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Tirzepatide for managing overweight and obesity

Technology appraisal committee A – 09 April 2024

Appraisal Committee Meeting 2

Chair: James Fotheringham

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External assessment group: Warwick Evidence

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Company: Eli Lilly

Recap

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Decision problem

	Final scope	Company
Population	Adults with BMI: • ≥30 (obese) or • ≥27 to <30 (overweight) and with at least 1 weight-related comorbidity	**Target population**: **Adults with BMI ≥30 (obesity) and at least 1 weight-related comorbidity** • Subgroups included liraglutide eligible population
Intervention	Tirzepatide	Tirzepatide ***as adjunct to reduced-calorie diet and increased physical activity****
Comparator	• Standard management without tirzepatide (reduced calorie diet and increased physical activity) • Semaglutide (for population recommended in TA875) • Liraglutide (for population recommended in TA664) • Orlistat (prescription dose)	For target population: • semaglutide plus diet and exercise • diet and exercise For population recommended in TA664: • semaglutide plus diet and exercise • liraglutide plus diet and exercise • diet and exercise
Outcomes	BMI; weight loss; waist circumference; T2DM incidence; glycaemic status; CV events; mortality; adverse effects of treatment; HRQoL	All other than cardiovascular events and mortality (covered by risk equations in model)

in line with marketing authorisation

Equality considerations

- People with mental health disorders (especially those receiving atypical antipsychotics) may have increased risk of developing obesity but ability to access tirzepatide may be hindered by their mental health condition; people with mental health disorders were excluded from SURMOUNT-1
- People with disabilities are disproportionately affected by obesity but ability to access treatment may be adversely impacted by their disability
- Tirzepatide may be suitable for people with disabilities who are unable to provide consent or be eligible for bariatric surgery
- Cardiometabolic risk occurs at a lower BMI for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds, so lower BMI thresholds are a practical measure of overweight and obesity in these populations (thresholds are usually reduced by 2.5 to identify obesity status; NICE Clinical Guideline 189)
- Health inequalities lead to and exacerbate overweight and obesity, disproportionately affecting lower socio-economic communities

Inequity in treatment access

- Access to SWMS is inequitable across the country
- Office for Health Improvement and Disparities data (2022) suggests that tier 2 services are also not equitably distributed across the country or according to local need

Committee discussion at ACM1 – issues for discussion

Issue	Committee discussion ACM1
Costs	Further information needed on the costs associated with delivering tirzepatide in a landscape where weight management services are changing
Generalisability	SURMOUNT-1 did not include people with T2DM or people with severe mental health disorders; introduced uncertainty around generalisability and which comorbidities should be defined as weight-related comorbidities in target population
Model	Assumption that no-one enters model without any future modelled comorbidities or complications (i.e. sleep apnoea) does not reflect the population in practice
T2DM cost	Prefers EAG approach estimating costs from UKPDS data; company's approach based on hospital admissions unlikely appropriate as small proportion of T2DM population
Long-term effect	Likely that natural history of weight increasing with age will occur to some extent in tirzepatide arm and comparator arms; so unlikely that treatment effect difference would continue to increase indefinitely
Loss of prediabetes reversal	Company base case models loss of prediabetes reversal for all at 2 years in diet and exercise support arm and 3 years after individual stops tirzepatide in tirzepatide arm
Risk equations	Unclear how much uncertainty is introduced due to compounding of risk of events over multiple years through annualisation of multi-year risk equations

Other issues

Issues not to be discussed – committee discussion at ACM1 in appendix slide 57

- Target population
- Comparator
- Dose
- Clinical effectiveness
- Stopping rule
- Proportion of non-responders
- Weight regain after treatment

Action since ACM1

No formal consultation on draft guidance after ACM1

- Committee was not able to make a recommendation at ACM1 as further information was required, most notably around the resource costs for weight management services needed to deliver tirzepatide
- Stakeholder feedback gathered through letters outlining committee's conclusions and requesting views on the appropriate set up of obesity management services needed for tirzepatide delivery
- NHS England were asked specifically about predicted resource needed for providing multidisciplinary team weight management services – company has responded to NHS England's proposal
- Scenarios and further evidence also requested and received from the company

Stakeholder responses

- Eli Lilly (company)
- NHS England
- Novo Nordisk (comparator company)
- British Obesity and Metabolic Surgery Society (BOMSS)
- Diabetes UK

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NHSE, company and comparator company response overview

NHSE:

- Suggested resource estimates for weight management services to be implemented alongside tirzepatide
- Expressed concerns around generalisability of SURMOUNT-1

Company:

- Responded to NHSE's suggested resource estimates
- Provided various scenarios responding to committee's conclusions at ACM1

Comparator company:

- Tirzepatide use in primary care not consistent with precedent agreed in TA875 for semaglutide; premature to assume the model of care for obesity can move into primary care before NHSE pilots have been assessed
- SURMOUNT-1 is not generalisable due to higher starting BMI in SURMOUNT-1 than expected in practice
- Questions if long-term rates of discontinuation has been properly considered
- Consistent willingness-to-pay threshold should be used as uncertainties are the same as in TA875

Patient and professional organisation response overview

British Obesity and Metabolic Surgery Society (BOMSS), Diabetes UK

MDT for obesity management

- Should include: 1 physician/GP, specialist nurse, dietician plus psychological expertise as needed
- RCTs show intensive MDT support only adds marginal weight loss and health gains
- After year 1 of treatment, assessment every 6 months by single healthcare professional sufficient with access to others in MDT if needed
- Agree no arbitrary stopping rule should be applied for responders

Obesity management services

- NHSE provided proposals for obesity management services needed for delivery of tirzepatide, based on view that proposed service model does not currently exist and will only be in place for people taking tirzepatide, while they are on treatment
- Company responded to NHSE proposals, suggesting the composition of services which are currently available as well as services which should be in place both for people taking tirzepatide and receiving only diet and exercise. Company suggest that assuming people not receiving tirzepatide receive diet and exercise intervention is in line with scope.
- These proposals are tabulated later

NHSE proposed obesity management services with tirzepatide (1)

Obesity services will need to adapt to account for tirzepatide use

NHS England:

- Proposed future clinical service (if tirzepatide is approved) and associated costs are mapped to interventions used in SURMOUNT-1, including the number of visits for counselling, dose titration and ongoing monitoring
- Proposed service model does not currently exist – costs associated with the proposed service are new costs as a direct consequence of delivering tirzepatide and are not expected to be provided for people not taking tirzepatide
- SURMOUNT-1 excluded groups of people with psychiatric disorders, therefore questions the generalisability of the trial to people with obesity in the NSHE. Suggests people receiving tirzepatide will need:
    - initial psychological assessment and routine screening for psychological issues during treatment
    - 1 in 3 will need ongoing psychological support (based on clinical opinion and experience with bariatric services) – estimates 70% of this 1/3 could be managed by Talking Therapies, 30% would need more intensive psychological input; NHSE resource estimates reflect this for people receiving tirzepatide
- No specific recommendations for setting of care but expects majority to be community led in primary care
- Proposed clinical services should be available for as long as tirzepatide is being used
- Assessment for eligibility should be via GP; continued prescription management may be GP led, through SWMS initially followed by GP, or through digital provider of SWMS (notwithstanding safety considerations)
- Wraparound care outside of prescribing will be provided by locally procured services or a nationally procured digital service
- Existing SWMS established to assess suitability for bariatric surgery not expected to change

Tirzepatide management and associated costs (2)

NHSE have provided estimated costs associated with delivering the obesity management services expected to be used alongside tirzepatide

The following steps broadly demonstrate the anticipated patient pathway provided by NHSE:

1. Patient assessment, counselling (including dietary and physical activity education) and training
2. Dose titration, monitoring and reinforcement of diet and physical activity education
3. Maintenance treatment for responders – ongoing as long as treated with tirzepatide – reflects SURMOUNT-1 with additional MDT overview of progress and prescribing + psychological support

Company response to NHSE obesity management service proposal (1)

Company:

Weight loss with tirzepatide is anticipated to lead to reduced resource use through avoidance of comorbidities – the impact on the ICER of the variation in the level of diet and exercise support provided alongside tirzepatide (in various company and NHSE scenarios) is outweighed by the long-term avoidance of costly comorbidities

NHSE: Proposed service model does not currently exist in the NHS – costs are new as a direct consequence of delivery of tirzepatide

Company response:

- Company's proposed service model aligns with what is currently available and recommended for people with obesity in primary care as per CG189
- Healthcare professionals already manage patients with overweight or obesity by providing lifestyle support – resources are available to support discussions in primary care; services are provided with or without use of anti-obesity medications so costs should not be attributed to tirzepatide
- GP market research surveyed 381 primary care GPs in England and Wales:
  - Respondents provided with hypothetical situation of managing a patient with BMI ≥30 + at least 1 comorbidity
  - Of 90% aware of CG189, 73% followed recommendations in CG189 always or very frequently; 78% already offer specific diet and exercise advice; 67% have access to a dietician; 80% have access to a qualified healthcare professional (exercise referral); of 94% with some access to diet and exercise referral, 88% confirmed use of community-based diet and exercise services for target population
- The target population are already being seen within primary care for management of comorbidities so further resource investment not needed

Company response to NHSE obesity management service proposal (2)

NHSE: Patients with obesity have high burden of psychological issues

Company response:

- Not corroborated by evidence – evidence shows common mental health disorders lead to increased risk of adiposity rather than obesity being causal link
- CG189 recommends that routine care for people with obesity includes assessing for common mental health disorders – people requiring mental health support would be provided it regardless of tirzepatide, so costs of psychological support shouldn't be included in model

NHSE: Estimates of proportion needing psychological support based on experience with bariatric surgery

Company response:

- Patients eligible for bariatric surgery not a suitable population from which to generalise the psychological needs for the population eligible for tirzepatide

Company response to NHSE obesity management service proposal (3)

NHSE: SWMS delivery in primary care pilots could provide info to firm up assumptions around the model of care required to deliver tirzepatide:

Company response:

- SWMS were established to assess suitability and readiness of bariatric surgery- not representative of most people potentially eligible for tirzepatide seen in primary care
- NHSE resource estimates are akin to MDT support provided in secondary care (SWMS)
- Focus should be on the primary care services already being used rather than trying to replicate SWMS in primary care

MDT wrap around care may be via digital delivery:

Company response:

- Support use of digital weight management technologies for diet and exercise support – wouldn't require additional touchpoints so could be used cost effectively alongside tirzepatide

Company response to NHSE's proposed 3 stage approach to weight management services needed to deliver tirzepatide

1 Patient assessment, counselling and training:

- Regardless of intervention, assessment should follow CG189: recommends that primary care providers explore and identify any comorbidities and underlying factors (e.g. environmental, social, psychological)
- Once comorbidities and underlying factors are identified and managed, then either lifestyle intervention alone (behavioural, physical, dietary) or adjunct to treatment with a pharmacological intervention can be discussed
- Injection training can be delivered as 1:1 or group sessions and using videos, similarly to how tirzepatide, and other incretins, are currently initiated in primary care for T2DM

2 Dose titration, monitoring and reinforcement of diet and physical activity:

- Gastrointestinal side effects are generally mild to moderate – anticipate nurses would be able to counsel on these and provide support, limiting need for additional touchpoints; already experienced with initiating and titrating incretin (e.g. GLP1-RA) therapies in primary care
- Reinforcement of diet and exercise via additional touchpoints beyond those recommended in CG189 not needed

3 Maintenance treatment for responders (ongoing as long as treated with tirzepatide):

- After a year on medium-term maintenance (1 touchpoint every 3 months), stable patients could transition to an annual review – similar to other chronic diseases
- Efficacy of tirzepatide wouldn't be meaningfully impacted by fewer touchpoints during long-term maintenance
- Ongoing costs would be annual review (but conservative given other comorbidities would already be reviewed)

NHSE proposals for composition of obesity services for people receiving tirzepatide and company response (1)

	NHSE	Company included?	Company justification and amendments
Assessment, counselling and training (week 0)	HCA review (blood pressure, BMI)	No	Not treatment specific
	Initial consult (45 mins, GP or alternative)	Yes - for both tirzepatide and D+E	10 mins - more realistic
	Blood + thyroid test	No	Not in SmPC
	Patient training	No	Duplicated in treatment initiation
	Patient education + diet/exercise advice (dietician)	Yes – for both tirzepatide and D+E	Dietician or suitably qualified HCA (as in SURMOUNT-1)
	Clinical review + prescription validation	No	Prescribing practice does not require
	Treatment initiation (including patient training) (40 mins)	Yes – for tirzepatide only	20 mins - feedback for other injectables that 40 mins excessive

HCA: healthcare assistant

NHSE proposals for composition of obesity services for people receiving tirzepatide and company response (2)

	NHSE	Company included?	Company justification and amendments
Titration and weight management support (weeks 4 to 26)	Titration 4 weeks until week 20 (5x 20 mins, GP)	Yes – for tirzepatide only	(1x 30 mins, 4x 15 mins, nurse) Nurse appointments most needed to check if any adverse events or other issues with titrating up
	Dietary/exercise advice (2 x 30 mins, dietician)	Yes – for both tirzepatide and D+E	2 x 30 mins, dietician or suitably qualified HCA (as in SURMOUNT-1)
	Week 26 medicines review	No	Repeat of MDT patient review included under additional costs
Maintenance (weeks 26+)	Dietary/exercise advice every 12 weeks until end of year 2 (6x 30 mins, dietician	Yes - for both tirzepatide and D+E	6 x 30 mins, dietician or suitably qualified HCA (as in SURMOUNT-1)
	Dietary/exercise advice every 12 weeks for year 3 (4x 30 mins, dietician)	No	Expect target weight loss achieved end of year 2, and equipped to manage own diet and exercise

NHSE proposals for composition of obesity services for people receiving tirzepatide and company response (3)

	NHSE	Company included?	Company justification and amendments
Additional costs	MDT patient review (2x per year, 15 mins, from week 26; GP + nurse + clinical pharmacist + psychologist)	Yes – for tirzepatide only	1x per year, 10 mins, from week 52, GP only – MDT review likely to involve GP independently reviewing patient notes rather than in-person meeting Annual reviews consistent with other chronic diseases
	Psychological support (33% require; 30 mins psychologist/ psychiatrist, 5x per year)	No	People requiring psychological support would be provided it regardless of tirzepatide treatment (would apply equally to tirzepatide and diet and exercise or no intervention)
	Sharps disposal	Yes	No amendments

Summary of company proposals for obesity management services required specifically for introduction of tirzepatide (i.e. only included in tirzepatide arm of economic model):

- Treatment initiation, including patient training (20 mins, nurse led)
- Titration (1x 30 min, 4x 15 mins, nurse led)
- Annual MDT patient review (10 mins, GP led)

NHSE proposals for composition of obesity services for people receiving tirzepatide and company response (4)

EAG:

- EAG base case applies NHSE proposed weight management services for tirzepatide arm using GP led costs but uses data from SURMOUNT-1 to inform proportion with current or historic psychiatric problems ([redacted]%) who will require psychological support; costs applied to those remaining on treatment
- NHSE proposed service (without tirzepatide specific management) applied to diet and exercise arm for 2 years

Are the presented scenarios sufficient to give the committee confidence that the cost effectiveness of tirzepatide is not significantly impacted by the uncertainty around what weight management services will include?

Other key issues

- SURMOUNT-1 generalisability
- Company's model baseline comorbidities
- Cost of type 2 diabetes
- Long-term treatment effect
- Rate of prediabetes reversal loss
- Annualisation of multi-year risk of events
- New issue: long-term impact of prior obesity

Issues on non-responder rates and weight regain after stopping treatment presented in supplementary appendix

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SURMOUNT-1 generalisability

Key groups of people were not included in SURMOUNT-1

ACM1 conclusion:

- SURMOUNT-1 did not include people with T2DM or people with severe mental health disorders
- Uncertainty around the trial generalisability and which comorbidities should be defined as weight-related in the target population

NHS England:

- Trial excluded large groups of people (e.g. people with T2DM and severe mental health disorders) so generalisability should be treated with caution
- As trial excluded people with significant mental health disorders, expected that a proportion of the population given tirzepatide will require psychological support that wasn't needed in the trial

Comparator company:

- SURMOUNT-1 has higher baseline BMI than expected in primary care: mean BMI in SURMOUNT-1 was 38.0; 64% of people in England living with obesity have BMI 30 to 35

SURMOUNT-1 generalisability: company response (1)

BMI distribution and comorbidities in SURMOUNT-1 are generally aligned with general practice

Company:

- BMI distribution in primary care and community-led adult weight management services (data from April 2021-Dec 2022) is similar to distribution in SURMOUNT-1 target population:

BMI Class	SURMOUNT-1 target population (n=1,705)	Primary Care Adult Weight Management Services (n=85,550)
Overweight (BMI 25 to 29.9)	0 (0)	11,385 (13%)
Class I (BMI 30 to 34.9)	605 (35.5%)	29,390 (34%)
Class II (BMI 35 to 39.9)	501 (29.4%)	21,600 (25%)
Class III (BMI ≥40)	599 (35.1%)	21,905 (26%)

- Distribution of comorbidities (including historical or pre-existing psychiatric disorders) in people with BMI 30-34.9 and ≥35 in SURMOUNT-1 are broadly aligned with each other and the total target population
- Data presented indicates there is a greater proportion of people with prediabetes, hypertension and dyslipidaemia in SURMOUNT-1 than in the general population with BMI ≥30 (see appendix slide 58)
- Comorbidities allowing for eligibility in SURMOUNT-1 included:
  - hypertension, dyslipidaemia, obstructive sleep apnoea, atherosclerotic cardiovascular disease, prediabetes, hip or knee osteoarthritis, asthma, liver disease, cerebrovascular disease, disorder of the reproductive system, kidney disease or gout

SURMOUNT-1 generalisability: company response (2)

Company:

Only the following conditions were exclusion criteria for SURMOUNT-1:

- type 1 diabetes or type 2 diabetes
- a history of chronic or acute pancreatitis
- family history or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- a history of *significant active or unstable* major depressive disorder or other severe psychiatric disorders within the last 2 years
- any lifetime history of a suicide attempt

- Not all people with psychological issues were excluded (if considered stable): 21.6% of SURMOUNT-1 participants report a pre-existing psychiatric disorder (including but not limited to depression, anxiety, insomnia and major depressive disorder) – no additional support was provided for these participants
- PHQ-9 score of ≥15 (moderate to severe depression) was not an exclusion criteria in itself – it resulted in participants being referred to a mental health professional (as would be expected in primary care); 4 participants had PHQ-9 score ≥15 , 2 were randomised into SURMOUNT-1

SURMOUNT-1 generalisability: EAG critique of BMI distribution

EAG:

- Primary care adult weight management services BMI distribution in people with obesity presented by the company is to the left of the SURMOUNT-1 target population and general population BMI distribution is further to the left (66% of people with BMI ≥30 in general population have BMI 30 to 34.9)
- Cost effectiveness is less favourable for people with lower BMI
- EAG concerned that the assumed distribution may not be realistic for the lower end of the BMI scale, giving too little weight to these people and their relatively poor cost effectiveness; company model samples very few patients at the bottom end of the BMI distribution
- Company has not provided detailed gradation of BMI distribution which is only reliable means of assessing extent of bias
- EAG uses company's assumed BMI distribution in its base case (due to lack of detailed gradation) and applies the general population distribution in a scenario analysis

- Is the proportion of people with, and severity of, mental health disorders in SURMOUNT-1 generalisable to the population with a BMI ≥30 + ≥1 weight-related comorbidity seen in primary care?
  - Will those who receive tirzepatide in primary care most likely match the BMI distribution of those currently receiving primary care adult weight management services or the general primary care population?
- How would inclusion of lower proportions of people with prediabetes, hypertension and dyslipidaemia, including people with T2DM and including more people with BMI 30 to 34.9 be expected to influence clinical and cost effectiveness estimates?

Company's model overview

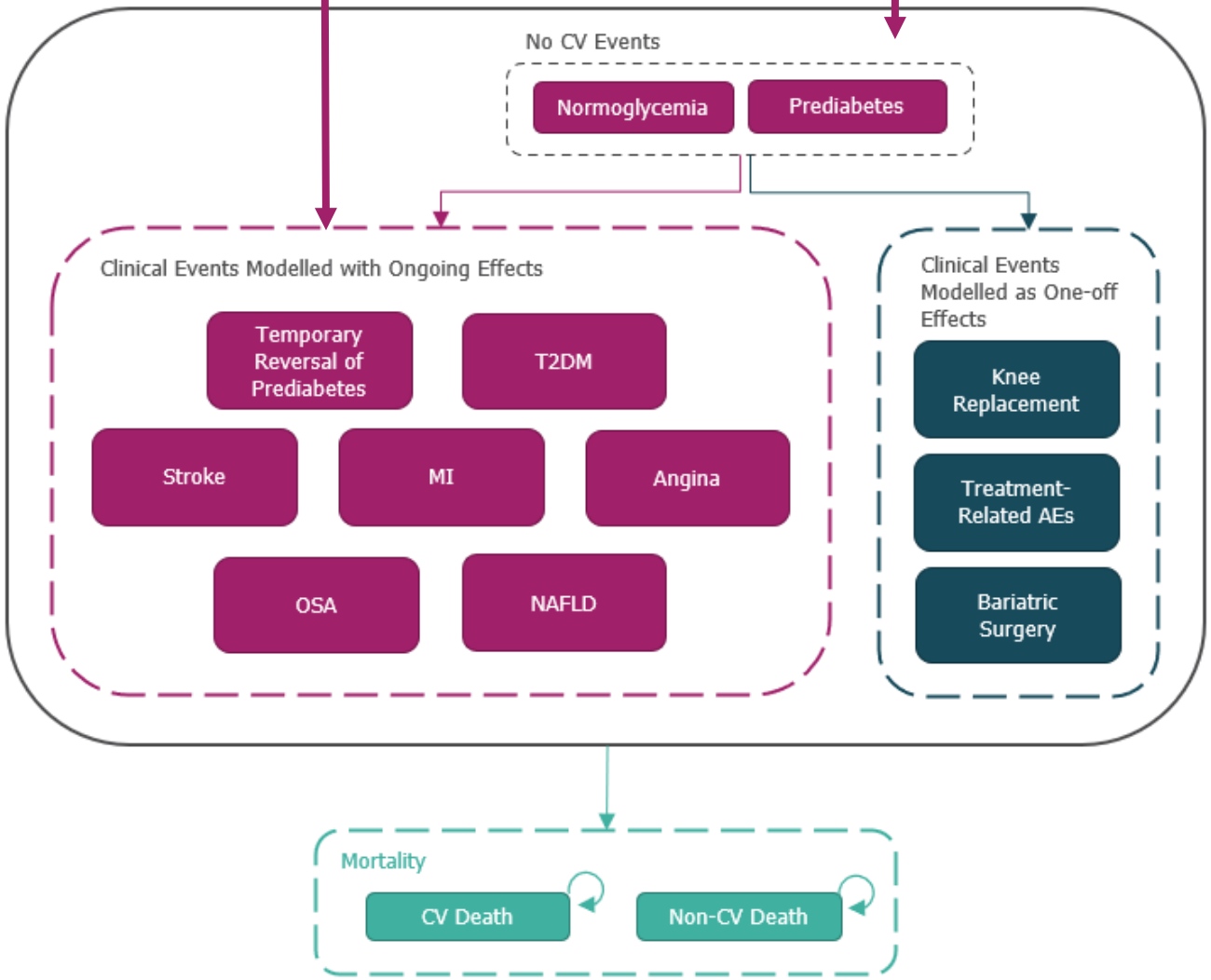
- Population: BMI ≥30 + ≥1 weight-related comorbidity
- Uses risk equations to estimate events

ACM1 conclusion:

- Assumption that no-one enters model without any future modelled comorbidities or complications (i.e. sleep apnoea) does not reflect population in practice

Baseline population:

- have none of the clinical events which are included in the model
- proportion with prediabetes from SURMOUNT-1



Company's model overview

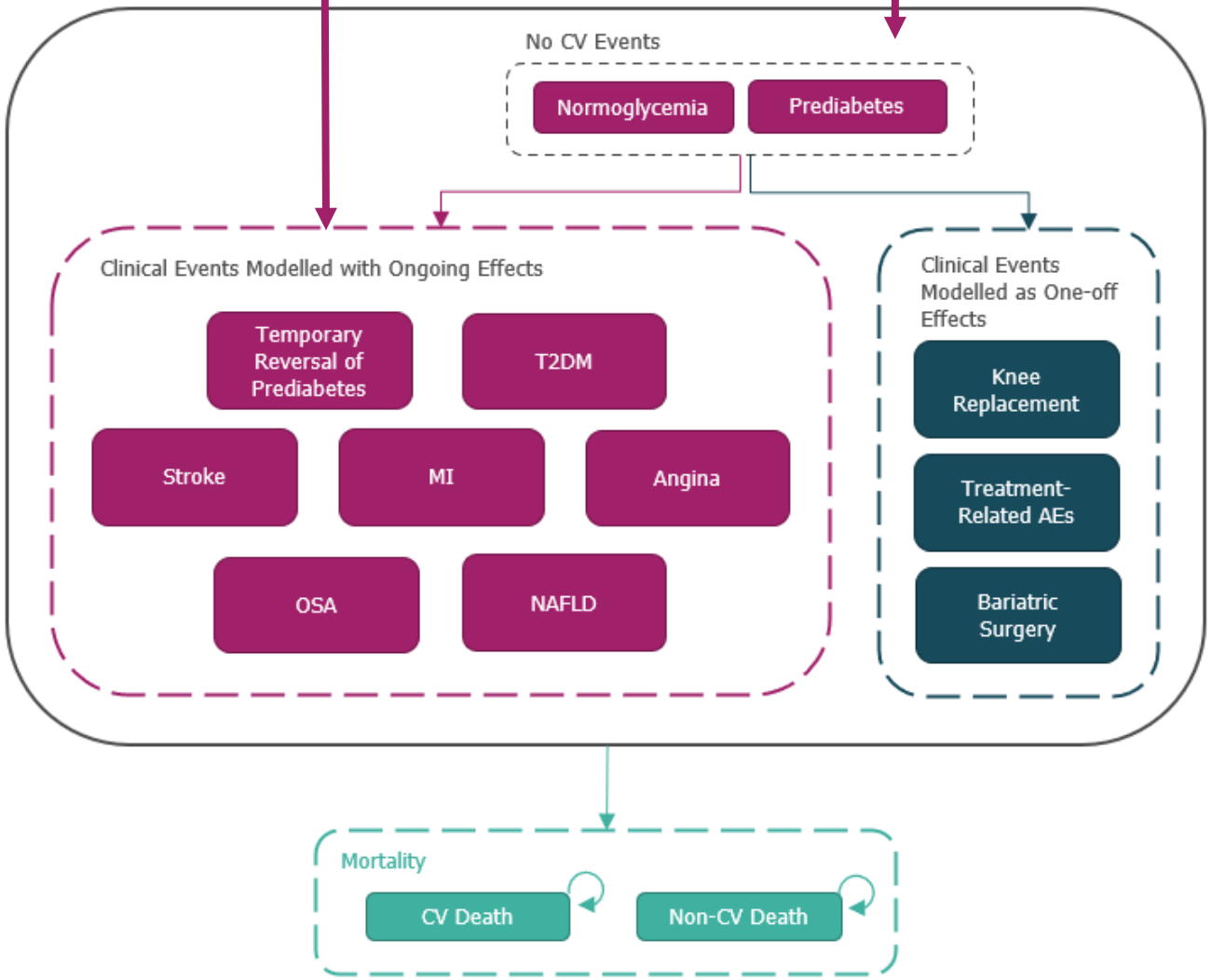
- Population: BMI ≥30 + ≥1 weight-related comorbidity
- Uses risk equations to estimate events

Company:

- Provided scenario with proportion of patients entering the model assumed to have prior MI (assumed all prior CVD events were MI), OSA and NAFLD, from baseline SURMOUNT-1 target population
- Model structure does not allow inclusion of proportion with T2DM at baseline without undue bias:
  - once T2DM develops, HbA1c and diabetes associated costs are assumed to stay constant
  - prediabetes reversal is only glycaemic benefit of treatment modelled
  - if people were modelled to enter with T2DM, the model would ascribe no glycaemic benefit to use of tirzepatide to treat obesity
- SURMOUNT-2 (trial in obesity with T2DM) and SURPASS (trial in T2DM and overweight or obesity) show benefit on HbA1c in people with T2DM and obesity (see appendix slide 59); model already biased against tirzepatide as people who develop T2DM don't benefit from glycaemic benefits of tirzepatide

Baseline population:

- have none of the clinical events which are included in the model
- proportion with prediabetes from SURMOUNT-1



Company's model overview

- Population: BMI ≥30 + ≥1 weight-related comorbidity
- Uses risk equations to estimate events

EAG:

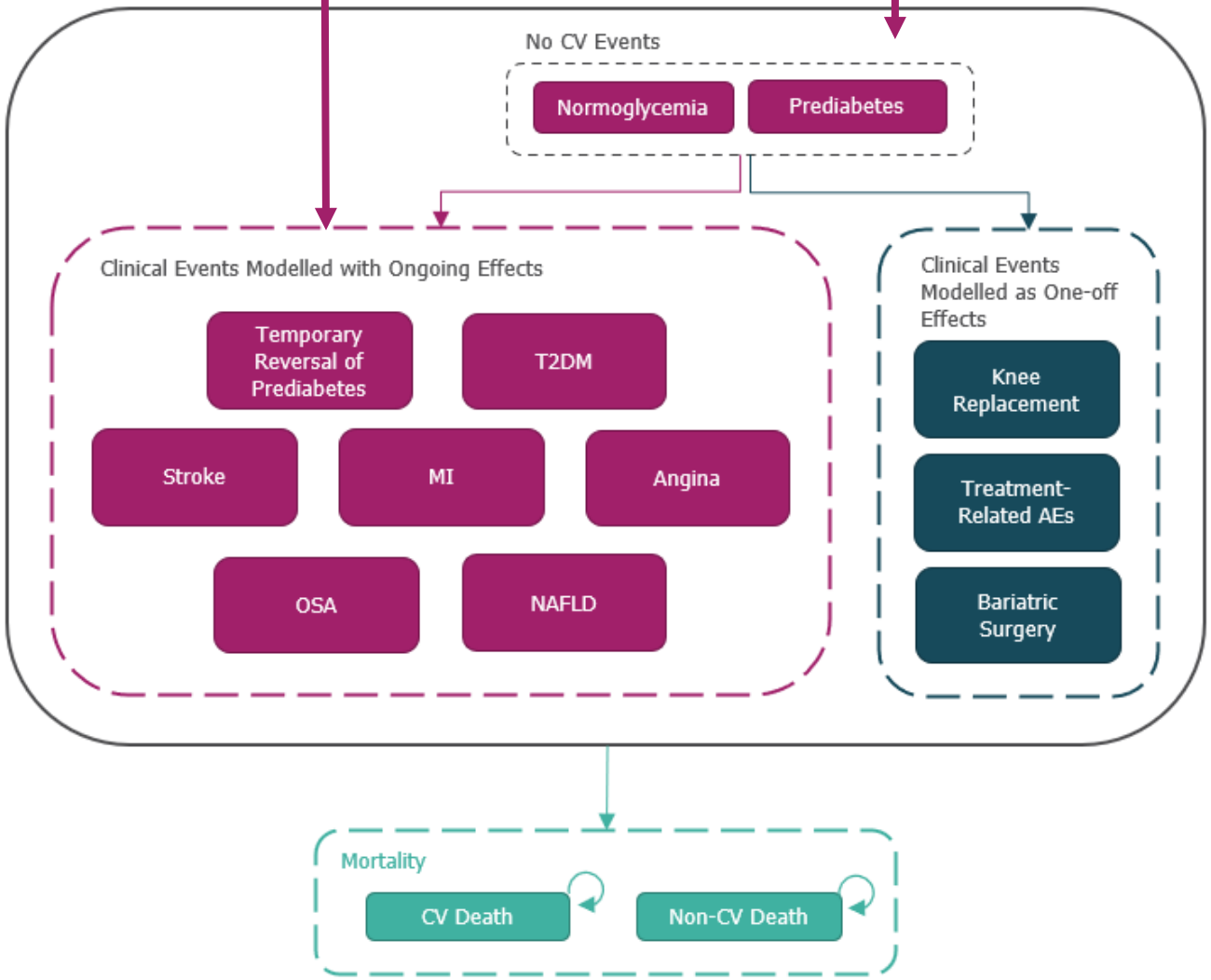
- Estimates of cost effectiveness of tirzepatide in people with T2DM can only be made within a T2DM model
- Current cost effectiveness modelling for tirzepatide relates to those who do not have T2DM at baseline and the model results are driven by the cost offsets and utility gains from avoiding T2DM
- Given lack of evidence for this population in the current model and NICE TA924 recommendation for tirzepatide for T2DM, questions if people with T2DM need to be included in population in this evaluation

Is the population entering the model acceptable for decision making?

- Is it appropriate to consider optimised recommendations based on the characteristics of people entering the model (i.e. without T2DM)?

Baseline population:

- have none of the clinical events which are included in the model
- proportion with prediabetes from SURMOUNT-1



Cost of type 2 diabetes (1)

Company present alternative source for estimating type 2 diabetes costs in model

ACM1 conclusion:

- EAG's approach estimating costs using UKPDS data preferred; company's approach based on hospital admissions unlikely to be appropriate

Company:

- EAG's ACM1 approach (using UKPDS study) is overly conservative
- EAG's costs for T2DM do not capture drug treatment costs:
  - but multiple pharmacological treatments may be needed over time with high acquisition costs and not including these underestimates costs of T2DM
- EAG approach excludes UKPDS inpatient costs, only capturing non-hospital costs because complications causing inpatient costs are likely to be captured elsewhere in the model:
  - but by excluding all inpatient costs, any inpatient admissions which are not associated with the modelled complications will not be accounted for
- UKPDS study based on low-risk newly diagnosed T2DM:
  - but this does not account for T2DM patients with more advanced disease who require more intensive treatment
- Presents 2 scenarios to address uncertainty, with alternative costs for a patient with T2DM:
  - Scenario 1: uses costs sourced from Capehorn et al. 2021 with annual cost of £940.86 (for microvascular complications) + £551.89 (for insulin and oral treatments); accepted in TA875
  - Scenario 2: EAG's UKPDS cost (£674) + Capehorn et al. drug costs (£551.89); company consider overly conservative as UKPDS costs do not account for high-risk T2DM populations

Cost of type 2 diabetes (2)

EAG:

- Company's choice of T2DM cost (NHS reference costs) is not appropriate – it applies the high costs associated with a small proportion of T2DM patients (74,041 hospital attendees) to all people with T2DM

<u>Diabetes drugs costs</u>

- Company uses Capehorn et al. to source costs in scenario - average duration of T2DM in population in Capehorn et al. was 7 years so EAG suggests this overestimates drug treatment costs:
  - Capehorn population does not reflect most people with T2DM in the model, as people with T2DM in the model will be newly diagnosed (no one enters model with T2DM)
  - Initial drug treatment for recently diagnosed T2DM (required by most people in the model) is cheaper than the drug treatment for people who have had T2DM for 7 years (population in Capehorn)
- EAG base case retains ACM1 preference for UKPDS costs to estimate T2DM costs but also adds estimates for drug costs based on duration of treatment data from UKPDS and drug tariff costs of NICE recommended diabetes medicines

<u>Microvascular complications</u>

- Company used Capehorn et al. to source costs for microvascular complication costs – which was an industry sponsored study with interest in estimating higher costs
- Capehorn et al. does not appear to report additional net costs of developing a complication with T2DM over the costs for someone with obesity, therefore likely overestimating the costs associated with T2DM
- Provides a scenario including Capehorn T2DM costs for microvascular events, but adjusting these costs for the 7 years mean duration of diabetes in Capehorn et al.

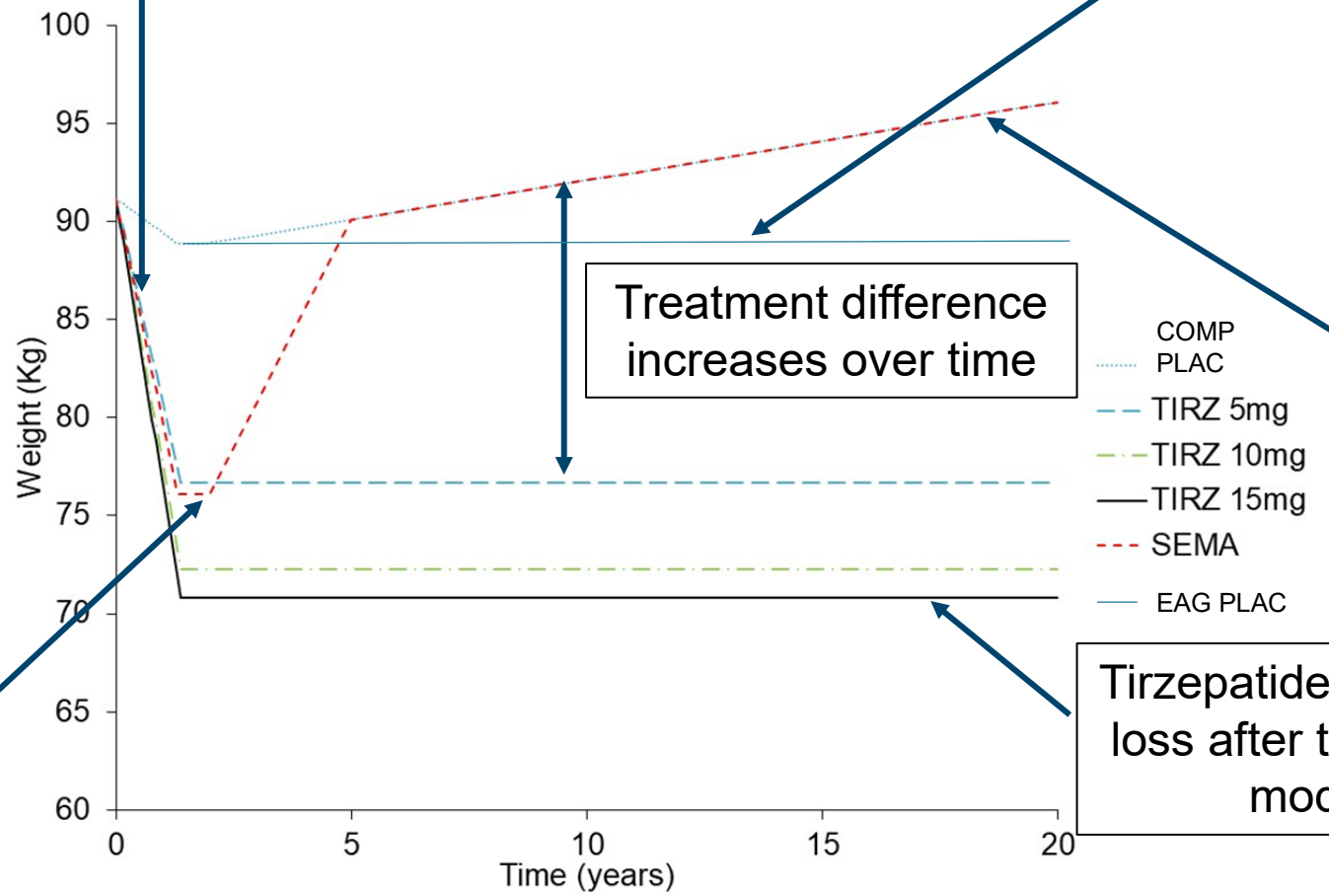
- Are the costs of T2DM appropriately captured by either the EAG's or company's updated scenarios?

Recap: Model includes net increase in tirzepatide treatment effect over time

20-year treatment effect modelled in company base case and EAG base case:

Semaglutide and tirzepatide weight loss during trial treatment period

EAG: prefer to remove the net increase in weight between arms over time horizon by removing the annual BMI increase for diet and exercise arm



Treatment difference increases over time

Diet and exercise arm weight increases every year after trial period

Semaglutide weight loss maintained while on treatment and regained over 3 years after stopping and increases in line with diet and exercise arm

Tirzepatide (no stopping rule) weight loss after trial period maintained for modelled time horizon

Long-term treatment effect

ACM1 conclusion:
- Likely that natural history of weight increasing with age will occur to some extent in tirzepatide arm and comparator arms; so unlikely that treatment effect difference would continue to increase indefinitely

Company:
- No evidence that there will be weight regain while on treatment and no biological rationale for why it would
- But, provided scenarios:
  - applying natural weight gain for people on tirzepatide at end of trial (72 weeks), start of year 3 and year 5
  - assuming annual weight increases for people on tirzepatide treatment by 5 or 10% of the difference in weight loss between diet and exercise and tirzepatide arms at 72 weeks – results in tirzepatide-treated patients reaching the same weight as diet and exercise arm after 20-30 years

Comparator company:
- If there was loss of treatment effect over time while on tirzepatide, it may influence the rates of treatment discontinuation – length of time on treatment is uncertain

EAG:
- Company scenarios explore relatively small changes in treatment effect
- Provides further scenarios exploring loss of 20% of effect at 5 and 10 years on company base case – this would likely have a proportionally greater impact on EAG base case

- Is there sufficient evidence to demonstrate the impact on the ICER if treatment effect waning while on tirzepatide (weight regain in line with natural history or returning to same weight as people on diet and exercise only) is assumed?

Rate of prediabetes reversal loss

Company presents scenario to demonstrate impact of longer prediabetes reversal in people receiving diet and exercise

ACM1 conclusion:

- It is uncertain whether the rate of loss of prediabetes reversal would differ between diet and exercise support arm and active treatment arms after stopping

Company:

- It is not possible to 'discontinue' diet and exercise as ongoing diet and exercise support should always be in place for people managing obesity – therefore, not possible to exactly replicate the approach to loss of prediabetes reversal in the diet and exercise arm that is used in the active treatment arms
- Company base case: prediabetes reversal loss for diet and exercise support arm at 2 years
- Presents scenario where the time point for loss of reversal of prediabetes in diet and exercise arm aligns to timepoint at which diet and exercise arm average weight returns to baseline in the model (8 years) – this aligns more with approach in tirzepatide arm where prediabetes reversal occurs at the same point that weight is regained in line with if no treatment had been taken (at end of 3-year period after stopping treatment)
- Scenario likely to overstate duration of prediabetes reversal in diet and exercise arm

- Does the company's scenario sufficiently address concerns around timing of prediabetes reversal loss?

Annualisation of multi-year risk of events

ACM1 conclusion:

- It is unclear how much uncertainty is introduced into the model due to the compounding of risk of events over multiple years through annualisation of multi-year risk equations

Company:

- Conducted analysis to explore level of uncertainty introduced due to compounding of risk events occurring over multiple years – shows that there isn't uncertainty introduced by this issue
- Risk equations impacted by this issue cover T2DM risk, initial CV event risk for non-T2DM patients (both 10-year predictions) and obstructive sleep apnoea risk (5-year prediction) – T2DM used as illustrative example.
- Company base case: includes risk of events annualised assuming a constant rate and updated yearly
- Scenario analysis 1: showed an 87% overestimation of per-cycle probability of developing T2DM would have been needed for tirzepatide ICER to reach £20,000 per QALY
- Scenario analysis 2: reducing number of T2DM events occurring by 25% and 50% - moderate impact on ICER, but company base case remains cost effective

EAG:

- Presents illustrative ad hoc adjustments to the 10-year risk functions to adjust for the overestimation of risk of events for average person in model - exploratory analyses have limited impact on EAGs ICER but issue increases uncertainty and is not wholly quantifiable

- Do the company's and EAGs scenario analyses alleviate the uncertainty around the compounding of risk events?

Long-term impact of prior obesity

EAG:

- Company model assumes that health risks for someone with a high BMI which lowers (for example) to a BMI of 32 on tirzepatide are the same for someone who has always had a BMI of 32
- Questions if BMI related damage may be long lasting in some instances
  - EAG expert opinion that if someone has been obese and insulin resistant for decades, there will be an impact on CVD health, for example
  - Similarly, it could be expected that knee damage acquired at a high BMI would be sustained after weight loss
- Evidence from Haase et al. 2021 retrospective study of UK databases which estimated the effect of weight loss on the risks of various weight related complications suggests it may be unreasonable to assume that there is no long-term impact of prior obesity, especially for the subgroup with BMI 30 to 35
  - EAG acknowledge limitations to Haase et al. including arbitrary data cuts and subgroup definitions and selective reporting
- EAG suggest the model may overestimate the effect of weight loss on obesity related complications and mortality
- Explores impact on ICER through ad hoc adjustments to direct effects of obesity related complications, based on data from Haase et al.

- Is it reasonable to assume that prior obesity is not associated with long term effects?

Summary of company and EAG base case assumption differences (1)

Assumption	Company base case	EAG base case
Obesity management service costs	Cost associated with company proposals for appropriate obesity management services (see slides 18 to 20)	Costs associated with NHSE proposals for appropriate obesity management services (see slides 18 to 20)
BMI long-term net effect difference	Long-term constant BMI on tirzepatide + increasing BMI on diet and exercise	Applies constant annual natural increase in BMI in both arms
T2DM costs	Data from average costs of ~74,000 NHS admissions	Data from UK Prospective Diabetes study (representative of average of ~4 million with T2DM), plus estimated medication costs
BMI mortality multiplier	Mortality multipliers for BMI + history of angina, MI and stroke	Only mortality modifiers for BMI – others covered by BMI modifier
Adverse event discontinuation	Applies ongoing annual discontinuation due to adverse events calculated from 72-week data	Mainly applying adverse event discontinuation in 1st year followed by annual 1% discontinuation rate
Stopping rules	No stopping rule other than stopping for non-responders at 6 months	No stopping rule other than stopping for non-responders at 6 months
Weight regain after stopping treatment	Weight regained over 3 years after stopping treatment	Weight regained over 2 years after stopping tirzepatide
Non-responder rates	Applies EAG inferred 48-week 5% weight loss responder rates	Applies 72-week 5% weight loss responder rates as only trial-based data presented from SURMOUNT-1

Summary of company and EAG base case assumption differences (2)

Assumption	Company base case	EAG base case
Baseline comorbidities	Does not include comorbidities which are later modelled at baseline	Includes baseline prevalence of MI, OSA and NAFLD
NAFLD hazard ratio and incidence rate	Uses NAFLD incidence rate and risk of developing NAFLD HR from different literature sources with different HRs	Company takes HR from source with higher HR than HR reported in source from which general population incidence rate is estimated – so adjusts NAFLD incidence rate so that it aligns with the hazard ratio from the same source
OSA 5-year risk	Assumes risk of OSA for people with BMI 30 to 35 equal to general population	OSA prevalence for BMI 30 to 35 increased to reflect risk of OSA in this group (from UK CPRD OSA prevalence of 2.85% in this group)
QoL functions	Soltøft et al. QoL function to derive utilities for BMI >35 and amended version to estimate QoL function for BMI ≤35	Aligns QoL functions to avoid discontinuity, whereby better QoL suggested when BMI increases beyond 39 (men) and 46.5 (women)
Disutilities	Disutilities applied for obesity related complications	Removes disutilities for obesity related complications as covered by Soltøft QoL function

Plus, EAG minor changes (minor cumulative impact on ICER)

Implementation

There are potential issues around implementation if tirzepatide is recommended

- Approximately 6 million people will be eligible if recommended
- There will be increased pressure on GPs and implementation may be compromised by additional prescribing requirements
- Current lack of necessary dieticians and counsellors needed in primary care
- Tirzepatide for type 2 diabetes was not available within the 3-month implementation date, so concerns around availability
- National patient safety alert for diabetes which restricts stock of GLP-1 agonists for management of diabetes; but there is only 1 formulation of tirzepatide, making restricting access for diabetes difficult

- NICE's methods allow for a funding variation to be requested by NHSE&I, which must be approved by NICE's guidance executive
- If a funding variation is accepted, certain groups may be prioritised for earlier implementation – NICE's guidance executive has asked for committee input into which groups may potentially be prioritised

Implementation

Stakeholder views on unmet need and groups with the potentially greatest benefits with tirzepatide:

- People who are not eligible for surgery may particularly benefit
- Would not necessarily be routinely used in people with BMI over 45 as this population is best served by surgery
- May be particularly beneficial for people with metabolic associated steatotic liver disease – evidence suggests weight loss can reduce liver fat content in people with T2DM which may be associated with improvement in steatosis and fibrosis
- Some people with type 2 diabetes and obesity treated with tirzepatide will achieve diabetes remission

Cost effectiveness differs by starting BMI:

- Subgroup analysis shows greater QALY gain for people with higher baseline BMI and lower QALY gain for people with a lower baseline BMI

- Which groups of people are likely to have the greatest unmet need and clinical benefit from tirzepatide?
- Can the committee advise which groups of people could be prioritised for treatment with tirzepatide, should a funding variation be accepted?

Cost-effectiveness results

vs diet and exercise

Company scenarios: obesity weight management services

All scenarios for target population BMI ≥30 with ≥1 comorbidity, tirzepatide 15mg vs diet and exercise support and include other company preferred assumptions

Scenario	Incremental costs	ICER (£/QALY)
NHSE proposed resource use while on tirzepatide; no resource use for diet and exercise arm	[redacted]	16,910
NHSE proposed resource use while on tirzepatide and for 2 years for diet and exercise arm followed by dietician appointments and psychological support for 1/3 patients for 2 years	[redacted]	16,274
NHSE proposed resource use while on tirzepatide followed by 1 GP appointment per year for 2 years; 1 GP appointment per year for 2 years for diet and exercise arm	[redacted]	16,812
Company proposed resource use for tirzepatide for duration of time horizon; company proposed resource use for diet and exercise for 2 years, followed by no resource use	[redacted]	12,863
Company preferred resource use for tirzepatide (replacing nurse visits at weeks 8, 12, 16 and 20 with 1 appointment at week 24) for duration of time horizon; company proposed resource use for diet and exercise for duration of time horizon	[redacted]	12,783

See slides 18 to 20 for description of proposed services

Company scenarios: obesity weight management services

All scenarios for target population BMI ≥30 with ≥1 comorbidity, tirzepatide 15mg vs diet and exercise support and include other company preferred assumptions

Scenario	Incremental costs	ICER (£/QALY)
SWMS NHSE consultant led costs for tirzepatide for 2 years then company proposed resource use for duration of time horizon; SWMS costs for diet and exercise for 2 years then no resource use	[redacted]	12,446
SWMS NHSE consultant led costs for tirzepatide for 2 years then NHSEs propose resource use for 2 years; SWMS costs for diet and exercise for 2 years, then 1 GP appointment per year until 2 years	[redacted]	14,649
NHSE proposed resource use applied to tirzepatide and diet and exercise arms for duration of time horizon	[redacted]	16,073

See slides 18 to 20 for description of proposed services

Scenarios on company base case vs diet and exercise (1)

All scenarios for target population BMI ≥30 with ≥1 comorbidity, tirzepatide 15mg vs diet and exercise support and include other company preferred assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	0.685	12,218
Baseline characteristics for CVD, OSA and NAFLD reflect SURMOUNT-1	[redacted]	0.771	12,084
Cost of T2DM:			
Capehorn et al. microvascular complications and drug treatment costs	[redacted]	0.685	13,304
EAG UKPDS costs + Capehorn et al. drug treatment costs	[redacted]	0.685	14,346
Weight regain while on tirzepatide:			
Natural history weight gain after end of trial follow-up	[redacted]	0.604	14,268
Natural history weight gain 2 years after end of trial follow-up	[redacted]	0.622	13,724
Natural history weight gain 3 years after end of trial follow-up	[redacted]	0.634	13,406
5% loss of effect after 5 years on treatment	[redacted]	0.581	14,823
10% loss of effect after 10 years on treatment	[redacted]	0.579	14,786
20% loss of effect after 10 years on treatment (conducted by EAG)			20,151

Scenarios on company base case vs diet and exercise(2)

All scenarios for target population BMI ≥30 with ≥1 comorbidity, tirzepatide 15mg vs diet and exercise support and include other company preferred assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	0.685	12,218
Weight regain after stopping treatment:			
Treatment effect lost after 2 years	[redacted]	0.670	12,909
Treatment effect lost after 1 year	[redacted]	0.651	13,877
Prediabetes reversal: aligned with average return to baseline weight (8 years)	[redacted]	0.682	14,218
Annualisation of multi-year risks:			
Reduction of T2DM incidence in all arms by 25%	[redacted]	0.674	13,566
Reduction of T2DM incidence in all arms by 50%	[redacted]	0.655	15,411
Long-term discontinuation of tirzepatide:			
Stopping rule at 5 years	[redacted]	0.288	8,196
Stopping rule at 10 years	[redacted]	0.431	10,160
Non-responder rate at 6 months: 5% weight loss data from 48-weeks in SURMOUNT-1	[redacted]	0.774	12,921
Discontinuations due to AEs: 5% decrease in AE discontinuation rate	[redacted]	0.697	12,432

Company subgroup analyses

Uses relevant baseline characteristics but target population efficacy data due to small sample size

Company:

- Formal post hoc subgroup analysis would result in subgroup sizes too small (24% and 43% of trial population for each subgroup). Has presented subgroup analyses by applying baseline characteristics from requested subgroups, thus adjusting baseline risk between the subgroups, but applies efficacy inputs from the target population

EAG:

- Smaller population subsets were presented by the company in its original submission

Tirzepatide 15mg vs diet and exercise support (includes company preferred assumptions)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case (target population)	[redacted]	0.685	12,218
BMI ≥35 with ≥1 comorbidity (baseline characteristics)	[redacted]	0.739	11,184
BMI 30 to 34.9 with ≥1 comorbidity (baseline characteristics)	[redacted]	0.539	17,697

EAG base case analyses by subgroup

Tirzepatide 15mg vs diet and exercise support (includes EAG preferred assumptions)

No.	Population with all EAG preferred assumptions	ICER (£/QALY)
1	Target population	24,735
2	BMI 30 to 34.9 with ≥1 comorbidity (baseline characteristics)	30,533
3	BMI ≥35 with ≥1 comorbidity (baseline characteristics)	21,450
4	BMI 30 to 34.9 with ≥1 comorbidity or BMI ≥35 with no prediabetes and high CVD risk	27,682
5	BMI ≥35, prediabetes and high CVD risk	19,719

Biggest drivers of ICER presented in scenario analyses on EAG base case	Subgroups where ICER driver
Cost of T2DM	All subgroups
Aligning BMI distribution in model to general population normal distribution	1, 2 and 4
Adjusting for long-term effects of weight on complications	2 (and likely 1 although lack of data)
Other drivers of difference in ICER between company and EAG base case	
Natural increase in weight gain while on treatment	
Including NHSE proposals for weight management services	

Scenarios on EAG base case: target population

Tirzepatide 15mg vs diet and exercise support (includes EAG preferred assumptions)

Scenario	ICER (£/QALY)
EAG base case	24,735
General population BMI distribution truncated by modelled BMI bounds	29,176
Annualisation of multi-year risks:	
Adjusting risk of events for possible overestimation due to annualisation for a representative 40-year-old	25,319
Adjusting risk of events for possible overestimation due to annualisation for a representative 50-year-old	24,959
Weight service costs:	
Consultant led rather than GP led for tirzepatide	24,434
GP led weight management services for tirzepatide and diet and exercise	24,257
Consultant led weight management services for tirzepatide and diet and exercise	23,987
T2DM costs:	
Capehorn et al. drug costs	24,046
50% of Capehorn et al. microvascular complication costs	23,543
100% of Capehorn et al. microvascular complication costs	22,351
Company drug costs and 100% of company microvascular complication costs	21,662

Scenarios on EAG base case: BMI 30 to 34.9 with ≥1 comorbidity

Tirzepatide 15mg vs diet and exercise support (includes EAG preferred assumptions); population includes baseline characteristics for BMI 30 to 34.9 with ≥1 comorbidity

Scenario	ICER (£/QALY)
EAG base case	30,533
General population BMI distribution truncated by modelled BMI bounds	32,228
Long-term impact of obesity on complications:	
Assuming past obesity has long term effects based on Haase et al. retaining high partial effects	33,057
Assuming past obesity has long term effects based on Haase et al. retaining low partial effects	35,340
Assuming past obesity has long term effects based on Haase et al. retaining low partial effects plus reductions in effects on mortality	40,591
T2DM costs:	
Company drug costs	29,771
50% of company microvascular complication costs	29,215
100% of company microvascular complication costs	27,897
Company drug costs and 100% of company microvascular complication costs	27,134
EAG subgroup T2DM specific drug costs	31,001

Summary of questions for committee (1)

Weight management service costs:

- Are the scenarios presented for different weight management services sufficient to give the committee confidence that the cost effectiveness of tirzepatide is not significantly impacted by the uncertainty around what weight management services will include?
- Which weight management services are appropriate to include for people in the diet and exercise arm and for how long?

SURMOUNT-1 generalisability:

- Is the proportion of people with, and severity of, mental health disorders in SURMOUNT-1 generalisable to the population with a BMI ≥30 + ≥1 weight-related comorbidity seen in primary care?
- Will those who receive tirzepatide in primary care most likely match the BMI distribution of those currently receiving primary care adult weight management services or the general primary care population?
- How would inclusion of lower proportions of people with prediabetes, hypertension and dyslipidaemia, including people with T2DM and including more people with BMI 30 to 34.9 be expected to influence clinical and cost effectiveness estimates?

Baseline model characteristics:

- Is the population entering the model acceptable for decision making?
- Is it appropriate to consider optimised recommendations based on the characteristics of people entering the model (i.e. without T2DM)?

Costs of T2DM:

- Are the costs of T2DM appropriately captured by either the EAG's or company's updated scenarios?

50

Summary of questions for committee (2)

Treatment effect waning:

- Is there sufficient evidence to demonstrate the impact on the ICER if treatment effect waning while on tirzepatide (weight regain in line with natural history or returning to same weight as people on diet and exercise only) is assumed?

Weight regain after stopping treatment:

- Is the level of uncertainty around time to weight regain acceptable?

Rate of prediabetes reversal:

- Does the company's scenario sufficiently address concerns around timing of prediabetes reversal loss?

Annualisation of multi-year risk of events:

- Do the company's and EAG's scenario analyses alleviate the uncertainty around the compounding of risk events?

Long-term impact of prior obesity

- Is it reasonable to assume that prior obesity is not associated with long term effects?

Implementation:

- Can the committee advise which groups of people could be prioritised for treatment with tirzepatide, should a funding variation be accepted?

NICE National Institute for Health and Care Excellence

Thank you.

NICE National Institute for Health and Care Excellence

Supplementary appendix

Abbreviations and units

ASCVD: atherosclerotic cardiovascular disease

BMI: body mass index

CfB: change from baseline

CV(D): cardiovascular (disease)

GI: gastrointestinal

HDL: high-density lipoprotein

HRQoL: health-related quality of life

ICER: incremental cost effectiveness ratio

MDT: multi-disciplinary team

MI: myocardial infarction

NAFLD: non-alcoholic fatty liver disease

NMA: network meta-analysis

OSA: obstructive sleep apnoea

QoL: quality of life

QW: once weekly

RCT: randomised controlled trial

SBP: systolic blood pressure

SD: standard deviation

SE: standard error

SmPC: summary of product characteristics

SWMS: specialist weight management service

T2DM: type 2 diabetes mellitus

TEAE: treatment emergent adverse events

UKPDS: UK Prospective Diabetes Study

All BMI measures are in mg/kg^2

Patient and professional organisation response

Digital weight management services

- Digital weight management services more accessible for people who experience stigma
- Can play important role offering excellent support and saving time for healthcare professionals
- Patient choice to receive either face to face or digital services important to increase adherence
- Limited users of the internet more likely to be from ethnic minority backgrounds and people with learning difficulties more likely to have severe obesity – these groups may be disadvantaged if MDT can only be delivered digitally so important to keep multiple options

Tirzepatide (Mounjaro, Eli Lilly)

CONFIDENTIAL

Technology details

Marketing authorisation (November 2023)	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 presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidaemia, OSA, CVD, prediabetes, or T2DM)
Related indication (NICE TA924)	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
Administration	Subcutaneous injection once weekly, using a pre-filled pen device Initiation: 2.5 mg once weekly; maintenance (after 4 weeks): 5mg once weekly; if needed, dose can be increased in 2.5 mg increments every 4 weeks up to 15 mg
Price	List price for 4-week supply: • 5 mg: [redacted] • 10 mg: [redacted] • 15 mg: [redacted]

Committee discussion at ACM1 – issues not for discussion

Issue	Committee discussion ACM1
Target population	Company's target population (BMI ≥30 + 1 weight-related comorbidity) is appropriate
Comparator	Diet and exercise if delivered in primary care; semaglutide if delivered in specialist weight management services; evaluation is setting agnostic but different comparators are relevant for different settings; orlistat not a comparator
Dose	Likely that highest tolerated dose used (15 mg for most people)
Clinical effectiveness	SURMOUNT-1: tirzepatide is more effective than placebo for up to 72-weeks NMA: tirzepatide is more effective than semaglutide for weight loss for up to 52-weeks
Stopping rule	No stopping rule for tirzepatide and 2-year stopping rule for semaglutide appropriate
Proportion of non-responders	Appropriate to use closest available data from SURMOUNT-1 (48 weeks) to estimate proportion stopping tirzepatide due to lack of response after 46 weeks
Weight regain after treatment	It is uncertain how quickly weight lost while on tirzepatide would be regained after stopping treatment

Generalisability: SURMOUNT-1 comorbidities

Prevalence of comorbidities in SURMOUNT-1 compared with general population with BMI ≥30

Company:

- Presents prevalence data for baseline comorbidities in target population in SURMOUNT-1 vs general population with BMI ≥30:

Comorbidities	Target population (SURMOUNT-1; N=1,705)	General population (BMI ≥30kg/m^2)
Prediabetes	[redacted]	4.5*
Hypertension	[redacted]	39.3*
		~33†
Dyslipidaemia	[redacted]	22.8*
		~16†
Hip or knee osteoarthritis	[redacted]	16.1*
		~12†
Asthma	[redacted]	12.1*
		~15†
OSA	[redacted]	8.6*
ASCVD	[redacted]	3.8*
Gout	[redacted]	2.68‡

*Evans et al. (2023), cross-sectional survey reporting prevalence of comorbidities in people with obesity
†Hasse et al. (2021), retrospective observational study reporting prevalence of comorbidities in BMI subgroups
‡Soriano et al. (2011), epidemiological study of gout in UK general population

- Company notes limitations with data including different definitions of comorbidities and that data presents diagnosed population rather than true prevalence

Evidence for tirzepatide in people with type 2 diabetes

Company:

- SURMOUNT-2 (similar in design to the SURMOUNT-1 but only patients with T2DM and overweight or obesity) 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

Mean % change from baseline HbA1c at week 72

Parameters	Placebo (N=315)	TZP 15 mg (N=311)
Baseline (%)	7.95	8.07
Percent change from baseline at 72 weeks (%)	−0.16*	−2.22†
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	−2.06** (−2.24, −1.88)

* p value <0.1 vs placebo; ** p value <0.001 vs placebo; † p value <0.001 vs baseline

Consideration of T2DM population in TA875:

- Committee accepted that clinical trial informing model did not include people with T2DM
- Noted that people with T2DM would be likely to have less weight loss than people without T2DM but that a small amount of weight loss is associated with greater health gain in a higher risk population such as this
- Introduced uncertainty into the cost effectiveness results but accepted

Non-responder rate

Non-responders discontinue after 6 months due to less than 5% initial body weight loss

ACM1 conclusion:

- Appropriate to use closest available data from SURMOUNT-1 (48 weeks) to estimate proportion stopping tirzepatide due to lack of response after 46 weeks

Company:

- Proportion of people achieving <5% weight loss at week 48 not dramatically lower than at week 72 (data used in company base case); presents scenario using primary discontinuation rate adjusted to align with proportion with <5% weight loss from SURMOUNT-1 at 48 weeks
- Presents scenarios adjusting semaglutide non-responder rate by 5% either side of base case rate (10%)

Comparator company:

- Provides data on non-responder rate from trial in semaglutide

Weight regain after stopping treatment

Time to regain weight after stopping treatment is uncertain

ACM1 conclusion:

- It is uncertain how quickly weight lost while on tirzepatide would be regained (weight gained in line with weight in diet and exercise support arm at that time point) after stopping treatment

Company:

- Company base case: treatment effect lost 3 years after stopping treatment
- Presents scenarios where treatment effect is lost after 1 year and after 2 years

EAG:

- Amends base case to assume weight regain occurs over 2 years – has minimal impact on ICER

- Is the level of uncertainty around time to weight regain acceptable?

Implementation

Impact tirzepatide may have on health inequalities can be considered

NICE health inequalities analysis in obesity:

- Inequalities analysis of health outcomes for different diets in achieving and maintaining weight loss found:
  - the assessed intervention (low energy total replacement diet) yielded greatest health benefits in the most deprived groups (index of multiple deprivation 1 and 2)
- Weight management guidance health inequalities briefing found:
  - Deprivation is the major underlying inequality underpinning differences in obesity levels - greatest rates of adult obesity seen in the most deprived parts of the country
  - Higher levels of obesity in women than in men and in people from black family backgrounds or inclusion health groups
  - Lowest prevalence of obesity in people aged 16 to 24; greatest levels of obesity in men occur between ages 55 to 64 and for women between ages 65 to 74
  - Prevalence of obesity is 20% higher among disabled adults than those without a disability
  - Prevalence of obesity in adults with severe mental illness almost double that of other adults; adults with a learning disability have high levels of obesity
  - People from black and Asian family backgrounds have adverse health outcomes at a lower BMI than people from a white family background
  - Higher proportion of women die during or after pregnancy who are overweight or obese; risk factors for obesity in pregnancy and maternal mortality cluster as there is greater maternal mortality rates in women from black family backgrounds and in women aged over 40