apply subgroup specific baseline comorbidities (to align to approach in pre-ACM2 model)	B100 'EAG' tab: Change to 'FALSE'	£14,814	£13,798	£14,950
Apply the BMI ≥30 kg/m² + ≥1 comorbidity population efficacy inputs (to align to approach in pre-ACM2 model)	B101 'EAG' tab: Change to 'TRUE'	£14,940	£14,077	£15,478
EAG Base Case (Table 11 EAG Report)	All of the above settings applied	£24,281	£20,512	£21,450

Footnotes: *Corrections identified by Lilly following QC of the EAG model have been implemented as reversible dropdowns (further details on these corrections can be found in the separate report submitted on 29th April [File Name QC Report_EAG Model Pre ACM2]).

Abbreviations: CVD: cardiovascular disease; D&E: diet and exercise; EAG: external assessment group; ICER: incremental cost effectiveness ratio; MDT: multidisciplinary team; NAFLD: non-alcoholic fatty liver disease; NHSE: National Health Service England; QALY: quality-adjusted life years; QC: quality check; SWMS: Specialist Weight Management Service; T2DM: type 2 diabetes mellitus.

Table 7: EAG-preferred settings applied individually to the committee-preferred base case results for population with BMI ≥35 kg/m² with prediabetes and a high risk of CVD (vs. D&E)

Setting Applied to the Committee-Preferred Base Case	Model Implementation	ICER vs. D&E		
		Tirzepatide (5.0 mg)	Tirzepatide (10.0 mg)	Tirzepatide (15.0 mg)
Committee-Preferred Base Case	I18 'Settings' tab: Change to 'BMI ≥35 kg/m² + prediabetes + high ASCVD risk' B10 'EAG' tab: Change to 'BMI ≥35 kg/m² + prediabetes + high ASCVD risk'	**£12,985**	**£11,949**	**£13,574**
Change baseline comorbidities (OSA, NAFLD and MI) to be derived from the target population, retaining all other baseline characteristics as subgroup-specific	B100 'EAG' tab: Change to 'FALSE'	£13,022	£12,008	£13,637
Remove CVD event mortality	B29 'EAG' tab: Change to 'FALSE'	£14,592	£13,055	£14,624
Change the T2DM cost to the EAG preference	B39 'EAG' tab: Change to £780.37	£14,689	£13,436	£15,047
Change the primary treatment failure inputs used	B50 'EAG' tab: Change to 'FALSE' B90 'EAG' tab: Change to 'No'	£12,992	£11,912	£13,549
Apply EAG preferred resource use	B36 and B38 'EAG' tab: Change to 'TRUE' B37 and B62 'EAG' tab: Change to 'TRUE'	£17,544	£15,516	£17,008
Use a gamma distribution for sampling BMI	B77 'EAG' tab: Change to 'Gamma'	£14,683	£12,502	£14,321
Remove assumption on loss of prediabetes reversal in line with returning to baseline weight	B91 and B92 'EAG' tab: Change to 'No'	£11,193	£10,510	£12,232
Remove the Corrections Identified by Lilly Following their QC*				
Remove the NAFLD mortality multiplier Include the additional EAG.SWMS.Year1 Cost Implementation from all scenarios Remove MDT/NHSE resource use to patients regardless of response status	B97 'EAG' tab: Change to 'FALSE' B98 'EAG' tab: Change to 'FALSE' B99 'EAG' tab: Change to 'FALSE'	£13,114	£12,178	£13,833

EAG Base Case (Table 11 EAG Report)	All of the above settings applied	**£22,199**	**£18,135**	**£19,719**

Footnotes: *Corrections identified by Lilly following QC have been implemented as reversible dropdowns (further details on these corrections can be found in the separate report submitted on 29th April [File Name QC Report_EAG Model Pre ACM2]).
Abbreviations: CVD: cardiovascular disease; D&E: diet and exercise; EAG: external assessment group; ICER: incremental cost effectiveness ratio; NAFLD: non-alcoholic fatty liver disease; NHSE: National Health Service England; QALY: quality-adjusted life years; QC: quality check; SWMS: Specialist Weight Management Service; T2DM: type 2 diabetes mellitus.

Technical Appendix B

Resource use scenarios: Implementation

For completeness, the following tables provide a detailed breakdown of the costing and number of appointments that have been included in the model for the resource use scenarios presented in this report (with the exception of the EAG-preferred resource use, which is detailed in their pre-ACM2 report).

Lilly has presented the resource use associated with tirzepatide 15 mg only for concision; however, it should be noted that patients receiving 5 and 10 mg tirzepatide would have fewer appointments overall given that fewer titration appointments are required (for tirzepatide 10.0 mg and 5.0 mg, these are reduced to weeks 4, 8, and 12 and only week 4, respectively).

Table 8. Company-preferred resource use (applying the revised resource use outlined in Lilly's Response on 22nd March) for tirzepatide 15.0 mg*

		Year 1	Year 2	Year 3+	Cover age	Cost per slot	Year 1	Year 2	Year 3+
GP	10 min slots	1	1	1	-	£41.00	£41.00	£41.00	£41.00
Nurse	10 min slots	8	0	0	-	£18.55	£148.40	0	0
Dietician	30 min slots	7	4	0	-	£27.19	£190.33	£108.76	0
Total	-	-	-	-	-	-	£379.73	£149.76	£41.00

Footnotes: *The inputs (number of GP, Nurse and Dietician visits) remain the same for each dose of tirzepatide. The diet and exercise arm incurs a total of 1 GP appointment in Year 1, 7 Dietician appointments in Year 1 and 4 Dietician appointments in Year 2.

Table 9. Company-preferred resource use scenario (with additional nurse touchpoints) for tirzepatide 15.0 mg*

		Year 1	Year 2	Year 3+	Cover age	Cost per slot	Year 1	Year 2	Year 3+
GP	10 min slots	1	1	1	-	£41.00	£41.00	£41.00	£41.00
Nurse	10 min slots	11	0	0	-	£18.55	£204.05	0	0
Dietician	30 min slots	7	4	0	-	£27.19	£190.33	£108.76	0
Total	-	-	-		-	-	£435.38	£149.76	£41.00

Footnotes: *The tirzepatide 10.0 mg arm incurs 3 fewer Nurse appointments in Year 1 than in the tirzepatide 15.0 mg arm. The tirzepatide 5.0 mg arm incurs 6 fewer Nurse appointments in Year 1 than in the tirzepatide 15.0 mg arm. The number of GP and Dietician visits remained the same for each dose of tirzepatide.

Table 10. NHSE-proposed resource use applied to both the tirzepatide and diet and exercise arms for tirzepatide 15.0 mg*

		Year 1	Year 2+	Coverage	Cost per slot	Year 1	Year 2+
GP	10 min slots	21	3	-	£41.00	£861.00	£123.00
Nurse	10 min slots	4.5	3	-	£18.55	£83.48	£55.65
HCA	10 min slots	1	0	-	£7.14	£7.14	£0.00
Nurse Group	10 min slots	3	0	-	£18.55	£55.65	£0.00
Clinical Pharmacist	10 min slots	3	3	-	£11.29	£33.87	£33.87
Dietician	30 min slots	5	4	-	£27.19	£135.95	£108.76
Psychologist	30 min slots	6^	2 (15 mins)	0.33	£33.88	£67.08	£10.16
Total	-	-	-	-	-	£1,244.17	£331.44

Footnotes: *The tirzepatide 10.0 mg arm incurs 4 fewer GP appointments in Year 1 than in the tirzepatide 15.0 mg. The tirzepatide 5.0 mg arm incurs 8 fewer GP appointments in Year 1 than in the tirzepatide 15.0 mg. The diet and exercise arm incurs a total of 3 Nurse Group appointments in Year 1, 1 HCA appointment in Year 1, 4.5 GP appointments in Year 1, 5 Dietician appointments in Year 1, and 4 Dietician appointments in Year 2 and onwards (annually). ^Company derive a value of 6 x 30 min appointments, made up of the specified 5 appointments in Year 1 plus 2 MDT discussions per year starting from week 26 (2 x 15 mins = 1 x 30 mins). This differs slightly to the NHSE table of 5.5 appointments.

Table 11. NHSE-proposed resource use applied to tirzepatide arm only, for tirzepatide 15.0 mg*

		Year 1	Year 2+	Coverage	Cost per slot	Year 1	Year 2+
GP	10 min slots	21	3	-	£41.00	£861.00	£123.00
Nurse	10 min slots	4.5	3	-	£18.55	£83.48	£55.65
HCA	10 min slots	1	0	-	£7.14	£7.14	£0.00
Nurse Group	10 min slots	3	0	-	£18.55	£55.65	£0.00
Clinical Pharmacist	10 min slots	3	3	-	£11.29	£33.87	£33.87
Dietician	30 min slots	5	4	-	£27.19	£135.95	£108.76
Psychologist	30 min slots	6^	2 (15 mins)	0.33	£33.88	£67.08	£10.16
Total	-	-	-	-	-	£1,244.17	£331.44

Footnotes: *The tirzepatide 10.0 mg arm incurs 4 fewer GP appointments in Year 1 than in the tirzepatide 15.0 mg. The tirzepatide 5.0 mg arm incurs 8 fewer GP appointments in Year 1 than in the tirzepatide 15.0 mg. ***The diet and exercise arm incurs no costs as this scenario applies resource use to the tirzepatide arm only.*** ^Company derive a value of 6 x 30 min appointments, made up of the specified 5 appointments in Year 1 plus 2 MDT discussions per year starting from week 26 (2 x 15 mins = 1 x 30 mins). This differs slightly to the NHSE table of 5.5 appointments

External Assessment Group's report post AC2

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Ewen Cummins critiqued the cost-effectiveness evidence, Rhona Johnston reviewed and revised the VBA model implementation. Both implemented the revised EAG economic modelling. Mubarak Patel critiqued statistical aspects of the Company submission and provided statistical input to this report. Lena Al-Khudairy supported the critique of the clinical effectiveness evidence and coordinated the project.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

1. Background

NICE requested that the Company provide a set of analyses that make the changes outlined below. The full set of changes of EAG preferred base case changes are not listed, though some of this may be more ambiguity than omission. Those not listed are relatively minor. The Company has largely complied with the requested changes, but there is a degree of ambiguity in the specified changes. The EAG makes a few observations on the Company implementation which it will address further alongside consultation comments.

The Committee's preferred assumptions are principally aligned with the EAG base case as follows:

- including a proportion of people at baseline in the model reflective of the proportion with each comorbidity in SURMOUNT-1 with previous myocardial infarction, obstructive sleep apnoea and non-alcoholic fatty liver disease
    - The Company has adopted the EAG implementation of this.
- removing the net increase in tirzepatide treatment effect by applying the same natural progression increase in weight according to age to the tirzepatide arm after 72-weeks as in the diet and exercise arm
- assuming weight is regained over 2 years after stopping treatment
- using the costs for type 2 diabetes from UKPDS plus an estimate of drug costs associated with type 2 diabetes
    - The Company applies the UKPDS estimates plus the drug cost estimates of Capehorn et al. The annual ongoing resource use of patients who have not developed diabetes is not netted out and the gross annual cost of diabetes is applied in addition to the annual ongoing resource use of patients who have not developed diabetes.
- removing mortality modifiers applied in the Company's model for history of angina, myocardial infarction and stroke as the increased risk of death from these events is covered by the BMI mortality modifier
    - Due to it not being specified the Company retains the NAFLD mortality multiplier. It also retains its implementation of CVD deaths.

- amending the adverse event-related treatment stopping rate from annually applying the stopping rate due to adverse events from SURMOUNT-1 at 72-weeks (the Company's assumption), to mainly applying stopping due to adverse events in the first year of the model, followed by an annual 1% stopping rate
- halving the non-alcoholic fatty liver disease incidence rate to adjust for differences observed across the studies used by the Company to estimate incidence rate and hazard ratios for the development of non-alcoholic fatty liver disease
- increasing the prevalence of obstructive sleep apnoea for people with a BMI between 30 kg/m^2 and 35 kg/m^2 (2.85% sourced from the UK Clinical Practice Research Datalink database) compared with the Company's assumption that this population has equal risk of obstructive sleep apnoea to the general population
- amending the quality of life functions used by the Company to compensate for effects of the function where quality of life starts to improve as BMI increases beyond 39.0 kg/m^2 for men and 46.5 kg/m^2 for women
- removing disutilities for obesity related complications which are already covered by the quality of life functions
- other minor model amendments outlined in section 5.5.7 of the EAG report

Committee's preferred assumptions also included:

- assuming tirzepatide stopping rates at 6 months due to non-response based on the proportion of non-responders at 48-weeks in the target population in SURMOUNT-1
- prediabetes reversal loss modelled so that it aligns with the approximate time in the model that baseline weight is regained in all arms
- an adjustment for BMI distribution in the model to reflect the population who would be potentially eligible to receive tirzepatide in the general population
    - The Company applies the EAG implementation of the truncated normal distribution

- including the population specific efficacy results for each subgroup

The Committee would like to see subgroup analyses including all its preferred assumptions for the following subgroups, prioritising those in bold:

- People with a BMI of at least 30 kg/m^2 and at least 1 weight related comorbidity – the "Target Population"
- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight related comorbidity – the "BMI 30-35" subset
- **People with a BMI of at least 35 kg/m^2 and at least 1 weight related comorbidity** – the "BMI 35+" subset
- **People with a BMI of at least 35 kg/m^2, prediabetes and a high risk of cardiovascular disease** – the "High Risk" subset
- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight related comorbidity or with a BMI of at least 35 kg/m^2 without prediabetes and a high risk of cardiovascular disease – the "Lower Risk" subset

The EAG questions whether intended definition of the Lower Risk subset is those patients in the Target population who are not in the High Risk subset, the "EAG Lower Risk" subset:

- A BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight related comorbidity; or
- A BMI of at least 35 kg/m^2; and,
    - without prediabetes; or
    - without a high risk of cardiovascular disease; or
    - without prediabetes and high risk of cardiovascular disease.

The Company has presented subset specific baseline characteristics for the BMI 30-35 subset, the BMI 35+ subset and the High Risk subset. The EAG infers baseline characteristics for the EAG Lower Risk subset as outlined in Appendix 1.

The Company has presented subset specific effectiveness data for the BMI 35+ subset and the High Risk subset. The EAG infers effectiveness data for the BMI 30-

35 subset and the EAG Lower Risk subset as outlined in Appendix 2. The main clinical effect estimates for each of the subsets of the Target Population are little different from those of the Target Population.

The Company presents cost effectiveness estimates for the BMI 35+ subset and the High Risk subset.

- Within the Company amended model the Company preferred AC2 base case ICERs of £10,679 per QALY for the BMI 35+ subset and £7,181 per QALY for the High Risk subset change to £14,954 per QALY and £13,574 per QALY when the NICE requested changes are made.
- Within the EAG amended model the corresponding original ICERs of £10,783 per QALY and £7,574 per QALY respectively change to £14,901 per QALY and £13,629 per QALY when the Company changes are made. While correspondence with the Company estimates is not perfect, any differences are small and will not affect decision making.

The EAG presents cost effectiveness estimates for all of the groups requested by Committee, where necessary using the inferred baseline characteristics and effectiveness estimates. The Company has not had the opportunity to comment upon these. The Company will provide baseline characteristics and effect estimates for the BMI 30-35 subset and the Lower Risk subset during consultation, obviating the need for EAG inferred estimates.

2. **Scenario analyses:**

NIC notes that it is not within the Committee's remit to agree what the obesity management services will include for people receiving or not receiving tirzepatide. Given the uncertainty around what these services will include, it requested to see a range of scenarios on a base case including all its other preferred assumptions. These scenarios should include:

- Scenario 1: the EAG's preferred assumption (applying the resource use proposed by NHS England for obesity management services to the tirzepatide arm for the duration of tirzepatide treatment and no resource use to the diet and exercise arm)

- Scenario 2: the Company's preferred assumptions for obesity management services in each arm
- Scenario 3: other scenarios presented by the Company in the submission to NICE on 22nd March 2024.

Scenario 4: The Committee would also like to see scenario analyses on a base case including all its other preferred assumptions on the long-term impact on outcomes from previously having had a higher BMI.

The EAG raises two issues about the Company scenarios.

Scenario 1: Application of NHSE MDT estimates

The Company implementation of MDT resource use does not apply the NHSE estimates, rather applying the MDT resource use outlined in Appendix 3. The Company scenario applying the EAG MDT preferred values has adjusted the original EAG implementation due to errors in the EAG implementation, but still does not correspond with the NHSE supplied estimates. As a consequence, the EAG augments the Company analyses with a scenario of the NHSE MDT resource use.

Scenario 4: Implementation of the findings of Haase et al

Haase et al explored whether patients having been at a higher weight for some time and then losing weight causes their risks of events to:

1. remain unchanged at the level of patients who remain at the higher weight: No Effect
2. fall to that of those who had always been at the lower weight: Full Effect
3. fall to somewhere between these two values above: Residual Risk[1]

The EAG implementation of the effects of Haase et al simply conditioned the direct QoL and cost effects of the modelled complications by multipliers. For No Effect the multiplier is 0%. For Full Effect the multiplier is 100%. For Residual Risk the EAG applied the previous Company arbitrary risk multipliers of 50% and 75%, yielding two scenario analyses.

[1] Haase et al also consider the possibility of weight loss resulting in risks lower than of those who have always been at the lower weight. This is omitted here for ease of explanation. This is considered within the EAG analyses using multipliers of 100% and 125% as per the EAG AC2 report.

The Company implementation raises the risk of an event by an arbitrary hazard ratio. This does not limit the complications' effects to lie somewhere between no effect and 100% effect. Suppose that for someone at 40 kgm-2 the risk of an event was 18.0%, with the base case model assuming that weight loss to 35 kgm-2 reduces this to the risk of someone who has always been at 35kgm-2 of 15.0%. Applying an arbitrary HR revises this risk to be (1-(1-P)^HR). HRs of 1.25, 1.50 and 2.00 increase the 15.0% risk to 18.4%, 21.6% and 27.8% respectively. The Company method does not restrict the probability of the event to lie between the values of 18% and 15%.

The key aspect of Haase et al is that the risks and effects that are applied for Residual Risk must cause the effects to lie between the two extremes. The EAG method achieves this. The EAG does not further consider the Company method, and retains its simpler application of the 50% and 75% effect modifiers for where Haase et al estimate Residual Risk.

3. Additional EAG analyses

Table 1: EAG scenarios around Company changes

	Target	BMI30-35	BMI35+	LowerRisk	High Risk
All Company changes	£19,500	£27,236	£14,901	£21,777	£13,629
EAG MDT tirzepatide	£25,406	£35,314	£19,535	£28,169	£18,220
EAG MDT both arms	£24,520	£34,052	£18,850	£27,201	£17,528
Haase high scenario	n.a.	£29,554	£14,171	n.a.	n.a.
Haase low scenario	n.a.	£31,925	£15,609	n.a.	n.a.
Haase low with mort.	n.a.	£36,093	£15,678	n.a.	n.a.

Note that the Lower Risk subset is the EAG Lower Risk subset; i.e. the Target Population splits into the EAG Lower Risk subset (68%) and the High Risk subset (32%).

Haase et al only provide estimates for the BMI 30-35 subset and the BMI 35+ subset. The EAG does not think that these can be applied to the Target Population, the Lower Risk subset or the High Risk subset.

The above are EAG scenarios around the Company revised modelling. The EAG will provide its preferred ICERs and scenarios in response to consultation.

Appendix 1: Baseline characteristics for EAG Lower Risk subset

The Target Population splits into the (EAG) Lower Risk subset (68%) and the High Risk subset (32%). The weighted means for these subsets should equal the mean of the Target Population, so the mean for the Lower Risk subset can be inferred from the means of the Target Population and the High Risk subset.

The inferred s.d.s for the Lower Risk subset are based upon an inferred variance, being of the form $s.d._{LowerRisk} = SQRT((s.d._{All} \text{ ^ } 2) * N_{All} - (s.d._{HighRisk} \text{ ^ } 2) * N_{HighRisk}) / N_{LowerRisk})$. The accuracy of this approximation is likely to fall the greater the differences in the mean values of the subset.

Table 2: Inferred baseline characteristics for (EAG) Lower Risk subset

	Target Pop		Lower Risk		High Risk	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
Age	47.4	12.0	47.8	12.1	46.6	11.8
Female	66%		66%		66%	
Weight (kg)	107.1	22.5	102.1	22.8	117.7	21.6
Height (m)	1.7	0.1	1.7	0.1	1.7	0.1
BMI (kg/m2)	38.8	6.8	37.0	7.0	42.6	6.3
SBP (mmHg)	124.8	12.8	123.9	12.4	126.5	13.4
Total Chol. (mg/dL)	194.0	39.6	210.6	40.3	158.8	79.2
HDL (mg/dL)	48.7	12.9	50.3	13.5	45.3	11.4
eGFR (ml/min/1.73 m2)	95.4	18.0	94.9	17.7	96.5	18.6
Triglycerides (mg/dL)	133.9	67.1	129.1	68.2	144.1	64.8
FPG (mmol/L)	5.4	0.6	5.3	0.6	5.7	0.6
Hypertension	44%		45%		41%	
Treated Hypertension	40%		41%		38%	
COPD	1%		1%		1%	
Hypothyroidism	12%		13%		12%	
Gestational Diabetes	1%		1%		2%	
Lupus	0%		0%		0%	
Female with PCOS	2%		2%		1%	
Male with Erectile Dysfunc.	6%		7%		4%	
Corticosteroids	2%		2%		2%	
Statins	18%		20%		13%	
Prediabetes	58%		38%		100%	

The inferred s.d. for total cholesterol does not compute. The EAG has assumed that for the Lower Risk subset it is equal to that of the BMI 30-35 subset.

Appendix 2: Effect estimates for BMI 30-35 subset and EAG Lower Risk subset

The Target Population splits into the (EAG) Lower Risk subset (68%) and the High Risk subset (32%). It also splits into the BMI 30-35 subset (35%) and the BMI 35+ subset (65%).

Table 3: Inferred 48 week response rates

	Target	BMI30-35	BMI35+	LowerRisk	High Risk
Tirzepatide 5mg Tirzepatide 10mg Tirzepatide 15mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The effects upon the continuous risk factors and the proportion of those with prediabetes at baseline who experience prediabetes reversal are reported below.

Table 4: Inferred risk factor effects and prediabetes reversal: BMI 30-35

	Target Pop.		BMI 30-35		BMI 35+	
	PLAC	TIR15mg	PLAC	TIR15mg	PLAC	TIR15mg
Weight SBP (mmHg) Total Chol. HDL Chol.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PreD reverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Inferred risk factor effects and prediabetes reversal: (EAG) Lower Risk

	Target Pop.		Lower Risk		High Risk	
	PLAC	TIR15mg	PLAC	TIR15mg	PLAC	TIR15mg
Weight SBP (mmHg) Total Chol. HDL Chol.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PreD reverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 3: NHSE and Company MDT Resource Use estimates

The NHSE supplied annual resource use estimates for tirzepatide of £1,239 in year 1 and £355 thereafter. Committee previously requested a scenario of MDT resource use being applied for diet and exercise. Removing the titration elements from year 1 results in a cost of £665. NHSE indicates that if these are applied for diet and exercise their duration would be at most for 2 years.

Assuming that only [redacted] of patients require psychological help compared to the 33% assumed by the NHSE reduces the total costs to [redacted] and [redacted] for year 1 and annually thereafter, and the year 1 costs net of titration to [redacted].

The Company MDT resource use within its scenarios is outlined below for those on tirzepatide treatment, those who have discontinued tirzepatide treatment and those who are in the diet and exercise arm.

Table 6: MDT Resource Use in Company Scenarios

EAG preferred resource use (previous implementation Company adjusted)							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7+
On Tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off Tx	[redacted]	[redacted]	[redacted]	£0	£0	£0	£0
D&E	£0	£0	£0	£0	£0	£0	£0
Company preferred							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7+
On Tx	£421	£109	£0	£41	£41	£41	£41
Off Tx	£231	£109	£0	£0	£0	£0	£0
D&E	£231	£109	£0	£0	£0	£0	£0
Company preferred scenario							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7+
On Tx	£476	£109	£0	£41	£41	£41	£41
Off Tx	£231	£109	£0	£0	£0	£0	£0
D&E	£231	£109	£0	£0	£0	£0	£0
NHSE in both arms							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7+
On Tx	£1,245	£355	£355	£246	£246	£246	£246
Off Tx	£383	£109	£109	£0	£0	£0	£0
D&E	£383	£109	£109	£0	£0	£0	£0
NHSE only in tirzepatide arm							
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7+
On Tx	£1,245	£355	£355	£246	£246	£246	£246
Off Tx	£383	£109	£109	£0	£0	£0	£0
D&E	£0	£0	£0	£0	£0	£0	£0