

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

1. **Company submission** from Sanofi
2. **Company summary of information for patients (SIP)** from Sanofi
3. **Clarification questions and company responses**
 - a. Clarification response
 - b. Clarification response appendix 1
 - c. Clarification response appendix 2
 - d. Clarification addendum response
4. **Patient group, professional group and NHS organisation submissions** from:
 - a. Breakthrough T1D
 - b. Diabetes UK
 - c. British Society for Paediatric Endocrinology and Diabetes
 - d. Royal College of General Practitioners
 - e. UK Clinical Pharmacy Association
 - f. NHS England
5. **Expert personal perspectives** from:
 - a. Dr Fulya Mehta – clinical expert, nominated by NHS England
 - b. Amy Norman – patient expert, nominated by Diabetes UK
 - c. Rachael Chrisp – patient expert, nominated by Breakthrough T1D
6. **External Assessment Report** prepared by Kleijnen Systematic Reviews
7. **External Assessment Report – factual accuracy check**

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

Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]

Document B Company evidence submission

File name	Version	Contains confidential information	Date
ID6259_Teplizumab_Document B_5Dec2024_noCON	2.0	No	5Dec2024

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE	1
Contents	2
Tables and figures	2
Abbreviations	5
B.1 Decision problem, description of the technology and clinical care pathway	7
B.1.1 Decision problem	8
B.1.2 Description of the technology being evaluated	12
B.1.3 Health condition and position of the technology in the treatment pathway	13
B.1.4 Equality considerations	30
B.2 Clinical effectiveness	33
B.2.1 Identification and selection of relevant studies	33
B.2.2 List of relevant clinical effectiveness evidence	34
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence	35
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	43
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence	46
B.2.6 Clinical effectiveness results of the relevant studies	47
B.2.7 Subgroup analysis	50
B.2.8 Meta-analysis	51
B.2.9 Indirect and mixed treatment comparisons	51
B.2.10 Adverse reactions	51
B.2.11 Ongoing studies	53
B.2.12 Interpretation of clinical effectiveness and safety evidence	54
B.3 Cost-effectiveness	58
B.3.1 Published cost-effectiveness studies	59
B.3.2 Economic analysis	61
B.3.3 Clinical parameters and variables	69
B.3.4 Measurement and valuation of health effects	80
B.3.5 Cost and healthcare resource use identification, measurement and valuation	86
B.3.6 Severity	94
B.3.7 Uncertainty	95
B.3.8 Managed access proposal	95
B.3.9 Summary of base-case analysis inputs and assumptions	95
B.3.10 Base-case results	101
B.3.11 Exploring uncertainty	102
B.3.12 Subgroup analysis	108
B.3.13 Benefits not captured in the QALY calculation	108
B.3.14 Validation	109
B.3.15 Interpretation and conclusions of economic evidence	114
B.4 References	116

Tables and figures

Table 1 The decision problem	9
Table 2 Technology being evaluated	12
Table 3 Risk of progression to onset of Stage 3 T1D	16
Table 4 Signs of (Stage 3) T1D	18
Table 5. Clinical effectiveness evidence for TN-10	35
Table 6. Summary of trial methodology	36
Table 7. Eligibility criteria for TN-10	38

Table 8. TN-10 trial objectives and endpoints	41
Table 9. Disposition of participants in the primary analysis of TN-10.....	42
Table 10. Baseline characteristics of participants in the primary analysis of TN-10	42
Table 11. Summary of statistical analyses	44
Table 12. Quality assessment results for TN-10.....	46
Table 13. Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis).....	48
Table 14. Sensitivity analysis of time to onset of Stage 3 T1D (TN-10; ITT population; sensitivity analysis at 5 years).....	49
Table 15. C-peptide AUC at 6 months after enrolment (TN-10; ITT population)	50
Table 16. Insulin interval secretion (2 hours) at 6 months after enrolment (TN-10; ITT population).....	50
Table 17. Summary of TEAEs at a median follow-up of 745 days (TN-10; safety population; primary analysis).....	51
Table 18. TEAEs by preferred term occurring in >5% of participants in the teplizumab or placebo group at a median follow-up of 745 days (TN-10; safety population; primary analysis).....	52
Table 19. Incidence of AEs ^a by category during active follow-up (TN-10; safety population; primary analysis).....	53
Table 20. Studies evaluating teplizumab in individuals with T1D.....	54
Table 21. Summary list of published cost-effectiveness studies in Stage 2 T1D.....	60
Table 22. Key model assumptions and inputs	66
Table 23. Baseline Characteristics	69
Table 24. AIC and BIC estimates using individual curves (ITT population).....	72
Table 25. AIC and BIC goodness-of-fit for each distribution using individual curves relative to the distribution with the lowest AIC and BIC (ITT population)	72
Table 26. Proportion of individuals in Stage 2 T1D receiving established clinical management by parametric fitting	75
Table 27 AIC and BIC estimates using a joint parametric distribution (ITT population).....	75
Table 28 AIC and BIC goodness-of-fit for each distribution using a joint parametric distribution relative to the distribution with the lowest AIC and BIC (ITT population).....	75
Table 29. HRs stratified by age at onset of Stage 3 T1D.....	79
Table 30. Adjusted HRs for all-cause mortality stratified by age at onset of Stage 3 T1D....	80
Table 31. Meta-regression model for excess mortality	80
Table 32. EQ-5D-3L utilities for the UK general population	81
Table 33. Infusion-related disutility for people with Stage 2 T1D	82
Table 34. Disutilities for Stage 3 T1D	83
Table 35. Disutility values for people with Stage 3 T1D based on time since onset of Stage 3	83
Table 36 Number of carers/parents in families with dependent children in the UK	85
Table 37. AE disutility.....	86
Table 38. Teplizumab acquisition cost	87
Table 39. Teplizumab administration cost	87
Table 40. Teplizumab confirmatory test costs	88
Table 41. Teplizumab pre-medication costs	89
Table 42. Teplizumab laboratory evaluation costs.....	89
Table 43. Teplizumab infusion-related resource costs.....	90
Table 44. Annual HCRU costs for Stage 2 T1D.....	90
Table 45. Monthly HCRU costs for Stage 2 T1D stratified by age and time before onset of Stage 3 T1D ^a	91
Table 46. Regression models for Ou et al. (2016)	93
Table 47. AE frequency (for teplizumab) and management costs	94
Table 48. Summary of base-case variables applied in the economic model	96
Table 49. Model assumptions	101

Table 50. Discounted base-case results.....	102
Table 51. DSA settings	104
Table 52 Scenario analysis (based on a probabilistic approach)	107
Table 53. Comparison of Sanofi model with NICE TA943 EAG Stage 3 T1D model	112
Table 54 Comparison of Sanofi model with published Stage 3 T1D model.....	113
Table 55 Comparison of Sanofi model with the Mital et al. (2020) model	113
Figure 1. The stages of T1D.....	14
Figure 2 Proposed clinical pathway of care for Stage 2 T1D in the UK, including the positioning of teplizumab.....	26
Figure 3. Trial design of TN-10 in the primary analysis and extended follow-up analysis	37
Figure 4. KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis).....	49
Figure 5. Model structure	61
Figure 6. Observed KM curves (ITT population).....	70
Figure 7 Log-cumulative hazard plot (ITT population)	71
Figure 8. Schoenfeld residuals plot (ITT population)	71
Figure 9 Time to Stage 3 T1D parametric fits for individuals on teplizumab using individual curves (ITT population)	73
Figure 10 Time to Stage 3 T1D parametric fits for individuals receiving placebo using individual curves (ITT population)	74
Figure 11 Time to Stage 3 T1D parametric fits for individuals on teplizumab using a joint parametric distribution (ITT population).....	76
Figure 12 Time to Stage 3 T1D parametric fits for individuals on placebo using a joint parametric distribution (ITT population).....	77
Figure 13. Linear regression model for Stage 3 T1D disutilities according to time from onset	84
Figure 14. Disease management cost digitised from Ou et al. (2016)	92
Figure 15. Regression models vs. observed data from Ou et al. (2016).....	93
Figure 16. PSA convergence test.....	102
Figure 17. PSA scatterplot	103
Figure 18. Cost-effectiveness acceptability curve.....	103
Figure 19. Tornado diagram: incremental cost	105
Figure 20. Tornado diagram: incremental QALYs	105
Figure 21. Tornado diagram: ICER	106

Abbreviations

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BGM	Blood glucose monitoring
BIC	Bayesian information criterion
BMI	Body Mass Index
BNF	British National Formulary
BSA	Body surface area
BSPED	British Society for Paediatric Endocrinology and Diabetes
CD3/8	Cluster of differentiation 3/8
CGM	Continuous glucose monitoring
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
DKA	Diabetic ketoacidosis
DPT-1	Diabetes Prevention Trial–Type
DQoL	Diabetes-related QoL
DSA	Deterministic sensitivity analysis
DSMB	Data and Safety Monitoring Board
EAG	External assessment group
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
FDA	Food & Drug Administration
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GBP	Great British Pound
HbA1c	Glycosylated haemoglobin
HCL	Hybrid closed loop
HCP	Healthcare provider
HCRU	Healthcare resource utilisation
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life
IA2	Tyrosine phosphatase-like insulinoma antigen 2
ICER	Incremental cost-effectiveness ratio
INR	International normalisation ratio
IQR	Interquartile range
IRP	International Recognition Procedure
ISPAD	International Society for Pediatric and Adolescent Diabetes

Abbreviation	Definition
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LY	Life years
LYG	Life years gained
mcg	Microgram
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not applicable
NaDIA	National Diabetes Inpatient Audit
NCT	National Clinical Trials
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NPDA	National Paediatric Diabetes Audit
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
OGTT	Oral glucose-tolerance test
ONS	Office of National Statistics
OR	Odds ratio
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PedsQL	Pediatric Quality of Life Inventory
PH	Proportional hazards
PK	Pharmacokinetic
PLGS	Predictive low-glucose suspend
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RWE	Real world evidence
SAE	Serious adverse event
SAP+LGS	Sensor-augmented pump therapy + low glucose suspend
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
SLR	Systematic literature review
SmPC	Summary of product characteristics
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse event
TN	TrialNet
UK	United Kingdom
US	United States
VAT	Value-added tax
YHEC	York Health Economics Consortium
ZnT8	Zinc transporter 8

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

Disease overview and burden

- Type 1 diabetes (T1D) is a chronic autoimmune disease that progresses as a continuum across 3 stages, affecting both children and adults,¹⁻³ which can lead to serious complications⁴⁻⁶ and a substantial impact on everyday lives.¹ Stage 2 T1D (the anticipated indication of teplizumab) is characterised by the presence of ≥ 2 pancreatic islet autoantibodies and abnormal blood glucose levels without overt hyperglycaemia; Stage 2 T1D is asymptomatic despite continued beta-cell damage and cell death, making it a silent but active disease.¹⁻³
- The epidemiology of Stage 2 T1D is poorly understood given that there are no extensive general population early detection programmes for Stage 2 T1D in the UK⁷ and the typical duration of Stage 2 is uncertain.⁸
- The majority of people with presymptomatic Stage 2 T1D will progress to symptomatic Stage 3 T1D (~75% risk of progression in 4 to 5 years),⁹ with a conservative estimate of 62% of children with 2 islet autoantibodies progressing to Stage 3 T1D by 15 years of age.¹⁰ Most people with T1D are diagnosed at Stage 3 due to the onset of symptoms relating to hyperglycaemia.¹
- The clinical burden of Stage 3 T1D includes acute metabolic complications (hypoglycaemia and diabetic ketoacidosis [DKA]) when blood glucose levels are outside of the normoglycaemic range, and elevated risk of several long-term complications (e.g., kidney disease, eye disease, nerve damage and cardiovascular disease),⁴⁻⁶ contributing to an increased mortality risk vs. the general population.¹¹
- Even if blood glucose levels are typically within the recommended target range, there is still substantial humanistic burden associated with Stage 3 T1D and the reality of lifelong daily disease management,¹ with reduced quality of life (QoL) compared with the general population.¹²⁻¹⁴ Individuals with Stage 3 T1D also incur substantially higher healthcare costs compared with those without T1D in the UK.¹⁵

Clinical pathway of care and teplizumab place in therapy

- Worldwide, teplizumab is the first and only disease-modifying therapy approved to delay the onset of Stage 3 T1D in people with Stage 2 T1D,¹⁶⁻¹⁸ offering a step change in treating the condition.¹⁹
- At present, Stage 2 T1D is rarely detected in the UK. In the absence of pharmacological treatments, management of Stage 2 T1D focuses on metabolic monitoring for progression to Stage 3 T1D, as well as education and psychosocial support for those with Stage 2 T1D and their family members.^{1,20,21}
- The management of Stage 3 T1D with insulin replacement therapy, blood glucose monitoring (BGM), carbohydrate counting and exercise can be complex and burdensome.²² The act of continuously managing their own blood glucose can make people feel worn down or depressed,^{23,24} and when not adequately managed can lead to hypoglycaemia and hyperglycaemia, as well as DKA which is a life-threatening condition.^{5,25}
- Individuals in the UK place significant value on T1D treatments that can delay the need for insulin,²⁶ and this remains a substantial unmet need in the UK.
- Delaying the progression from Stage 2 to Stage 3 T1D could delay the complications and damage due to dysglycaemia associated with Stage 3 T1D,⁵ postponing the need for exogenous insulin to achieve optimal blood glucose levels.²⁷ Retaining endogenous insulin production is also associated with clinical benefits such as better glycaemic control, reduced rates of severe hypoglycaemia²⁸⁻³¹ and lower rates of long-term complications (e.g., hypertension, nephropathy and retinopathy).^{29,32,33}
- In the UK, the anticipated indication of teplizumab in the proposed clinical pathway of care is for individuals aged 8 and over with Stage 2 T1D to delay the onset of Stage 3 T1D.

B.1.1 Decision problem

This single technology appraisal will evaluate the clinical- and cost-effectiveness of teplizumab in delaying the onset of Stage 3 T1D. Teplizumab is anticipated to be indicated to delay the onset of Stage 3 T1D in adults and paediatric patients aged 8 years and older with Stage 2 T1D.³⁴

The final scope for teplizumab for Stage 2 T1D was issued by National Institute for Health and Care Excellence (NICE) in September 2024. The decision problem addressed in this submission, compared with the final scope, is summarised in Table 1.

Table 1 The decision problem

	Final scope issued by NICE³⁵	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia)	As per final scope	N/A
Intervention	Teplizumab	As per final scope	N/A
Comparator(s)	Established clinical management without teplizumab including, but not limited to: • monitoring blood glucose • psychosocial support • education	As per final scope	N/A
Outcomes	The outcome measures to be considered include: • progression from Stage 2 to Stage 3 T1D • time to starting insulin treatment • levels of stimulated C-peptide • symptoms and complications of T1D including incidence of DKA • mortality • adverse effects of treatment • HRQoL.	In line with the final scope, the outcome measures to be considered include: • progression from Stage 2 to Stage 3 T1D (specifically, time to progression and rate of progression) • levels of stimulated C-peptide • mortality • adverse effects of treatment • HRQoL Additional relevant outcome measures to be considered include: • impact on the patient • impact on caregiver	• 'Time to progression of Stage 3 T1D' (the outcome measured in the teplizumab TN-10 trial) is largely the same as 'time to starting insulin treatment'.³⁶ In children with newly diagnosed Stage 3 T1D after presentation of symptoms alongside hyperglycaemia, insulin therapy and education are most often initiated immediately.³⁶ • Stage 3 T1D is known to have an impact on the individual including time spent managing the condition,³⁷ time spent off school,³⁸ time spent off work,³⁹ and distress in the workplace.⁴⁰ Given teplizumab is expected to delay the onset of Stage 3 T1D in people with Stage 2 T1D, it is important that the potential benefit of delaying these impacts are captured. • T1D is known to have an impact on caregivers, for example, through burden of care, financial implications and sense of vigilance.⁴¹ Given the anticipated marketing authorisation includes children above the age of 8, it is important this outcome is included.

	Final scope issued by NICE ³⁵	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Teplizumab is not expected to have a direct impact on the symptoms, complications or incidence of DKA at diagnosis. The longer-term effect of teplizumab on DKA has not been fully elucidated.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for pancreatic islet autoantibodies in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	The economic analysis will be carried out in line with the NICE reference case. The costs associated with diagnostic testing for pancreatic islet autoantibodies in people who would not otherwise have been tested are not included in the economic modelling.	In line with the anticipated marketing authorisation, the population of interest will already have received testing for autoantibodies and be diagnosed with Stage 2 T1D when considered for treatment with teplizumab. The economic analysis accounts for the cost of confirmatory tests in line with the SmPC prior to administration of teplizumab.³⁴
Subgroups to be considered	If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.	No subgroups to be considered.	Given the small number of people diagnosed with Stage 2 T1D and the limited evidence on patient subgroups, the entire eligible patient population should be considered. In particular, the effect of teplizumab was consistent by age, and subgroups are therefore not considered. We would advise caution in interpreting data for subgroups given the small size of the TN-10 trial population.

	Final scope issued by NICE ³⁵	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	None specified.	Potentially relevant equality considerations related to factors such as SES, ethnicity and age should be taken into account.	Potential equality issues have been identified by NICE in previous T1D assessments, including those related to SES, ethnicity, age, having cystic fibrosis-related T1D, and having other conditions that prevent or hinder optimal use of an HCL device (e.g., skin conditions or allergies, learning difficulties, vision or hearing impairments, blood clotting disorders). These are explored further in Section B.1.4.

DKA = diabetic ketoacidosis; FDA = Food and Drug Administration; HRQoL = health-related quality of life; SES = socioeconomic status; SmPC = summary of product characteristics; T1D = type 1 diabetes; UK = United Kingdom
Source: NICE 2024 Final scope³⁵

B.1.2 Description of the technology being evaluated

A description of teplizumab, the technology being appraised, is presented in Table 2. As noted in Appendix C, the UK public assessment report and final approved summary of product characteristics (SmPC) for teplizumab in Stage 2 T1D are not yet available to be included in this submission. Sanofi will provide these once available.

Table 2 Technology being evaluated

UK approved name and brand name	Teplizumab (Tziel®)
Mechanism of action	Teplizumab binds to CD3 (a cell surface antigen present on T lymphocytes) and delays the onset of Stage 3 T1D (defined by overt hyperglycaemia accompanied by clinical symptoms) in adults and paediatrics aged 8 years and older with Stage 2 T1D (defined as ≥2 pancreatic islet autoantibodies and abnormal blood glucose levels, without overt hyperglycaemia or clinical symptoms). The mechanism may involve partial agonistic signalling and deactivation of pancreatic beta-cell autoreactive T lymphocytes. Teplizumab leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Marketing authorisation/ CE mark status	Teplizumab does not currently have a marketing authorisation in any indication from the MHRA. An application to the MHRA was submitted [REDACTED] for teplizumab to delay the onset of Stage 3 T1D in adult and paediatric patients 8 years of age and older with Stage 2 T1D [REDACTED]. Teplizumab does not include a medical device component. The current expected date of approval from the MHRA is [REDACTED].
Indications and any restriction(s) as described in the SmPC	Teplizumab is anticipated to be indicated to delay the onset of Stage 3 T1D in adult and paediatric patients aged 8 years and older with Stage 2 T1D.
Method of administration and dosage	Teplizumab is administered by IV infusion (over a minimum of 30 minutes), using a BSA-based dosing, once daily for 14 consecutive days as follows: • Day 1: 65 mcg/m² • Day 2: 125 mcg/m² • Day 3: 250 mcg/m² • Day 4: 500 mcg/m² • Days 5 through 14: 1,030 mcg/m²
Additional tests or investigations	Before teplizumab treatment can be initiated, the diagnosis of Stage 2 T1D must be confirmed by documenting the presence of at least two positive pancreatic islet cell autoantibodies and dysglycaemia without overt hyperglycaemia. A complete blood count and liver enzyme tests are required prior to initiating teplizumab. Individuals who are treated with teplizumab will be monitored for CRS (liver enzymes and bilirubin) and lymphopenia (white blood cell counts) during the 14-day treatment course, and for signs and symptoms of infection during and after treatment.
List price and average cost of a course of treatment	[REDACTED] per 14-vial treatment course
Patient access scheme	A PAS is planned, with a simple discount of [REDACTED] % off the list price for teplizumab. With the PAS, the cost of treatment shown above is reduced to [REDACTED] per 14-vial treatment course

BSA = body surface area; CD3 = cluster of differentiation 3; CD8+ T cells = cytotoxic CD8+ T lymphocytes; CRS = cytokine release syndrome; FDA = Food and Drug Administration; IRP = International Recognition Procedure;

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

B.1.3.1 Disease overview

T1D is a chronic autoimmune disease involving a progressive T-cell mediated attack of pancreatic islet beta-cells, which are responsible for the production and release of insulin (a hormone that regulates blood glucose levels); this leads to the progressive destruction of beta-cell function and hence compromised endogenous insulin production, ultimately resulting in chronic high blood glucose levels (hyperglycaemia).¹⁻³ Pancreatic islet autoantibodies (antibodies produced by the immune system that react with self-antigens)⁴² such as glutamic acid decarboxylase (GAD), tyrosine phosphatase-like insulinoma antigen 2 (IA2), zinc transporter 8 (ZnT8) and insulin autoantibodies (IAA) autoantibodies, are the main markers of pancreatic autoimmunity in T1D.^{2,3}

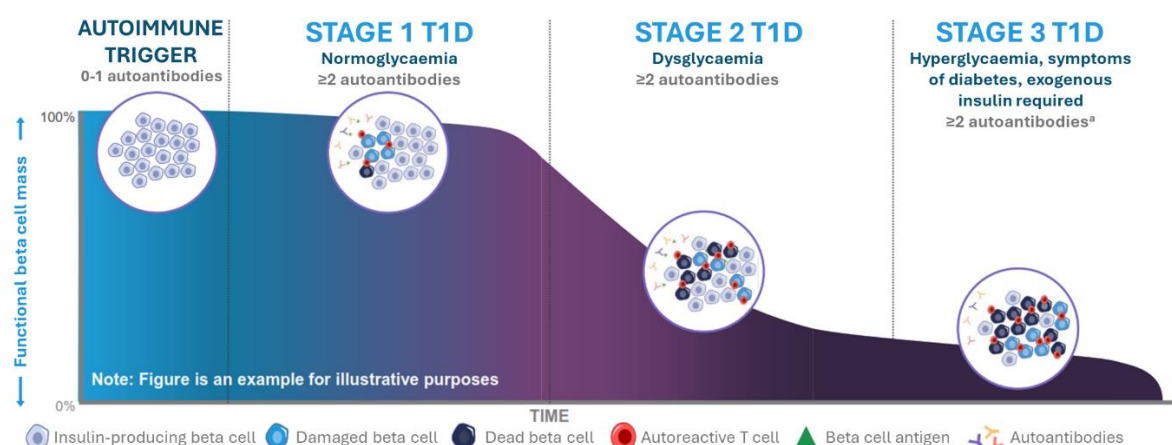
T1D progresses as a continuum across the following 3 stages (Figure 1):¹⁻³

- **Stage 1 T1D**, the presence of ≥ 2 pancreatic islet autoantibodies indicates that the autoimmune attack and beta-cell loss has begun, but people with Stage 1 T1D have a normal concentration of blood glucose levels (normoglycaemic; typically defined as blood glucose levels of 4–8 mmol/L, with fasting plasma glucose [FPG] of < 5.6 mmol/L and 2 hour plasma glucose following oral glucose-tolerance test [OGTT] of < 7.8 mmol/L). Clinical symptoms are not present at Stage 1.
- **Stage 2 T1D**, continued autoimmune attack by autoreactive T cells causes further beta-cell loss. Stage 2 T1D is defined as ≥ 2 pancreatic islet autoantibodies and abnormal blood glucose levels (typically defined as FPG of 5.6–6.9 mmol/L and 2 hour plasma glucose following OGTT of 7.8–11.1 mmol/L) without overt hyperglycaemia. Clinical symptoms are not present at Stage 2.

- **Stage 3 (clinical) T1D^a**, is defined by overt hyperglycaemia (FPG of ≥ 7.0 mmol/L and 2 hour plasma glucose following OGTT of ≥ 11.1 mmol/L), accompanied by clinical symptoms, and is when most people with T1D are typically diagnosed. It is in Stage 3 that people with T1D will usually require lifelong exogenous insulin therapy.

Individuals with a first-degree relative with T1D (vs. those without), with obesity (vs. those with normal body mass index [BMI]) and aged 4 to <6 years (vs. those aged <3 years) have a greater adjusted relative risk of Stage 1 and 2 T1D, based on the Fr1da study of a German public health early detection programme for islet autoantibodies in children.⁴³

Figure 1. The stages of T1D



^aIn some people, autoantibodies may become absent in Stage 3 T1D.

T1D = type 1 diabetes

Source: Insel 2015;⁹ van Belle 2011;⁴⁴ Jacobsen 2018;⁴⁵ ADA 2022;⁴⁶ McCall 2013⁴⁷

Of note, as discussed and confirmed with NICE during the scoping meeting, some sources, including Breakthrough T1D (formerly Juvenile Diabetes Research Foundation),⁴⁸ refer to Stage 4 T1D in reference to established/long-standing disease, in which health-complications of T1D are common; however, this terminology is not currently widely used in routine clinical practice.

B.1.3.1.1 Clinical presentation

Stage 2 T1D is characterised by the presence of multiple islet autoantibodies and abnormal blood sugar levels, as described above. The majority of people with presymptomatic Stage 2

^a Many studies of individuals with T1D do not identify the disease stage, but it is generally understood from the stage definitions in treatment guidelines that 'clinical/symptomatic T1D' is equivalent to 'Stage 3 T1D'; thus the 'Stage 3 T1D' terminology is used as such hereafter in this dossier.

T1D will progress to symptomatic Stage 3 T1D.^{9,10} As the disease progresses, the symptoms of Stage 3 T1D present heterogeneously, including:^{3,49}

- Fasting hyperglycaemia
- Polyuria (excessive urine) and polydipsia (excessive thirst)
- Nocturia (the need to urinate at night)
- Enuresis (inability to control urination)
- Weight loss, possibly accompanied by fatigue and behavioural disturbances
- Blurred vision

If left untreated or not sufficiently managed, recurrent hyperglycaemia may lead to life-threatening DKA which can lead to coma and death (discussed further in Section B.1.3.3.1).³

B.1.3.1.2 *Progression to Stage 3 T1D*

The overall risk of progression from presymptomatic Stage 2 T1D to symptomatic Stage 3 T1D is high, reported to be approximately ~75% at 4 to 5 years and approaches a 100% lifetime risk (Table 3), with a conservative estimate of 62% of children with 2 islet autoantibodies progressing to Stage 3 T1D by 15 years of age.^{9,10} Findings from the Fr1da study of a German public health early detection programme for islet autoantibodies indicated that the median time to progression from Stage 2 T1D to Stage 3 T1D was 32.3 months (95% CI: 6.2, 43.7) among individuals aged 8 to 15 years.⁵⁰ There is uncertainty regarding the timing of progression and the typical duration of Stage 2 T1D, as highlighted by UK clinical experts during an advisory board convened by Sanofi in May 2024 (discussed further in Appendix M).⁸

The risk of progression to Stage 3 T1D is associated with age, with individuals <13 years old at Stage 2 having a significantly greater risk of progression at 5 years than those ≥13 years old (94% vs. 40%, respectively; $p=0.001$).⁵¹

Of note, family history of T1D is not significantly associated with the risk of progression through the T1D continuum. Among children aged 1.75 to 5.99 years with Stage 1 or 2 T1D in the Fr1da study aforementioned, a similar proportion of those having and not having a first-degree relative with Stage 3 T1D progressed to Stage 3 (21.9% vs. 18.5% respectively; $p=0.96$) after a median follow-up of 1.9 years.⁴³ Additionally, the risk of progression to Stage 3 T1D was similar among individuals in Fr1da *without* a first-degree relative with Stage 3 T1D and among those in the TN-10 trial *with* a first-degree relative (unadjusted hazard ratio

[HR]: 1.3; adjusted HR: 1.1; see Section B.2.5.2).⁵² The vast majority of individuals with Stage 2 T1D will progress to Stage 3 T1D, regardless of whether they have a first-degree relative with T1D.^{43,53} UK clinical experts in the May 2024 advisory board convened by Sanofi also indicated that there is no difference expected between those with and without a first-degree relative in terms of T1D progression rates.⁸

Table 3 Risk of progression to onset of Stage 3 T1D

Study	Population	Risk of progression to onset of Stage 3 T1D at		
		2 years	4 years	5 years
Among individuals diagnosed with Stage 2 T1D				
TrialNet Natural History Study ⁵⁴	First- and second-degree relatives ^a aged 1 to 45 years	~60%	74%	NR
DPT-1 ⁵¹	First- and second-degree relatives ^a aged 3 to 45 years ⁵⁵	NR	65%	~75%
Fr1da ⁵³	Children aged 1.75 to 10 years from the general population, including 3.9% with a first-degree relative	58.6%	NR	NR

CI = confidence interval; DPT-1 = Diabetes Prevention Trial–Type 1; HR =hazard ratio; NR = not reported; T1D = type 1 diabetes

^a Of people with Stage 3 T1D

Sources: Krischer 2013⁵⁴; Sosenko 2009⁵¹; Weiss 2022⁵³

B.1.3.1.3 T1D diagnosis criteria

Stage 2 T1D

Stage 2 T1D is defined as ≥2 pancreatic islet autoantibodies and abnormal blood glucose levels, without overt hyperglycaemia.¹⁻³ In the UK, some individuals with Stage 2 T1D are identified through research studies (e.g., ELSA, T1DRA and INNODIA) or ad hoc clinical testing.^{3,7,8,56-58} Of note, to reflect the growing need to capture this diagnosis, a new SNOMED code for presymptomatic T1D was recently created (1290118005).⁵⁹ An ICD-10-CM code has also been newly issued for Stage 2 T1D (E10.A2).^{60,61}

The 2024 international consensus monitoring guidelines that were initiated by Breakthrough T1D, endorsed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and authored by an expert panel including UK representatives, report an unmet need for evidence-based expert clinical advice for monitoring of islet autoantibodies in order to follow individuals with presymptomatic (Stage 1 or 2) T1D.²⁰ The International Society for Pediatric and Adolescent Diabetes (ISPAD) note that early detection of T1D is primarily conducted via population-wide or genetic risk-

stratified islet autoantibody identification.¹ Glycaemic staging and ongoing monitoring should be offered to those with multiple islet autoantibodies, with the OGTT being recommended as the gold standard for staging T1D. People with multiple islet autoantibodies, as well as impaired fasting glucose (FPG of ≥ 100 and < 126 mg/dL [5.6–6.9 mmol/L]) and glucose-tolerance (two-hour glucose of ≥ 140 and < 200 mg/dL [7.8–11.1 mmol/L] during an OGTT), are classified as having Stage 2 T1D per the ISPAD guidelines.¹ Consensus guidelines also include other methodology to determine dysglycaemia (e.g., random venous glucose, glycosylated haemoglobin [HbA1c] or continuous glucose monitoring [CGM]).^{1,20} Additional UK-specific monitoring guidelines from the British Society for Paediatric Endocrinology and Diabetes (BSPED) are expected to be published soon and are available on request to clinicians prior to publication.

Ongoing metabolic monitoring is recommended for individuals with Stage 2 T1D by the 2024 international consensus guidelines;²⁰ this is discussed further in Section B.1.3.4.1.

In England, NICE diagnostic criteria for T1D in children and adults do not include disease staging,^{62,63} and there are no extensive general population early detection programmes for presymptomatic Stage 2 T1D in place outside of research.

Stage 3 T1D

NICE has separate diagnostic guidelines for T1D (assumed to be symptomatic Stage 3 T1D) in paediatrics (aged < 18 years) and adults (aged ≥ 18 years).^{62,63} The typical signs and symptoms of T1D in paediatrics and adults used to inform a diagnosis are presented in Table 4.^{62,63} The guidelines specify that in adults, age or BMI alone should not be used to exclude or diagnose T1D.⁶² Additionally, serum C-peptide should not be routinely measured to confirm T1D in adults, but can be revisited if there are doubts that T1D is the correct diagnosis in subsequent clinical reviews.⁶² Similarly, the paediatric guidelines note that C-peptide should not be measured at initial presentation to distinguish T1D from type 2 diabetes (T2D), but may be considered after initial presentation to distinguish between types.⁶³

Table 4 Signs of (Stage 3) T1D

Paediatrics	Adults
Hyperglycaemia (random plasma glucose >11 mmol/L)	Hyperglycaemia
Polyuria	Ketosis
Polydipsia	Rapid weight loss
Weight loss	Age of onset <50 years
Excessive tiredness	BMI <25 kg/m ²
-	Personal and/or family history of autoimmune disease

BMI = body mass index; T1D = type 1 diabetes

Source: NICE NG17 guideline,⁶² NICE NG18 guideline⁶³

NICE recommend confirming T1D in children and young people using the plasma glucose criteria in the World Health Organization (WHO) 2006 report, namely FPG ≥ 7.0 mmol/L (126 mg/dl) or 2 hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl).^{63,64}

The NICE diagnostic guidelines for adults recommend measuring diabetes-specific autoantibodies at diagnosis.⁶² A diagnosis of T1D may be differentiated from T2D by the presence of GAD, IA2, ZnT8 and/or IAA autoantibodies in the plasma.^{2,3} In an advisory board convened by Sanofi in July 2024 (discussed further in Appendix M), clinical experts noted that any two of the autoantibodies GAD, IA2, ZnT8 and insulin are used to diagnose T1D; which two autoantibodies are used varies by region.²¹

B.1.3.2 Epidemiology

The epidemiology of Stage 2 T1D is poorly understood given that there are no extensive general population early detection programmes for Stage 2 T1D in the UK (beyond research studies such as ELSA and T1DRA)⁷ and there is uncertainty regarding the typical duration of Stage 2⁸ (as discussed in Section B.1.3.1.2). Due to the lack of a formal pathway of care, clinical experts in the advisory board convened by Sanofi in May 2024 noted that clinicians do not usually identify Stage 2 T1D in routine clinical practice.⁸ Therefore, with the current clinical landscape, the number of people diagnosed with Stage 2 T1D in England and Wales is expected to be low. This is in line with observational studies being conducted in the UK, given early reports from the ELSA study in children.⁶⁵ Given that the majority of people with Stage 2 T1D will progress to Stage 3 T1D,^{9,10} it was assumed that Stage 2 T1D incidence rates are the same as Stage 3 T1D in the budget impact analysis, in the absence of specific epidemiology data.

Most people with T1D are currently diagnosed at Stage 3 due to the onset of symptoms relating to hyperglycaemia,¹ with a conservative estimate of 62% of children with 2 islet autoantibodies progressing to Stage 3 T1D by 15 years of age (as described in Section

B.1.3.1.2).¹⁰ The incidence of Stage 3 T1D in England and Wales in 2021-2022 as reported by the National Diabetes Audit (NDA) was 9,760 individuals across all ages; the incidence in children and adolescents aged <19 years during the same period was 4,390 individuals.⁶⁶ According to the NDA in England and Wales between 2019 and 2020, the peak age of T1D diagnosis is 12 years of age.⁶⁷ The prevalence of Stage 3 T1D in England and Wales in 2021-2022 was 287,025 individuals across all ages.⁶⁶

Some individuals in the UK may be diagnosed with Stage 2 T1D as part of various studies, such as clinical trials and observational studies (e.g., ELSA in children [N=20,000 to be screened]⁶⁸ and T1DRA in adults [N=20,000 to be screened]),⁶⁸ including those which are conducted specifically in individuals with a first-degree relative with Stage 3 T1D (e.g., INNODIA).^{7,56}

B.1.3.3 Disease burden

T1D imposes a substantial burden on individuals with the condition, their families, carers and society. Stage 2 T1D is asymptomatic despite continued beta-cell damage and cell death, making it a silent but active disease.¹⁻³ For children who are diagnosed with Stage 1 or 2 T1D, the diagnosis has been associated with increased psychological distress (generally of low or moderate severity) in the children's mothers.⁴³

Most people with Stage 2 T1D will eventually progress along the T1D continuum to Stage 3 T1D with the lifetime risk approaching 100%.^{1,9} The majority of the burden associated with T1D is driven by symptomatic Stage 3 T1D, including lifelong daily disease management, risk of acute and long-term complications and high mortality.

B.1.3.3.1 Clinical burden of Stage 3 T1D

Burden of management of Stage 3 T1D

The management of Stage 3 T1D with BGM, carbohydrate counting, exercise and exogenous insulin is complex and burdensome and many people with Stage 3 T1D spend a substantial proportion of time outside of the normoglycaemic range.^{22,69} The treatment landscape for Stage 3 T1D and the associated burden of management has evolved with the introduction of newer technologies, such as hybrid closed loop (HCL) systems, which were recommended by NICE in December 2023.⁷⁰ HCL systems automatically deliver insulin by continuous subcutaneous insulin infusion in response to glucose levels that are monitored via real-time CGM.⁷¹ Even with the availability of HCL systems that improve the amount of time spent within normoglycaemic levels (i.e., time in range), widespread uptake in the UK is

expected to take time, and a proportion of individuals using HCL systems continue to have HbA1c levels that are above target.^{70,72}

Burden of acute and long-term complications of Stage 3 T1D

The clinical burden of Stage 3 T1D includes acute metabolic complications (hypoglycaemia, hyperglycaemia and DKA) when blood glucose levels are outside of the normoglycaemic range.⁵ DKA is a life-threatening condition that is often present at diagnosis of Stage 3 T1D.²⁵ DKA is caused by counter-regulatory metabolic responses to very low circulating endogenous insulin levels and can result from worsening beta-cell function in untreated Stage 3 T1D at onset.²⁵ The prevalence of DKA at onset of Stage 3 T1D was 23% among children and young people in 2022-2023 in England and Wales, with 2% of those with Stage 3 T1D having ≥ 1 hospital admission for DKA in 2022-2023^{b, 73}

Hypoglycaemia (low blood glucose) and hyperglycaemia (high blood glucose) can become serious, even fatal, if not managed immediately, leading to altered consciousness and coma, and potentially requiring hospitalisation.²⁵ In the UK, 1% of children and young people with Stage 3 T1D had ≥ 1 hospital admission for hypoglycaemia in 2022-2023 according to the National Paediatric Diabetes Audit (NPDA) in England and Wales^{b, 73} Individuals with Stage 3 T1D are also more likely to be hospitalised for any cause than those without Stage 3 T1D, as found by a Scottish study of schoolchildren aged 4 to 19 years^{b, 74}

Individuals with Stage 3 T1D have an elevated risk of several long-term complications including kidney disease (nephropathy), eye disease (retinopathy), nerve damage (neuropathy), cardiovascular disease, foot and circulation problems, gum disease and sexual problems.⁴⁻⁶ The risk of complications may be higher in individuals with onset of Stage 3 T1D at <12 years of age, and can increase over time with disease duration.⁷⁵

As individuals with Stage 3 T1D age through adulthood, the clinical burden of the disease persists, with diabetes-related complications being compounded with the onset of age-related conditions.⁷⁶ Together these may exacerbate the existing challenges associated with managing Stage 3 T1D.⁷⁶ Older adults with Stage 3 T1D remain at risk of experiencing

^b Similar UK-specific data for adults have not been identified.

hyperglycaemia as well as hypoglycaemia.⁷⁶ Hypoglycaemia in adults may lead to hospitalisation, and hospitalisation rates are high overall:

- The National Diabetes Inpatient Audit (NaDIA) collected data from 209 hospitals in England and Wales in 2016.⁷⁷ It reported that 20% of hospital inpatients with Stage 3 T1D had one or more hypoglycaemic episodes in the prior seven days.⁷⁷
- Among individuals with Stage 3 T1D aged 15 years and older in England and Wales, the diabetes-related hospitalisation rate in 2020 was 81.6 per 100,000 persons, an increase of more than 10% from 1999.⁷⁸

DKA may occur in people with established Stage 3 T1D as a result of missed insulin doses, insufficient insulin administration during infection/gastrointestinal illness and stress.²⁵ Among adults with Stage 3 T1D in England and Wales, the incidence of hospitalisation due to DKA was 25.8 per 1,000 person-years for women and 20.6 per 1,000 person-years for men in 2020 per the NDA.¹¹ DKA can lead to further complications, including brain swelling, dysregulation of potassium levels, stroke, infection and pulmonary oedema.²⁵

Mortality in Stage 3 T1D

People with Stage 3 T1D have an increased mortality risk compared with the general population.¹¹ Based on 2015-2016 NDA data for England and Wales, the relative risk of death for those with Stage 3 T1D vs. the general population is increased at all ages, and the mortality rate ratio is higher in individuals aged 15 to 34 years compared with individuals aged ≥35 years.⁷⁹ A younger age at onset of Stage 3 T1D may be associated with an increased risk of early mortality, with a 2016 Swedish study based on data from 1998 to 2012 reporting approximately 16 years lower life expectancy for those diagnosed before the age of 10 years compared with matched controls without T1D.⁸⁰ Furthermore, children and young adults with Stage 3 T1D had an increased risk of premature death compared with the general population (HR 1.57; 95% CI: 1.16, 2.12), as reported in another Swedish study based on 2000 to 2019 data.⁸¹

Diabetes-related causes of death include acute metabolic complications such as DKA and hypoglycaemia^{82,83} and chronic complications/comorbidities such as kidney disease and cardiovascular disease.⁸⁴⁻⁸⁷

B.1.3.3.2 Humanistic burden of Stage 3 T1D

Once Stage 3 T1D progresses, people with T1D and their families/carers face a substantial humanistic burden associated with the condition and the reality of lifelong daily disease

management.¹ People with Stage 3 T1D are required to make an additional 180 decisions per day about their health compared with someone without diabetes.⁸⁸

Adolescents and young adults with Stage 3 T1D have reduced QoL compared with the general population.¹²⁻¹⁴ Several aspects of health-related quality of life (HRQoL) are impacted by the disease and development of complications/comorbidities. Children and adolescents with Stage 3 T1D experience impact on daily activities, pain and discomfort, and have a higher prevalence of psychiatric/mental health disorders than peers without T1D.⁸⁹⁻⁹¹ Approximately 21% to 52% of teenagers living with Stage 3 T1D experience diabetes-related distress.⁹²⁻⁹⁶ Diabetes-related distress describes “the ongoing challenges and efforts that self-management demands, the perceived threats and potential despair regarding long-term complications, concerns about access to needed treatments and social stigma”.⁹⁷ This distress is mirrored in parents and carers, with 26% to 54% experiencing diabetes-related distress,^{98,99} and an additional 1 in 5 parents/carers of children with Stage 3 T1D suffering from depression or depressive symptoms.¹⁰⁰ This captures the treatment burden that is initially managed by the parent/carer in childhood T1D, but shifts to the person living with Stage 3 T1D as they transition into young adulthood and thus independence. US estimates state that 30% of adults with T1D experience diabetes-related distress for an extended period.¹⁰¹

Individuals who have had Stage 3 T1D for multiple years have generally been found to have worse overall HRQoL compared with those who have had the disease for only 1 year.¹² Other factors reported to worsen HRQoL and/or diabetes-related QoL (DQoL) in people with Stage 3 T1D include poor glycaemic control in children, adolescents and adults,^{90,102-106} occurrence of severe hypoglycaemia/hypoglycaemia requiring assistance in adolescents and adults,^{105,107} fear of hypoglycaemia in children and adolescents^{106,108} and diabetes-related distress in adults.¹⁰⁹ Additionally, a recent UK parliamentary inquiry on T1D with disordered eating¹¹⁰ has highlighted that up to 40% of women and 15% of men with Stage 3 T1D are reported to have disordered eating behaviours.¹¹¹

The age at onset of Stage 3 T1D has a significant impact on educational attainment.¹¹² In the UK, educational attainment is substantially reduced for children with less than optimal glycaemic control, with 10% of these children progressing to higher education compared to 30% of their peers.³⁸ In a Swedish cohort study of 5,159 children, the risk of not finishing compulsory school education was significantly increased for children who were less than 2 years old at onset of Stage 3 T1D, compared with children aged 2 or above.¹¹²

Adults with Stage 3 T1D report that continuously managing their blood glucose levels can make them feel worn down, depressed, or embarrassed, and that their condition can seem relentless.^{23,24,113}

- *“It [fluctuating blood glucose levels] takes a lot of energy... It takes a lot, it’s a great strain... I’d say, it wears me down. It really wears me down.”*
- *“This is a condition that requires CONSTANT monitoring, awareness and cautiousness... it isn’t just a mental load, it’s mentally exhausting and debilitating.”*

Families and carers of children with Stage 3 T1D are also negatively impacted by the disease and its management.⁹⁹ Qualitative studies identified several factors impacting parents, including constant worry, disruption to family life and routines and social isolation, with many parents seeking professional support.⁹⁹ In a Swiss study, parents of children with Stage 3 T1D reported a greater fear of hypoglycaemia, more worry, and worse DQoL scores compared with their children.¹⁰⁶ Parent QoL in terms of family impact was worse in parents of young children (<13 years of age) than in parents of adolescents (≥13 years of age).¹⁰⁶ Additionally, siblings of children with Stage 3 T1D experience psychosocial maladjustment, with 18% of younger siblings (aged 7 to 11 years) and 20% of older siblings (aged 12 to 17 years) having increased emotional and behavioural problems.¹¹⁴ Furthermore, based on a report of four SLRs, the burden of Stage 3 T1D affects children with the condition and their carers/parents, both independently and through transactional interaction within the family unit.¹¹⁵

Interventions that improve awareness of hypoglycaemia and/or glycaemic control in people with Stage 3 T1D have been found to alleviate some of the humanistic burden associated with T1D based on evidence from the UK.¹¹⁶⁻¹¹⁸ Continuous or flash glucose monitoring has led to reductions in diabetes-related distress¹¹⁶ and improvements in insulin treatment satisfaction in adults.¹¹⁷ Structured education programmes have resulted in improved QoL in parents of children with Stage 3 T1D.¹¹⁸ However, glycaemic targets may not be attained by all people with Stage 3 T1D with currently available interventions, which may worsen the existing clinical and humanistic burden experienced by these individuals.²² The management of Stage 3 T1D is complex compared with other chronic conditions, which can place additional burden on the individual in terms of understanding their condition, changing their behaviours, and administering treatment (see Sections B.1.3.4.2 and B.1.3.4.3 for more information on treatment of Stage 3 T1D and its limitations).²²

In conclusion, even if blood glucose levels are typically within the recommended target range, there is still substantial humanistic burden associated with Stage 3 T1D and the reality of lifelong daily disease management,¹ with reduced QoL compared with the general population.¹²⁻¹⁴

B.1.3.3.3 *Economic burden of Stage 3 T1D*

The economic burden of Stage 3 T1D is substantial, costing the UK healthcare system an estimated £1.6 billion in 2021/2022 (calculated as £4,982.63 per patient per year, equivalent to £415.22 per patient per month) in a recent review of UK data sources.¹¹⁹ Ongoing management and T1D-related complications drive the majority of these costs (74% and 25%, respectively).¹¹⁹

Total per person annual hospital costs associated with Stage 3 T1D are substantially higher compared with total hospital costs for individuals without T1D in the UK.¹⁵ In an analysis of 2017-2018 hospital data from the National Health Service (NHS) in England, total annual hospital costs were £3,280 per person for Stage 3 T1D compared with £560 per person for individuals without diabetes.¹⁵ Individuals with Stage 3 T1D also required 5.9 times more secondary care than those without diabetes, which was largely due to emergency and non-elective care.¹⁵

UK clinical experts indicated in an advisory board convened by Sanofi in May 2024 that they expect that annual costs of care per person with Stage 3 T1D have increased with increasing utilisation of technology (i.e., HCL systems) and its associated costs.^{8,70,71} Although HCL systems are considered the most effective type of exogenous insulin management in terms of lowering the risk of hypoglycaemia and providing flexibility for managing carbohydrate intake, these systems are the most expensive available continuous insulin delivery regimen.²² NHS England has set out a 5-year strategy for implementing HCL systems according to the NICE recommendations made in December 2023.⁷¹

The indirect costs of Stage 3 T1D are also high, driven by costs associated with mortality, work productivity loss and caregiving.³⁹ In the UK, total indirect costs for Stage 3 T1D in 2010-2011 were estimated to be £899,238,255, most of which were attributed to deaths (£560,343,917).³⁹ Work productivity loss as a result of sick days and presenteeism (loss of productivity while at work) contributed £94,557,277 and £91,045,606, respectively, to indirect costs.³⁹ Informal caregiving for people with Stage 3 T1D was estimated to cost £153,291,454 based on the opportunity costs of an equivalent home care service.^{39,120}

B.1.3.4 Clinical pathway of care and teplizumab place in therapy

B.1.3.4.1 Management of Stage 2 T1D in the UK

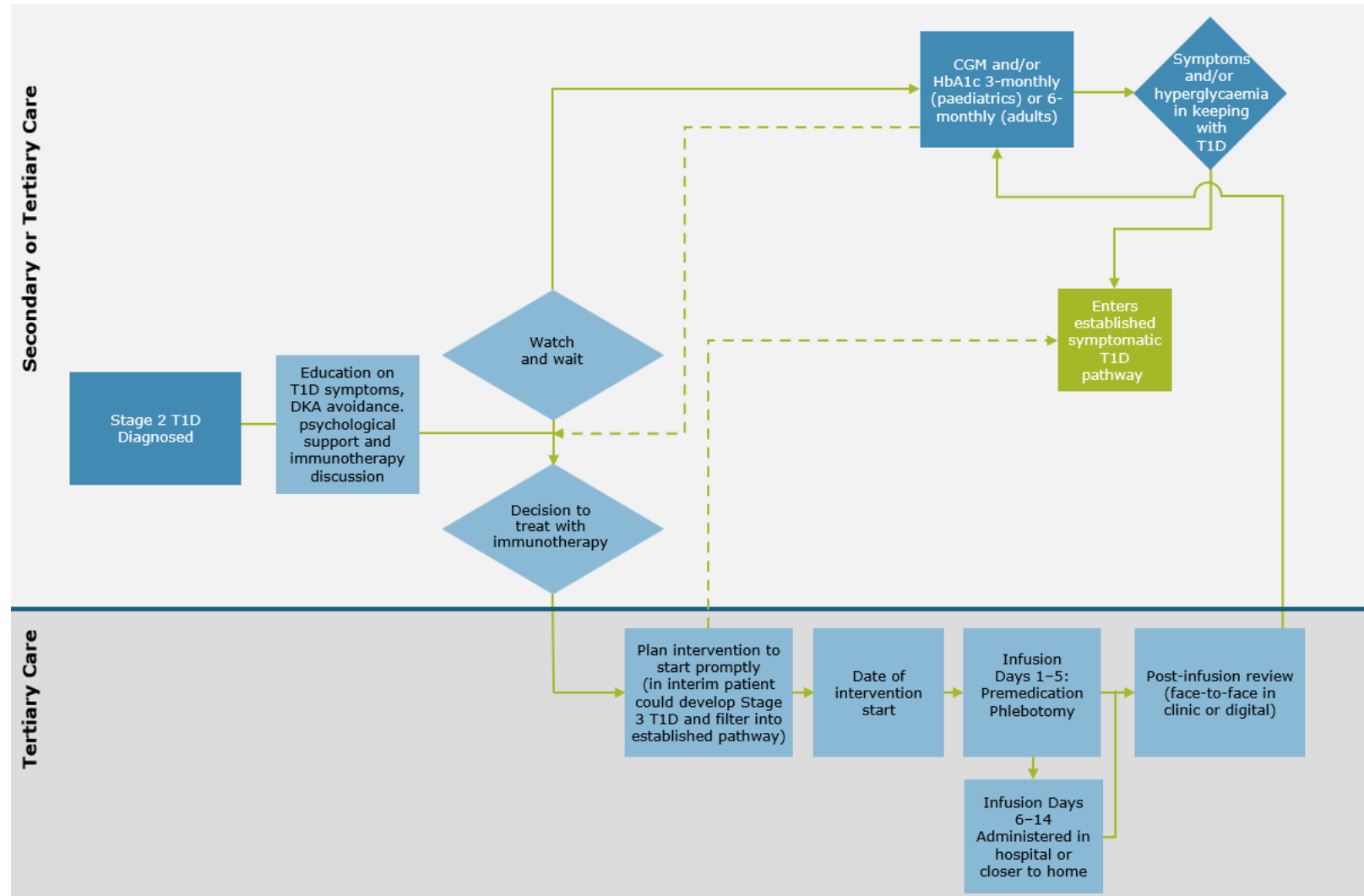
At the point of submission, there are no specific UK or NHS guidelines on the management of Stage 2 T1D published. The ISPAD Clinical Practice Consensus Guidelines recommend that children with Stage 2 T1D should be monitored for progression to Stage 3 T1D.¹ More detailed recommendations, including monitoring of adults, are provided by 2024 international consensus monitoring guidelines endorsed by the ADA and the EASD (described above).²⁰ These international guidelines recommend metabolic monitoring (i.e., HbA1c levels) to confirm glycaemic status in individuals with Stage 2 T1D, every 3 months in paediatrics and every 6 months in adults.²⁰ The guidelines also recommend education and psychosocial support for individuals with Stage 2 T1D and their family members.²⁰ In countries with approved therapeutic options for Stage 2 T1D or locations with access to intervention studies, children and adults with Stage 2 T1D should be referred to a clinical centre with expertise in the specific treatment.²⁰

In line with the international monitoring guidelines, paediatric and adult diabetes clinicians in England indicated that individuals with Stage 2 T1D should undergo glycaemic monitoring in an advisory board convened by Sanofi in July 2024.²¹ The clinicians specified that adults with Stage 2 T1D should be monitored every 6 months, with more frequent monitoring for children (at least every 3 months).²¹ The clinicians noted that existing presymptomatic T1D clinics are well-placed to develop knowledge for optimal monitoring protocols.²¹ The clinicians also highlighted the need for education and psychological support for individuals with Stage 2 T1D and their families, in accordance with the international monitoring guidelines.²¹

Although the 2021 EASD Consensus Report for the management of T1D in adults acknowledged that immunotherapies were in development for Stage 2 T1D to delay progression to Stage 3 T1D, the report did not provide any formal recommendations for the management of Stage 2 T1D.²² There are no interventions recommended by EASD, NICE, or ISPAD for delaying progression from Stage 2 to Stage 3 T1D.^{1,22,27} In 2023, the ADA updated their standards of care in diabetes to include consideration of pharmacologic intervention to delay the onset of Stage 3 T1D (Section B.1.3.4.4).¹⁹

The proposed clinical pathway of care based on best practices for Stage 2 T1D in the UK is shown in Figure 2, including the positioning of teplizumab (discussed further in Section B.1.3.4.4).

Figure 2 Proposed clinical pathway of care for Stage 2 T1D in the UK, including the positioning of teplizumab



CGM = continuous glucose monitoring; DKA = diabetic ketoacidosis; HbA1c = glycosylated haemoglobin; T1D = type 1 diabetes; UK = United Kingdom
Source: Data on File - Sanofi 2024²¹

B.1.3.4.2 *Management of Stage 3 T1D in the UK*

The main goal of treatment for Stage 3 T1D is achieving optimal blood glucose levels through the use of insulin treatment, to limit the occurrence of hypoglycaemic events.²⁷ Frequent BGM is important in the management of Stage 3 T1D, to guide insulin dosage, food intake and prevention of hypoglycaemia with physical activity.^{22,27}

Sufficient glycaemic control may be achieved from intensive insulin management, i.e., multiple daily injections (e.g., basal-bolus regimen) or insulin pump therapy, as recommended by NICE.^{22,27} Insulin replacement regimens aim to reproduce the endogenous insulin production usually carried out by the pancreas.²² NICE recommends the use of HCL systems in adults with Stage 3 T1D who have an HbA1c of ≥ 58 mmol/mol (7.5%) or disabling hypoglycaemia, and in all children and young people with Stage 3 T1D (irrespective of HbA1c).⁷⁰

NICE and EASD also recommend diabetes self-management education and support programs, with a goal to communicate the importance of nutrition, carbohydrate counting and physical activity in achieving better management of blood glucose levels.^{22,27}

B.1.3.4.3 *Limitations and burden of Stage 3 T1D management*

As described in Section B.1.3.3.1, management of Stage 3 T1D can be complex and burdensome, including BGM, carbohydrate counting, exercise and exogenous insulin, as well as attending self-management education and support programmes.²⁰ Being faced with this at diagnosis can be overwhelming for individuals with T1D and their carers/parents, and psychological support may be required.²¹

Burden of technology in Stage 3 T1D management

The use of technology in Stage 3 T1D management may convey its own burden on people with the condition.^{121,122} People with Stage 3 T1D and carers/parents of children with Stage 3 T1D in the UK have reported frustrations with wearing and calibrating a CGM device,¹²¹ as well as lacking confidence in adjusting insulin dosing and analysing CGM data without support from a healthcare provider (HCP).¹²¹ Device alarms in particular had negative impacts on the daily lives of people with Stage 3 T1D, causing sleep interruptions and distractions at school or at work, as well as negative impacts on individuals' emotional state by constantly reminding them of their condition and their failure to manage it.¹²¹ The easy access to a wealth of information that is provided by CGM can also be psychologically burdensome, leading some individuals to become fixated on measuring and correcting their levels and to develop rigid routines.^{123,124}

Carers/parents in the US who chose not to have their children use an insulin pump to administer insulin (instead of injection therapy) expressed concerns related to physical interference (i.e., issues arising from wearing the device), therapeutic effectiveness (i.e., hypo- or hyperglycaemia while using the pump, complicated instructions for using the pump) and cost.¹²² Carers/parents and partners/spouses of individuals with Stage 3 T1D are also impacted by the burdens of technology, such as sleep disturbance as a result of device alarms.¹²⁵

Equality issues in Stage 3 T1D management

Equality concerns persist with regards to current management of Stage 3 T1D, including issues with access to technology and appropriate care; for example, use and uptake of HCL systems could be impacted by variability in the availability of and access to training for individuals with Stage 3 T1D.⁷⁰ Additionally, in the May 2024 advisory board convened by Sanofi, UK clinical experts raised equality concerns that HCL systems would not be suitable or accepted in all individuals, particularly among the estimated 10% to 15% of people with the poorest glycaemic control (i.e., with the highest HbA1c).⁸ Thus, not all individuals with Stage 3 T1D will eventually transition to an HCL system; individuals using other diabetes management technologies in the UK may not qualify for NHS funding and may face out-of-pocket costs.¹²⁶ Additionally, the recommendations for use of HCL systems introduce the potential for inequality in adults, as HCL is only recommended in those who have an HbA1c of ≥ 58 mmol/mol (75%), or have disabling hypoglycaemia, despite best possible management.⁷⁰

Limitations of standard of care for Stage 3 T1D

The current standard of care for Stage 3 T1D, insulin replacement therapy,^{1,22,27} does not target the underlying pathophysiology and cannot restore the body's own insulin production capacity, with insulin-producing beta-cells reaching a terminal decline when endogenous insulin needs replacing (as depicted in Figure 1).

Current insulin treatments for Stage 3 T1D are associated with adverse events (AEs), e.g. weight gain, which negatively impact the daily lives of people with the condition.^{22,27,105,107}

The main risk of insulin treatment is hypoglycaemia (due to poor glycaemic control resulting from the (in)ability of the individual to adjust insulin dose),^{22,27} which is associated with increased rates of acute and long-term complications. These are, in turn, associated with increases in healthcare resource utilisation (HCRU) and direct costs.¹²⁷ Severe

hypoglycaemia and hypoglycaemia requiring assistance have been found to worsen HRQoL and/or DQoL in people with Stage 3 T1D in Italy and the US.^{105,107}

B.1.3.4.4 Proposed teplizumab place in therapy

There is currently no treatment available in the UK to delay the onset of Stage 3 T1D for people with Stage 2 T1D, and there is a substantial unmet need for disease-modifying therapies in this setting.

Worldwide, teplizumab is the first and only therapy approved to delay the onset of Stage 3 T1D in people with Stage 2 T1D.¹⁶ Teplizumab is currently approved in the US, Israel and United Arab Emirates (UAE).¹⁶⁻¹⁸ Since its approval in the US, teplizumab has been incorporated into the ADA standards of care, offering for the first time a step change in management of individuals with Stage 2 T1D.¹⁹ Teplizumab has the potential to delay the need for initiation of insulin replacement therapy and the burden associated with management of Stage 3 T1D, thereby improving long-term outcomes and reducing the risk of complications.

Teplizumab is the first disease modifying immunotherapy available for T1D, enabling the transition from reactive treatment to a future of proactive disease delay. Given the momentum behind immunomodulating therapies for the future of T1D treatment,^{128,129} investment in the pathway for teplizumab administration ensures any future treatments for pre-symptomatic disease will be more easily incorporated into UK clinical practice.

Individuals in the UK place significant value on having treatments for T1D that can delay the need for insulin,²⁶ which suggests that a disease-modifying therapy such as teplizumab would be well-received among individuals with Stage 2 T1D. A standard gamble utilities study in the UK published in 2010 found that adults with T1D, parents of children with T1D, and the general public valued reducing or avoiding the need for insulin injections.²⁶ In a more recent US survey, parents who were asked to assume that their child would become insulin dependent in 6 months to 2 years indicated a preference for a treatment that delays monitoring and dependence on insulin over monitoring alone.¹³⁰ The most important treatment attributes cited by parents, regardless of whether their child had T1D, included delaying insulin dependence from 6 months to 4 years (hypothetical timeframe utilised by the survey) and reducing the risk of long-term complications.¹³⁰ Delaying the progression from Stage 2 to Stage 3 T1D could delay the complications and damage due to dysglycaemia associated with Stage 3 T1D,⁵ postponing the need for exogenous insulin to achieve optimal blood glucose levels.²⁷

The anticipated indication of teplizumab in the proposed clinical pathway of care is for individuals with Stage 2 T1D to delay the onset of Stage 3 T1D (Figure 2). Diabetes clinicians in England who participated in the July 2024 advisory board convened by Sanofi anticipate that individuals with Stage 2 T1D will be managed in tertiary care centres and be followed in tertiary or secondary care centres.²¹ Teplizumab intravenous (IV) infusions are expected to take place in tertiary care settings, with most individuals anticipated to be suitable for administration in a closer-to-home setting, to offer additional flexibility and to address potential inequalities in access, if deemed acceptable by the individual and their clinician.²¹ For those wishing to have care in a closer-to-home setting, it is expected that days 1 to 5 of the infusion will be in a hospital setting, with days 6-14 administered closer-to-home.

B.1.4 Equality considerations

Potential equality issues have been identified by NICE in previous T1D-related assessments, including those related to socioeconomic status (SES), ethnicity, age, having cystic fibrosis-related T1D, and having other conditions that prevent or hinder optimal use of an HCL device (e.g., skin conditions or allergies, learning difficulties, vision or hearing impairments, blood clotting disorders).^{70,131-133} Individuals with Stage 3 T1D are also more likely to have other autoimmune diseases which may impose additional burdens beyond those of T1D itself.^{81,134}

B.1.4.1 Socioeconomic status

Among people with Stage 3 T1D, low SES is frequently associated with poorer outcomes in terms of acute and long-term complications (including DKA in some studies) and death.¹³⁵ People with Stage 3 T1D and lower SES tend to have worse glycaemic control,¹³⁶ lower participation in structured diabetes education¹³⁷ and reduced attendance at specialist diabetes services than people with higher SES.¹³⁸ In an interview study, individuals with Stage 3 T1D and low SES in the UK highlighted that work commitments are a common barrier to attending specialist services and structured education, both of which are associated with improved outcomes in Stage 3 T1D.¹³⁸ It is reasonable to assume that these impediments also apply to carers/parents of children living with Stage 2 T1D.

It is possible that delaying the onset of symptomatic Stage 3 T1D among people with Stage 2 T1D could provide valuable additional time for individuals of low SES to prepare for diabetes management (including attending structured education and specialist services) with more flexibility; delaying the onset of T1D symptoms also extends the window of time for

HCPs to engage with these individuals and establish support systems before the urgencies of managing hyperglycaemia set in.

B.1.4.2 Ethnicity

Differences between different ethnicities in clinical outcomes and use of CGM and insulin pumps have been observed in the UK and the US.^{73,139}

- An observational study of 443 children aged <19 years in East London between January 2005 and December 2015 found that children in ethnic minority groups presented with higher mean HbA1c levels at diagnosis than White children.¹³⁹
- The NPDA found that the use of real-time CGM and insulin pumps was higher in White children and young people with Stage 3 T1D in England and Wales in 2022-2023 compared with children and young people of Black, Asian or other ethnicities.⁷³

Careful consideration should be given to the equitable management of these individuals.

B.1.4.3 Impact of T1D on adolescents and young adults

Younger individuals with Stage 3 T1D may present with greater needs due to the nature of the disease course or challenges with disease management.⁸ The NHS RightCare Children and Young People Diabetes Toolkit reported that T1D outcomes decline through adolescence based on data from 2022-2023, and the highest rates of hospital admissions and repeat admissions are observed when children and young adults are transitioning to adult care.¹⁴⁰ Additionally, median HbA1c and the proportion of people achieving HbA1c treatment targets deteriorate steadily between age 15 and 20 years.¹⁴⁰ DKA emergency admissions with an existing T1D diagnosis increases steeply after age 10.¹⁴⁰ UK clinical experts who participated in an advisory board convened by Sanofi in May 2024 also indicated that teenagers and young adults are at risk of more severe disease than those diagnosed at an older age, with poor glycaemic control frequently observed among teenagers.⁸ Furthermore, advisory board participants noted a lack of interest in using technology for disease management among individuals aged 19 to 25 years.⁸ Ultimately, children and young adults with Stage 3 T1D have an increased risk of premature death compared with the general population, with a HR for mortality of 1.57 in a Swedish study based on 2000 to 2019 data.⁸¹

Therefore, delaying the onset of Stage 3 T1D could be particularly valuable in younger individuals diagnosed with Stage 2 T1D who will otherwise live with the burden of T1D for

the longest duration, potentially including during key educational milestones. Experts who participated in the May 2024 advisory board convened by Sanofi noted that by delaying Stage 3 T1D, younger people and their families gain more time to be better equipped to manage the disease effectively, both in terms of their cognitive development and preparation time.⁸

B.1.4.4 Other autoimmune diseases

Compared with the general population, Stage 3 T1D is associated with increased risk of having other autoimmune diseases, including hypothyroidism, coeliac disease, psoriasis, and inflammatory bowel disease. Data on the risk of people with Stage 3 T1D in the UK having other autoimmune diseases are limited; however, 1 in 5 adults with Stage 3 T1D in Finland and 1 in 5 children and adolescents with Stage 3 T1D in Sweden have been found to have ≥ 1 additional autoimmune disease.^{81,134} The collective burden imposed by having multiple autoimmune diseases including Stage 3 T1D⁸¹ could potentially be postponed by delaying the onset of Stage 3 T1D among people with Stage 2 T1D.

B.2 Clinical effectiveness

Teplizumab will be the first and only disease-modifying therapy to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D in the UK, thus postponing the need for insulin replacement and the onset of long-term complications associated with Stage 3 T1D.

Summary of methodology of relevant clinical effectiveness evidence (TrialNet [TN]-10 trial)

- A systematic literature review (SLR) identified one relevant randomised controlled trial (RCT) entitled “Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus,” also referred to as TN-10.
- TN-10 was a phase II, randomised, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of a single course of teplizumab (n=44) vs. placebo (n=32) administered once daily via IV infusion for 14 consecutive days in people with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D.¹⁴¹ The primary endpoint was the time from randomisation to the onset of Stage 3 T1D (determined with the use of criteria from the ADA).¹⁴¹

Clinical effectiveness results of the TN-10 trial

- The median time to onset of Stage 3 T1D was statistically significantly longer in individuals treated with teplizumab vs. individuals treated with placebo in the primary analysis with a median follow-up of 745 days (4.1 vs. 2.1 years; difference: 2.0 years; HR: 0.41; p=0.0066).¹⁴²
- In an extended follow-up analysis after participants had been followed for a median of 923 days, individuals treated with teplizumab also had a statistically significantly longer median time to onset of Stage 3 T1D than individuals treated with placebo (5.0 vs. 2.3 years; difference: 2.7 years; HR: 0.457; p=0.01).¹⁴³
- C-peptide response was preserved with teplizumab as shown by significantly higher average on-study C-peptide area under the concentration–time curve (AUC) vs. placebo (p=0.006) and a significant reversal of the decline in C-peptide AUC seen with placebo during the first 6 months of treatment (p=0.0015).¹⁴³

Adverse reactions (TN-10 trial and integrated safety analysis)

- Teplizumab has been studied for more than 20 years in approximately 1,000 children and adults,^{144,145} and has demonstrated an acceptable safety profile in TN-10 consistent with other clinical trials of teplizumab.^{141,144} The majority of AEs in TN-10 were grade 1 or 2 in severity and were resolved without intervention.¹⁴⁴

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify evidence in children (≥8 years old) and adults on the clinical efficacy and safety of treatments for the delay of Stage 3 T1D in:

- People at risk of developing T1D, including but not limited to:
 - Having a relative with T1D
 - Abnormal glucose-tolerance by OGTT
 - Presence of at least two confirmed diabetes autoantibodies
- People diagnosed with Stage 2 T1D.

This search strategy was designed to include clinical trials in the population of interest for this submission as outlined in the final NICE scope (Section B.1.1).

Electronic databases were searched from inception to 27 June 2024. Grey literature searches were performed from 2021 onwards. These included searches of conference proceedings^c, health technology assessment and regulatory websites and clinical trial registries.

The SLR identified one unique RCT entitled “Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus” (Provention Bio TrialNet [TN]-10 trial; NCT01030861) reported across four publications and one unpublished clinical study report (CSR). TN-10 was a multicentre, phase II, randomised, placebo-controlled, double-blind trial investigating treatment with teplizumab in people with Stage 2 T1D. Included participants were people with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D at the time of randomisation. The main clinical efficacy and safety findings from TN-10 are presented in Section B.2.6 and Section B.2.10.

Full details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix D.1.

B.2.2 List of relevant clinical effectiveness evidence

In line with findings from the clinical SLR described above, the direct evidence for the clinical effectiveness of teplizumab in delaying the onset of Stage 3 T1D in people with Stage 2 T1D comes from the phase II TN-10 trial (Table 5).¹⁴¹ Information in this submission on TN-10 is based on the following sources identified by the SLR:

- Herold et al. (2019)¹⁴¹ and the unpublished CSR dated 03 September 2020,¹⁴² which reported the primary analysis.
- Sims et al. (2021),¹⁴³ which reported an extended follow-up analysis for participants who had not progressed to Stage 3 T1D.

Note that the TN-10 trial was designed prior to staging nomenclature being widely accepted in clinical practice;⁹ therefore, these sources use the terms “nondiabetic, high-risk” to describe Stage 2 T1D and “clinical T1D” to describe Stage 3 T1D. This submission uses the Stage 2 and Stage 3 T1D terminology, as it increases clarity of the relevant patient population in relation to this submission, and is aligned with the final NICE scope.

^c American Diabetes Association (ADA), Diabetes Canada/Canadian Society of Endocrinology and Metabolism (CSEM), European Foundation for the Study of Diabetes (EFSD), ISPAD, EASD, Advanced Technologies and Treatments for Diabetes (ATTD) and European Society for Paediatric Endocrinology (ESPE).

Table 5. Clinical effectiveness evidence for TN-10

Study	Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk" (NCT01030861; TN-10)
Study design	Phase II, randomised, placebo-controlled, double-blind trial
Population	People with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D Participants had to have had ≥2 diabetes-related autoantibodies detected in two samples obtained within 6 months before randomisation, and evidence of dysglycaemia during an OGTT
Intervention(s)	Teplizumab, as a single dose given daily according to the following schedule: • Day 1: 51 µg/m² of BSA • Day 2: 103 µg/m² of BSA • Day 3: 207 µg/m² of BSA • Day 4: 413 µg/m² of BSA • Days 5 to Day 14: 826 µg/m² of BSA
Comparator(s)	Placebo
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	Not applicable
Reported outcomes specified in the decision problem	• Progression from Stage 2 to Stage 3 T1D (specifically, time to progression and rate of progression) • Levels of stimulated C-peptide • Mortality • Adverse effects of treatment
All other reported outcomes	• Insulin secretion
Sponsor	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

BSA = body surface area; DKA = diabetic ketoacidosis; OGTT = oral glucose-tolerance test; T1D = type 1 diabetes

Source: Herold 2019¹⁴¹

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

B.2.3.1 Summary of methodology

Participants in TN-10 were identified through the ongoing TrialNet Natural History/Pathway to Prevention study (TN-01; NCT00097292) that included relatives of people with Stage 3 T1D who were diagnosed with Stage 2 T1D.¹⁴⁶ Eligible participants were then randomised 1:1 to receive either teplizumab or placebo via IV infusion.¹⁴¹ For the duration of TN-10, participants underwent close monitoring for the progression to Stage 3 T1D.¹⁴¹

TN-10 was conducted at sites in the US, Canada, Australia and Germany.¹⁴² The primary analysis was conducted based on data from July 2011 through November 2018.^{141,142} When the TN-10 trial ended in June 2019, participants who had not progressed to Stage 3 T1D

continued to receive follow-up OGTT monitoring.¹⁴³ An extended follow-up analysis was conducted based on data through March 2020 for these participants.¹⁴³

The TN-10 trial methodology is summarised in Table 6.

Table 6. Summary of trial methodology

Trial number (acronym)	NCT01030861 (TN-10)
Location	US, Canada, Australia, Germany
Trial design	Phase II, randomised, placebo-controlled, double-blind
Eligibility criteria for participants	• People with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D at the time of randomisation • Presence of ≥2 or more diabetes-related autoantibodies detected in two samples obtained within 6 months before randomisation • Evidence of dysglycaemia during an OGTT
Settings and locations where the data were collected	Outpatient sites
Trial drugs	• Intervention: Teplizumab (n=44) • Comparator: Placebo (n=32)
Permitted and disallowed concomitant medication	• Prophylactic medications: Ibuprofen and antihistamine prior to infusion on the first 5 days of treatment; further dosing of ibuprofen, antihistamines and/or acetaminophen as needed • Prohibited medications: Steroids or other immunosuppressive agents for the duration of the trial; live vaccinations for one year after treatment; killed virus vaccine <4 weeks after treatment
Primary outcomes (including scoring methods and timings of assessments)	Time from randomisation to the onset of Stage 3 T1D (per ADA criteria), based on glucose testing, or the presence of unequivocal hyperglycaemia with acute metabolic decompensation (DKA); one of the following criteria must have been met on two occasions ≤1 day apart: • Symptoms of diabetes plus casual plasma glucose concentration >200 mg/dL (11.1 mmol/L), regardless of the time since last meal FPG ≥126 mg/dL (7 mmol/L) • 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) Glucose testing (e.g., OGTT) was performed 3 months and 6 months after the infusions and every 6 months thereafter, with random screening glucose levels evaluated at 3-month intervals.
Other outcomes specified in the scope	• Mortality
Pre-planned subgroups	• Age • Sex • BMI z score • HLA type • Baseline C-peptide level • Baseline glucose level • Autoantibodies
Analyses	• Primary analysis (data cut-off of 30 November 2018; median follow-up of 745 days) • Extended follow-up analysis (data cut-off of March 2020; median follow-up of 923 days)

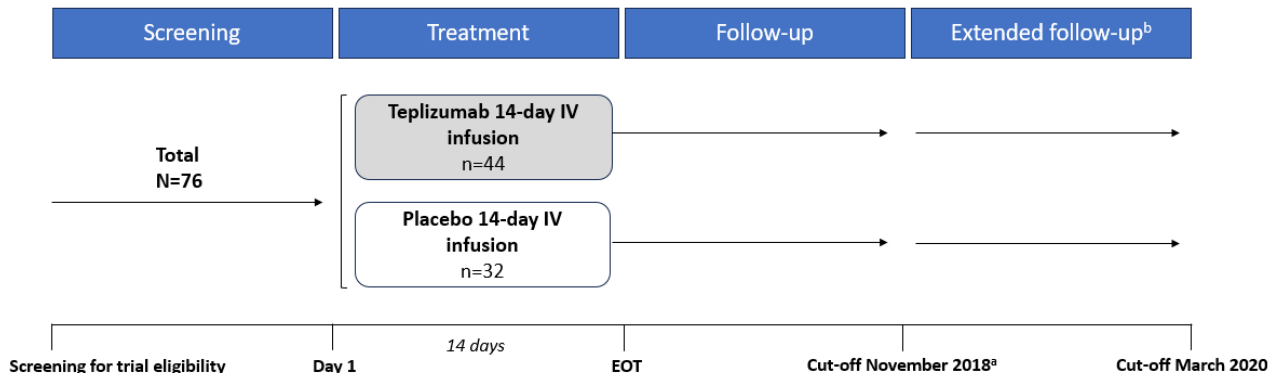
ADA = American Diabetes Association; BMI = body mass index; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; HLA = human leukocyte antigen; OGTT = oral glucose-tolerance test; T1D = type 1 diabetes
Source: Herold 2019;¹⁴¹ Data on File – Provention Bio Inc. 2020;¹⁴² ClinicalTrials.gov 2024.¹⁴⁷

B.2.3.2 Trial design

TN-10 was a phase II, randomised, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of teplizumab in people with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D.¹⁴¹

A total of 76 eligible participants identified from the TrialNet Natural History/Pathway to Prevention study (TN-01) were randomly assigned in a 1:1 ratio to receive either teplizumab (n=44) or placebo (n=32) for 14 days in an outpatient setting as part of the phase II TN-10 trial (Figure 3).¹⁴¹ Randomisation was stratified according to TrialNet site, age (<18 years or ≥18 years) and second OGTT results before treatment (i.e., impaired tolerance, normal tolerance or diabetes).¹⁴¹ Participants were followed up in the TN-10 trial until at least 40 participants were confirmed to have Stage 3 T1D as this cut-off provides 80% power to detect a reduction of 60% in the risk of Stage 3 T1D (see further details in Table 11).¹⁴¹ Following this, participants who had not progressed to Stage 3 T1D by the end of the TN-10 trial continued to received follow-up OGTT monitoring.¹⁴³

Figure 3. Trial design of TN-10 in the primary analysis and extended follow-up analysis



^a Data cut-off date for the primary analysis of TN-10
^b Data cut-off date for the extended follow-up analysis of TN-10
EOT = end of treatment; IV = intravenous; T1D = type 1 diabetes
Source: Herold 2019;¹⁴¹ Sims 2021.¹⁴³

B.2.3.3 Participant eligibility

Eligible participants enrolled in TN-10 were people with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D.¹⁴¹ This approach was undertaken in order to facilitate identification of participants given the lack of a general population early detection programme. In line with ISPAD diagnostic criteria for Stage 2 T1D,¹ participants were required to have ≥2 diabetes-related autoantibodies detected in two samples obtained within 6 months before randomisation, as well as evidence of dysglycaemia during an OGTT within 52 days before enrolment into the trial.¹⁴¹ Prior use of anti-CD3 treatment was prohibited at any time prior to randomisation and throughout the trial period.¹⁴²

Key inclusion and exclusion criteria for TN-10 are summarised in Table 7.

Table 7. Eligibility criteria for TN-10

Inclusion criteria	Exclusion criteria
• People with Stage 2 T1D who were relatives of people with Stage 3 T1D • Aged ≥ 8 years • Weight ≥ 26 kg at randomisation • OGTT demonstrating abnormal glucose^a tolerance within 7 weeks (52 days) of the baseline visit (visit 0). Abnormal glucose-tolerance was defined as: ◦ FPG ≥ 110 mg/dL and < 126 mg/dL (6.1 to 6.9 mmol/L), or ◦ 2-hour plasma glucose ≥ 140 mg/dL and < 200 mg/dL (7.8 to 11.1 mmol/L), or ◦ 30, 60, or 90-minute value on OGTT ≥ 200 mg/dL • Positive for ≥ 2 diabetes-related autoantibodies in two separate samples ◦ The autoantibodies to be confirmed were anti-GAD65, IA2 or ICA512, mIAA, ZnT8 antibody and/or ICA	• Participants aged ≥ 18 years with a diagnosis of diabetes or has a screening OGTT in which: ◦ FPG was ≥ 126 mg/dL, or ◦ 2-hour plasma glucose was ≥ 200 mg/dL • Participants aged < 18 years with a diagnosis of diabetes or has a screening random glucose ≥ 200 mg/dL • Abnormal blood counts or laboratory chemical values including: ◦ Lymphopenia ($< 1,000$ lymphocytes/μL) ◦ Neutropenia ($< 1,500$ PMN/μL) ◦ Thrombocytopenia ($< 150,000$ platelets/μL) ◦ Anaemia (haemoglobin < 10 g/dL) ◦ AST or ALT $> 1.5 \times$ ULN ◦ Total bilirubin $> 1.5 \times$ ULN with the exception of subjects with the diagnosis of Gilbert's syndrome who might be eligible if they had no other causes leading to hyperbilirubinemia ◦ INR > 0.1 above ULN • Vaccination with a live virus within 8 weeks or a killed virus within 4 weeks • Positive purified protein derivative test • Any of the following conditions: ◦ Current or past HIV, hepatitis B or hepatitis C infection ◦ History of asthma or atopic disease requiring chronic treatment ◦ Untreated hypothyroidism or active Graves' disease ◦ Chronic active infection other than localised skin infections ◦ Clinical evidence of acute infection with EBV or CMV ◦ Infectious mononucleosis within the prior 3 months ◦ Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject • Current pregnancy/lactation or anticipated pregnancy • Chronic use of steroids or other immunosuppressive agents • Prior anti-CD3 treatment • Administration of an mAb within the year before randomisation • Current use of non-insulin pharmaceuticals that affect glycaemic control

^a In this study, fasting glucose levels of 110-125 mg/dL qualified subjects as having abnormal glucose-tolerance, as it reflects the criteria used for entry into the DPT-1 study (National Diabetes Data Group 1979), which was used for the calculation of Stage 3 T1D risk in TN-10.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CD3 = Cluster of differentiation 3; CMV = cytomegalovirus; EBV = Epstein-Barr virus; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; HIV = human immunodeficiency virus; IA2 = islet antigen 2 antibody; ICA = islet cell antibodies; INR = international normalisation ratio; mAb = monoclonal antibody; mIAA = micro insulin autoantibody; OGTT = oral glucose-tolerance test; PMN = polymorphonuclear neutrophils; T1D = type 1 diabetes; ULN = upper limit of normal; ZnT8 = zinc transporter 8

Source: Herold 2019.¹⁴¹

B.2.3.4 Trial drugs and concomitant medications

B.2.3.4.1 Trial drugs

Participants in TN-10 were randomised to receive either teplizumab or placebo (saline) via IV infusion for 14-days in the outpatient setting.¹⁴¹ Teplizumab was given according to the following regimen:¹⁴¹

- a dose of 51 mcg/m² of body surface area (BSA) on day 1
- a dose of 103 mcg/m² of BSA on day 2
- a dose of 207 mcg/m² of BSA on day 3
- a dose of 413 mcg/m² of BSA on day 4
- followed by a dose of 826 mcg/m² of BSA on each of days 5 through 14.

It should be noted that the manufacturing process for teplizumab was updated and moved to a new facility in 2018. This resulted in a new drug product being manufactured, further referred to as the commercial product. To demonstrate the pharmacokinetic (PK) comparability between the clinical trial product and the planned commercial product, a single dose comparability study and a PK sub-study was conducted. It highlighted the lower drug exposure (AUC_{inf}) of the commercial product vs. the clinical trial product. This resulted in the validation of an alternative 14-day dosing regimen of the commercial product with a higher cumulative dose to match the drug exposure of the TN-10 clinical trial product. Aligned with this validation, the anticipated licensed dosing regimen for teplizumab is:³⁴

- A dose of 65 mcg/m² BSA on day 1
- A dose of 125 mcg/m² BSA on day 2
- A dose of 250 mcg/m² BSA on day 3
- A dose of 500 mcg/m² BSA on day 4
- A dose of 1,030 mcg/m² BSA on days 5 through 14

In a review by the US Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology (BLA761183), the adjusted dosing regimen for the commercial product matched the total exposure (AUC_{inf}), peak concentration (C_{max} after the last dose) as well as trough concentrations after the last dose (C_{trough} after the last dose) in comparison to the clinical trial product during the 14-day regimen.¹⁴⁸

B.2.3.4.2 Concomitant medications

Ibuprofen and antihistamine were administered prophylactically prior to teplizumab/placebo infusion on the first 5 days of treatment.¹⁴² Further dosing of ibuprofen, antihistamines and/or acetaminophen could be used as needed for fever, malaise, headache, arthralgia or rash.¹⁴²

Concomitant medications were assessed and recorded during the TN-10 trial.¹⁴²

Steroids or other immunosuppressive agents were prohibited for the duration of the trial in order to reduce the risk of infection and to prevent possible impact on progression to Stage 3 T1D.¹⁴² Additionally, participants were instructed to not receive live vaccinations for one year after treatment or vaccinations with a killed virus vaccine <4 weeks after treatment.¹⁴²

B.2.3.5 Outcomes used in the economic model or specified in the scope, including primary outcome

Primary and secondary study objectives and endpoints in TN-10 are summarised in Table 8.

The primary endpoint in TN-10 was the time from randomisation (day 0 visit) to the onset of Stage 3 T1D (determined with the use of criteria from the ADA).¹⁴¹ The TN-10 primary endpoint is the key outcome used in the cost-effectiveness analysis described in Section B.3.

C-peptide levels were assessed as a secondary endpoint to determine whether treatment with teplizumab was superior to placebo with respect to C-peptide responses to oral glucose.^{141,143} C-peptide, the pro-peptide of insulin, is often used as a surrogate marker for beta-cell function and endogenous insulin production given its longer half-life than insulin.^{149,150} Increased C-peptide levels are indicative of more residual beta-cell mass and endogenous insulin production,^{141,143} which is associated with better glycaemic control, lower HbA1c, lower daily exogenous insulin requirements and reduced rates of severe hypoglycaemia.²⁸⁻³¹ Increased C-peptide levels have also been associated with a decreased risk of long-term complications, such as cardiovascular disease.^{29,32,33}

Other secondary endpoints included assessment of AEs.^{141,143}

Additionally, insulin data from the OGTT were used to measure insulin secretion in TN-10;¹⁴¹ loss of early insulin secretion has been shown to reflect beta-cell dysfunction before progression to Stage 3 T1D.¹⁴³

Table 8. TN-10 trial objectives and endpoints

Objectives	Endpoints
Primary	
To determine the time from randomisation (day 0 visit) to the onset of Stage 3 T1D in participants treated with teplizumab	Time from randomisation to the onset of Stage 3 T1D
Secondary	
To determine whether treatment with teplizumab was superior to placebo with respect to C-peptide responses to oral glucose, as obtained from timed collections during longitudinal tests	C-peptide level
To compare the safety and tolerability of teplizumab to placebo	AEs

AE = adverse event; T1D = type 1 diabetes

Source: Herold 2019;¹⁴¹ Sims 2021.¹⁴³

B.2.3.6 Participant disposition

A total of 146 participants were identified from the TrialNet Natural History/Pathway to Prevention study (TN-01) trial and assessed for inclusion in TN-10.¹⁴² From this, 70 participants were excluded as they were screening failures, and thus 76 eligible participants were randomised 1:1 to receive teplizumab (n=44) or placebo (n=32).^{141,142} All 76 participants received the study treatment and were included in the intention-to-treat (ITT), full analysis set and safety populations.¹⁴²

The majority of participants completed the 14-day treatment course for both teplizumab (97.7%) and placebo (93.8%).¹⁴² The only reason for treatment discontinuation for all participants was due to protocol-specified drug withholding e.g., special circumstances, laboratory abnormalities or AEs (3.9%).¹⁴²

At the primary analysis (cut-off date 30 November 2018), 43.2% of participants in the teplizumab group and 65.6% of participants in the placebo group had completed the study (median follow-up: 745 days).¹⁴² A total of six participants from the teplizumab and placebo arms discontinued the study for the following reasons: lost to follow-up (n=1 in the placebo arm) and other (n=3 in the teplizumab group and n=2 in the placebo arm).¹⁴² Of the six participants who discontinued the study, three progressed to Stage 3 T1D prior to discontinuation (one in the teplizumab group and two in the placebo arm) and these events were included in the primary analysis.¹⁴² Table 9 summarises the participant disposition from the primary analysis.

Table 9. Disposition of participants in the primary analysis of TN-10

	Teplizumab	Placebo	Total
Screened	NA	NA	146
Randomised	44	32	76
Status at day 14			
Completed 14-day treatment course, n (%)	43 (97.7)	30 (93.8)	73 (96.1)
Discontinued from treatment course, n (%)	1 (2.3)	2 (6.3)	3 (3.9)
Protocol-specified drug withholding, n (%)	1 (2.3)	2 (6.3)	3 (3.9)
Status at time of primary analysis			
Completed study at cut-off date ^a , n (%)	19 (43.2)	21 (65.6)	40 (52.6)
Ongoing at cut-off date ^a , n (%)	22 (50.0)	8 (25.0)	30 (39.5)
Discontinued from study ^b , n (%)	3 (6.8)	3 (9.4)	6 (7.9)
Lost to follow-up, n (%)	0	1 (3.1)	1 (1.3)
Other, n (%)	3 (6.8)	2 (6.3)	5 (6.6)

^a TN-10 primary analysis cut-off date: 30 November 2018.

^b Of the six participants who discontinued from the study, onset of Stage 3 T1D occurred in two participants in the placebo group and one in the teplizumab group (i.e., the primary endpoint was met) and were therefore already included in the primary endpoint analysis before discontinuing.

NA = not applicable

Source: Data on File – Provention Bio Inc. 2020.¹⁴²

B.2.3.7 Baseline participant and disease characteristics

The baseline characteristics of participants in the primary analysis of TN-10 were generally well-balanced between treatment groups (Table 10).¹⁴¹ Most participants in the teplizumab and placebo arms were <18 years of age (66% and 81%), White (100% and 93.8%) and positive for the anti-GAD autoantibody (91% and 88%).¹⁴¹ The most common relationships participants had to people with Stage 3 T1D in the teplizumab and placebo arms were a sibling relationship (64% and 50%) followed by an offspring relation (14% and 19%).¹⁴¹

Table 10. Baseline characteristics of participants in the primary analysis of TN-10

	Teplizumab	Placebo
N	44	32
Age¹⁴¹		
Median (IQR)	14 (12, 22)	13 (11, 16)
Range	8.5, 49.5	8.6, 45.0
Age <18 years (n, %)	29 (66)	26 (81)
Male sex (n, %)	25 (57)	17 (53)
Race (n, %)¹⁴¹		
White	44 (100)	30 (93.8)
African American	0	0
Asian	0	2 (6.2)
Ethnicity (n, %)¹⁴²		
Hispanic or Latino	1 (2.3)	1 (3.1)
Non-Hispanic or Latino	43 (97.7)	29 (90.6)
Unknown	0	2 (6.3)
Relationship to person with Stage 3 T1D (n, %)¹⁴¹		
Sibling ^a	28 (64)	16 (50)

	Teplizumab	Placebo
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies^b (n, %)¹⁴¹		
Anti-GAD65, harmonised	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti-IA2, harmonised	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median autoantibodies titre (IQR)¹⁴¹		
Anti-GAD65, harmonised	240 (76.8, 464)	221 (42.3, 520)
Micro insulin	0.0070 (0.0020, 0.028)	0.0040 (0.0020, 0.0168)
Anti-IA2, harmonised	52 (0, 310)	187 (26, 253)
ICA	20 (0, 200)	80 (20, 160)
Anti-ZnT8	0.157 (0.0133, 0.496)	0.096 (0.028, 0.386)
Number of autoantibodies positive^c (n, %)¹⁴¹		
1	1 (2.4)	0
2	11 (25.0)	7 (21.9)
3	12 (27.3)	5 (15.6)
4	11 (25.0)	14 (43.8)
5	9 (20.5)	6 (18.8)
Median HbA1c (IQR) ¹⁴¹	5.2 (4.9, 5.4)	5.3 (5.1, 5.4)
C-peptide AUC Mean, Median OGTT (nmol/L) ¹⁴¹	1.76 (1.47, 2.18)	1.73 (1.44, 2.36)
HLA alleles present (n, %)¹⁴¹		
Neither DR3 or DR4	5 (11.6)	3 (9.4)
DR3 only	10 (23.3)	8 (25.0)
DR4 only	17 (39.5)	14 (43.8)

^a Participants in this category may have had more than one sibling with Stage 3 T1D.

^b Shown are the autoantibodies for which participants were positive at the time of randomisation. All participants were positive for at least two autoantibodies before randomisation.

^c This was at the time of randomisation. All subjects were positive for at least two autoantibodies prior to randomisation.

AUC = area under the concentration–time curve; GAD = glutamic acid decarboxylase; HbA1c = glycosylated haemoglobin; HLA = human leukocyte antigen; ICA = islet cell antibodies; IQR = interquartile range; OGTT = oral glucose-tolerance test; T1D = type 1 diabetes; ZnT8 = zinc transporter 8

Source: Herold 2019;¹⁴¹ Data on File – Provention Bio Inc. 2020.¹⁴²

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

A summary of the statistical analyses undertaken in TN-10 is provided in Table 11.

Table 11. Summary of statistical analyses

Item	TN-10
Hypothesis objective	The primary objective was to assess the effect of teplizumab vs. placebo on the risk of Stage 3 T1D in the ITT population based on the elapsed time from random treatment assignment to the progression to Stage 3 T1D or time of last contact. A sensitivity analysis of the primary endpoint was conducted at 5 years.
Statistical analysis	The primary analysis consisted of a one-sided Wald test using the Cox PH model, conducted in the ITT population, which included all randomised participants.
Sample size, power calculation	71 participants were to be followed until 40 participants had onset of Stage 3 T1D, providing 80% power to detect a reduction of 60% in the risk of Stage 3 T1D (HR [teplizumab vs. placebo] of 0.4) with a Wald test (one-sided alpha=0.025). Assuming a 5% drop-out rate, the study required a minimum of enrolment of 71 participants who were to be followed until 40 participants had onset of Stage 3 T1D.
Data management, patient withdrawals	All participant records are stored at the study sites and all study participant data are stored in electronic format in a secure computer system at the TrialNet Coordinating Centre. De-identified study data was shared with the drug manufacturer/IND sponsor. Participants who withdrew from the study were not replaced given the ITT approach for analyses. All data acquired prior to termination for the reasons outlined below were included in the primary analysis unless the participant withdrew consent: • Withdrawal of consent • Withdrawal by the participant • Withdrawal by the investigator • Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease
Censoring	The primary endpoint was censored at the last OGTT laboratory measurement or a visit without OGTT, whichever was later, before the subject ended study participation. A sensitivity analysis of the primary endpoint was conducted at 5 years, for which participants were censored at 5 years when the minimum number of Stage 3 T1D events were observed.
Missing data	Missing data were assumed to be missing completely at random unless there was empirical evidence to the contrary. Analysis of the primary endpoint was based on the maximum follow-up time recorded for each participant and no additional follow-up data was imputed for participants who were lost to follow-up. A complete-case analysis approach was used for analysis of secondary endpoints, in which only participants who had data for a given endpoint were included in the analysis. Imputation was used if missing at random could not be justified and for any sensitivity analyses of secondary endpoints. For covariate modelling analyses, if <10% of data is missing for the analytical cohort, missing values were assigned the mean from the known covariate cohort; if 10% to 20% of data is missing, a separate indicator for missing was included in the modelling; and if >20% of data is missing, the covariate was removed from consideration.

HR = hazard ratio; IND = investigational new drug; ITT = intention-to-treat; OGTT = oral glucose-tolerance test; PH = proportional hazards; T1D = type 1 diabetes

Sources: Herold 2019;¹⁴¹ Data on File – Provention Bio Inc. 2020.¹⁴²

B.2.4.1 Statistical analyses

The primary analysis assessed the effect of teplizumab vs. placebo on the risk of Stage 3 T1D onset in the ITT population.¹⁴¹ The cumulative incidence of Stage 3 T1D onset over time since randomisation within each treatment group was estimated using the Kaplan-Meier (KM) method (proportion surviving Stage 3 T1D-free as a function of time).¹⁴¹ The difference between groups in the cumulative incidence curves, and the associated hazard functions,

were tested with a one-sided Wald test at the 0.025 significance level using the Cox proportional hazards (PH) model with discrete time intervals at the 6-month OGTT intervals.¹⁴¹ The treatment effect (HR) of Stage 3 T1D onset between treatment arms was estimated from the PH model.¹⁴¹ The primary test of treatment effect was adjusted for design strata and any covariates identified as improving the log-likelihood at 0.10 level (two-sided).¹⁴¹ The candidate covariates tested for inclusion in the model were: sex, BMI, HbA1c, HLA (DR3/4 vs. others), baseline C-peptide (fasting, peak, area under the concentration–time curve [AUC]), baseline OGTT glucose (fasting, 2-hour, AUC), and autoantibody presence (mIAA, GADA, IA2A, ZnT8) at study entry.¹⁴¹

Sensitivity analyses of the primary endpoint conducted at 5 years evaluated 3 scenarios: (1) participants in the placebo group who had onset of Stage 3 T1D during the first year (before 12 months) were considered to have onset at 12 months; (2) participants who withdrew consent or were lost to follow-up and thus censored were considered to have onset of Stage 3 T1D on their date of withdrawal or the date when lost to follow-up; and (3) scenarios 1 and 2 combined.¹⁴²

Interim primary analyses were planned to occur periodically during the study for review by the TN-10 Data and Safety Monitoring Board (DSMB).¹⁴¹ An interim primary analysis was performed when 18 participants had onset of Stage 3 T1D.¹⁴¹ The significance level at this interim primary analysis was assessed using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets spending function.¹⁴¹

The primary analysis was planned for after 40 or more events (i.e., cases of Stage 3 T1D) had been reported in the full analysis set population, which included all participants who received any study drug and who participated in at least one post-baseline assessment.¹⁴¹ Based on the interim primary analysis and application of the Lan-DeMets decision rule, it was determined that the final primary analysis should be conducted at the 0.0242 significance level to preserve type I error.¹⁴¹ The interim primary analysis had a negligible effect on the significance threshold for the primary analysis (one-sided $p=0.0247$), so all p -values were reported as if a fixed-sample size test was conducted.¹⁴¹

Participants who had not progressed to Stage 3 T1D by the end of TN-10 continued to be followed up and were included in the extended follow-up analysis of the primary endpoint, which was conducted after participants had been followed for a median of 923 days.¹⁴³

Safety analyses were conducted in the safety population, which included all participants who received any study treatment.¹⁴¹

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Quality assessment

The TN-10 trial identified by the clinical SLR was assessed in terms of risk of bias using the Cochrane Risk of Bias Assessment Tool (RoB 2) in accordance with NICE recommendations. This tool assesses the risk of bias across five quality domains including study randomisation, deviation from intended interventions, missing data, outcome measurement and selection of the reported result. The overall final judgement of bias across all domains is also informed by the individual reviewer's judgement.

Overall, the risk of bias for TN-10 was considered to be low, indicating that the collected evidence is considered robust. The quality assessment findings for TN-10 are summarised in Table 12. The complete quality assessment is provided in Appendix D.3.

Table 12. Quality assessment results for TN-10

Trial number (acronym)	TN-10
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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

B.2.5.2 Generalisability assessment

The results of the TN-10 trial are expected to be relevant and generalisable to UK clinical practice.

The generalisability of time to progression outcomes with teplizumab in TN-10 (conducted in individuals with a relative with Stage 3 T1D) was assessed by UK clinical experts at an advisory board convened by Sanofi in May 2024.⁸ Although clinicians indicated approximately 20% of individuals with Stage 3 T1D have a relative with the condition, they did not expect the mechanism of T1D to be dissimilar for those that do and do not have a relative with Stage 3 T1D. Therefore, people would be expected to have the same outcome with teplizumab, in terms of time to progression, across the two groups.⁸ Findings from the

Fr1da study of a German public health early detection programme for islet autoantibodies in children support this assumption:

- As discussed in Section B.1.3.1.2, the Fr1da study demonstrated that the risk of progression in individuals with presymptomatic T1D is not significantly associated with having a first-degree relative.⁴³
- Further, outcomes were similar in the placebo group of TN-10 compared with a cohort of participants in the Fr1da study, of whom 87.5% vs. 29.6% had a first-degree relative with Stage 3 T1D.⁵² The risk of progression from Stage 2 to Stage 3 T1D was similar in both groups (with HRs of 1.3 and 1.1 in unadjusted and prognostic-factor-adjusted Cox proportional hazard models, respectively), suggesting that the results are generalisable to European populations.⁵²

Thus, the effectiveness of teplizumab demonstrated in TN-10 is likely to be generalisable to a broad population of people with Stage 2 T1D, regardless of whether individuals have a relative with Stage 3 T1D. Additionally, studies of new-onset Stage 3 T1D can also provide supporting evidence for effectiveness in a general Stage 2 T1D population.¹⁴⁵ There were no geographical differences in the response to teplizumab among people with new-onset Stage 3 T1D in the PROTECT study in North America and Europe (including UK sites).¹⁴⁵ While the majority (86.5%) of people living with Stage 3 T1D in England and Wales are of White race, based on NDA data from between 2003 and 2020¹⁵¹, it is acknowledged that TN-10 does not sufficiently reflect the distribution of races/ethnicities in UK clinical practice.

B.2.6 Clinical effectiveness results of the relevant studies

In the TN-10 trial, treatment with teplizumab resulted in a statistically significantly longer median time to onset of Stage 3 T1D compared with placebo (4.1 vs. 2.1 years; difference: 2 years; $p=0.0066$) at the primary analysis.¹⁴² The median time to onset of Stage 3 T1D was also statistically significantly longer in treatment with teplizumab vs. treatment with placebo at the extended follow-up analysis (5.0 vs. 2.3 years; difference: 2.7 years; $p=0.01$).¹⁴³ The results for the primary outcome of time to onset of Stage 3 T1D, which is also included in the cost-effectiveness model, are summarised in Table 13, and described in more detail in the following sections.

Table 13. Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Primary analysis		
Median	49.5 months	24.9 months
Median difference	24.6 months	
HR (95% CI); p value	0.41 (0.22, 0.78); p=0.0066	
Extended follow-up analysis		
Median	59.6 months	27.1 months
Median difference	32.5 months	
HR (95% CI); p value	0.457 (NR); p=0.01	

CI = confidence interval; HR = hazard ratio; NR = not reported; T1D = type 1 diabetes
Sources: Data on File – Provention Bio Inc. 2020;¹⁴² Sims 2021.¹⁴³

B.2.6.1 Primary endpoint and sensitivity analyses: time to onset of Stage 3 T1D

B.2.6.1.1 Primary analysis

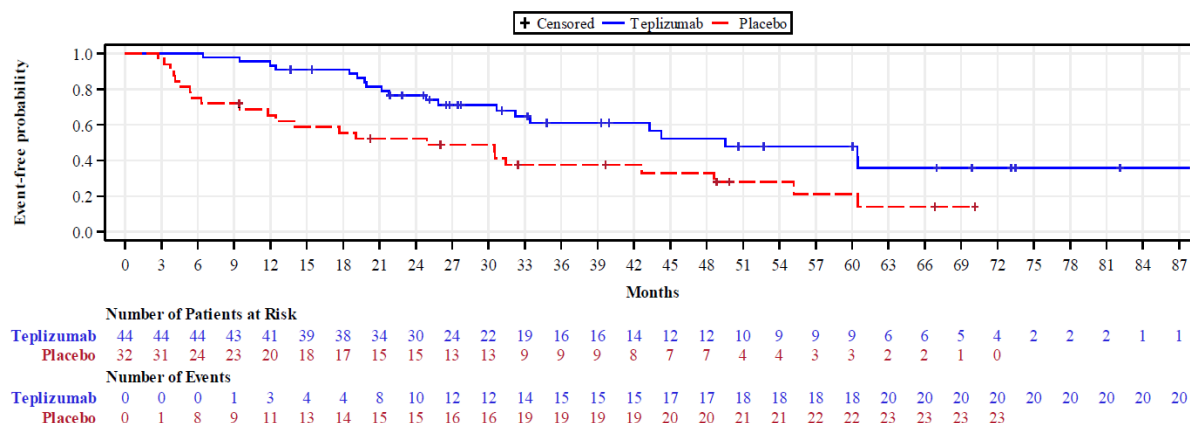
The median time from randomisation to onset of Stage 3 T1D, the primary endpoint of TN-10, was 49.5 months in the teplizumab group and 24.9 months in the placebo group, with a difference of 24.6 months.¹⁴² Onset of Stage 3 T1D occurred in 45% (20/44)^d of the individuals treated with teplizumab and in 72% (23/32) of the individuals treated with placebo as of the data cut-off date of 30 November 2018.¹⁴²

With a median follow-up time of 745 days (range: 74, 2,683), treatment with teplizumab resulted in a statistically significant delay in the progression to Stage 3 T1D (HR: 0.41; 95% confidence interval [CI]: 0.22, 0.78; p=0.0066 by adjusted Cox PH model) (Figure 4).^{141,142}

The results of the 5-year sensitivity analysis of the primary endpoint are summarised in Table 14. Across all three scenarios, teplizumab was statistically significantly superior to placebo in delaying the onset of Stage 3 T1D, consistent with the primary analysis outcome.¹⁴²

^d Note that there is a discrepancy between the TN-10 CSR and the Herold et al. 2019 publication in the number of participants with Stage 3 T1D in the teplizumab group (20 vs. 19, respectively). In the teplizumab arm, 1 participant's onset of Stage 3 T1D occurred before the study data cut-off date (30 November 2018) so it was included in the CSR, but the publication authors were unaware of this case until after the manuscript was published so it is not included in the publication.

Figure 4. KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis)



ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

Source: Data on File – Provention Bio Inc. 2020.¹⁴²

Table 14. Sensitivity analysis of time to onset of Stage 3 T1D (TN-10; ITT population; sensitivity analysis at 5 years)

Scenario	HR (95%CI); p value
1: Stage 3 T1D onset was delayed from <12 months to 1 year for participants in the placebo group ^a	0.43 (0.22, 0.81); p=0.0089
2: Participants with early withdrawal considered ^b	0.42 (0.22, 0.78); p=0.0065
3: Combined assumptions for scenarios 1 and 2	0.43 (0.23, 0.81); p=0.0086

^a Stage 3 T1D onset was delayed to 1 year for 13 participants who had a follow-up duration <12 months and had onset of Stage 3 T1D.

^b Stage 3 T1D onset was assumed at last evaluation for 3 participants who prematurely withdrew from the study or were lost to follow-up, including 1 participant in the placebo group and 2 participants in the teplizumab arm.

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; T1D = type 1 diabetes

Source: Data on File – Provention Bio Inc. 2020.¹⁴²

B.2.6.1.2 Extended follow-up analysis

In the extended follow-up analysis of teplizumab- and placebo-treated participants, the median follow-up time was 923 days (range: 74, 3,119).¹⁴³ Fifty percent (22/44) of individuals treated with teplizumab had not progressed to Stage 3 T1D at the time of the extended follow-up analysis compared with 22% (7/32) of placebo-treated participants.¹⁴³ Teplizumab significantly delayed the median time to onset of Stage 3 T1D by 2.7 years compared with placebo (59.6 vs. 27.1 months, respectively; HR: 0.457; p=0.01 by adjusted Cox PH model).¹⁴³

B.2.6.2 Secondary endpoint: C-peptide response

C-peptide was assessed as a marker for beta-cell function and endogenous insulin production, with preserved C-peptide levels indicating more residual beta-cell mass and endogenous insulin production.^{141,143,149,150}

C-peptide response was preserved with teplizumab as shown by significantly higher average on-study C-peptide AUC vs. placebo (mean of 1.94 vs. 1.72 pmol/ml, respectively; $p=0.006$ [adjusted for age and baseline C-peptide AUC]) and a significant reversal of the decline in C-peptide AUC seen with placebo during the first 6 months of treatment ($p=0.0015$) (Table 15).¹⁴³

Table 15. C-peptide AUC at 6 months after enrolment (TN-10; ITT population)

	Teplizumab (n=44)	Placebo (n=32)
C-peptide AUC at 6 months (pmol/ml), mean (IQR)	2.06 (1.55, 2.58)	1.68 (1.20, 2.15)
Difference between pre- vs. post-treatment slopes	$p=0.04$	$p>0.05$
Difference between post-treatment slopes ^a	$p=0.0015$	

^a ANCOVA comparison corrected for age and pre-treatment slope

ANCOVA = analysis of covariance; AUC = area under the concentration–time curve; IQR = interquartile range;

ITT = intention-to-treat

Source: Sims 2021.¹⁴³

C-peptide AUC preservation for the 24-month analysis was statistically significant for teplizumab compared with placebo in all participants (██████) and in those who progressed to Stage 3 T1D during the study (██████).¹⁴²

B.2.6.3 Insulin secretion

Insulin data from the OGTT were used to measure insulin secretion in TN-10;¹⁴¹ loss of early insulin secretion has been shown to reflect beta-cell dysfunction before progression to Stage 3 T1D.¹⁴³

Total insulin secretion was significantly higher with teplizumab at 6 months compared with pre-treatment values ($p=0.01$) and the change from baseline was significantly higher compared with placebo ($p=0.0004$) (Table 16).¹⁴³

Table 16. Insulin interval secretion (2 hours) at 6 months after enrolment (TN-10; ITT population)

	Teplizumab (n=44)	Placebo (n=32)
Pre-treatment slope	-1,024.0	-1,245.0
Post-treatment slope	1,085.8	-1,037.4
Difference between pre- and post-treatment slope ^a	$p=0.01$	$p=0.80$
Difference between post-treatment slopes ^a	$p=0.0004$	

^a Wilcoxon signed-rank (paired) test

ITT = intention-to-treat

Source: Sims 2021.¹⁴³

B.2.7 Subgroup analysis

Full details of the subgroup analysis results are presented in Appendix E.1.

B.2.8 Meta-analysis

No meta-analyses have been conducted since there is currently only one study available (TN-10) with teplizumab data for the target patient population.

B.2.9 Indirect and mixed treatment comparisons

Teplizumab is a first-in-class treatment, representing the only therapy approved worldwide to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D.^{16-18,152} The only comparator described in the final NICE scope is established clinical management without teplizumab (e.g., monitoring blood glucose, psychosocial support, education). Therefore, indirect comparisons are not possible or relevant in this context.

B.2.10 Adverse reactions

B.2.10.1 Primary analysis

B.2.10.1.1 Overview of TEAEs

An overview of the incidence of treatment-emergent adverse events (TEAEs) and treatment discontinuations reported in the teplizumab and placebo arms of TN-10 is presented in Table 17.

Table 17. Summary of TEAEs at a median follow-up of 745 days (TN-10; safety population; primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Any TEAE, n (%)	██████████	██████████
Any treatment-emergent AESI, n (%) ^a	██████████	█
Any treatment-emergent SAE, n (%)	7 (15.9) ^b	1 (3.1)
TEAE leading to treatment interruption, n (%)	██████████	█
TEAE leading to treatment withdrawal, n (%)	1 (2.3)	2 (6.3)
TEAE related to study drug, n (%)	██████████	██████████
Death	0	0

^a AESI included the following: Grade ≥3 infections (including all opportunistic infections), acute mononucleosis-like illness, lymphomas or other malignancies, major hypoglycaemia, Grade ≥3 liver function abnormalities (AST, ALT, bilirubin), Grade ≥3 thrombocytopenia, Grade ≥3 neutropenia, Grade ≥4 allergic/hypersensitivity reaction (through Study Day 365), Grade ≥3 rash, Grade ≥4 cytokine release syndrome (through Study Day 365), lymphocyte count <500 mm³ for 7 days or longer

^b Eight SAEs occurred in 7 participants in the teplizumab arm

ALT = aspartate aminotransferase; AST = alanine aminotransferase; AESI = adverse event of special interest; TEAE = treatment-emergent adverse event; SAE = serious adverse event

Source: Data on File – Provention Bio Inc. 2020.¹⁴²

B.2.10.1.2 TEAEs by preferred term

The most common TEAEs in the teplizumab group were lymphopenia (72.7%), leukopenia (20.5%), rash pruritic (██████%) and nasopharyngitis (██████%).¹⁴² A summary of TEAEs by

preferred term occurring in >5% of participants in either treatment group at a median of 745 days of follow-up is provided in Table 18.

Table 18. TEAEs by preferred term occurring in >5% of participants in the teplizumab or placebo group at a median follow-up of 745 days (TN-10; safety population; primary analysis)

Preferred term, n (%)	Teplizumab (n=44)	Placebo (n=32)
Any TEAE	████████	████████
Leukopenia	9 (20.5)	0 █████
Lymphopenia	32 (72.7)	2 (6.3)
Neutropenia	████████	████████
Nasopharyngitis	████████	████████
Pneumonia	████████	████████
Sinusitis	████████	████████
Upper respiratory tract infection	████████	████████
Rash	████████	██████
Rash pruritic	████████	██████
Headache	5 (11.4)	████████
Vomiting	████████	████████
Bronchospasm	████████	██████
Cough	████████	██████
Hypertension	████████	████████
Hyperbilirubinemia	██████	████████

TEAE = treatment-emergent adverse event
Source: Data on File – Provention Bio Inc. 2020.¹⁴²

B.2.10.1.3 AEs associated with teplizumab by category

AEs that were attributed as possibly, probably or definitely related to the trial agent by the investigator occurred more frequently in the teplizumab group vs. the placebo group (112 vs. 23 AEs, respectively).¹⁴¹ The incidence of infections was similar between treatment groups.¹⁴¹ In the teplizumab group, lymphopenia accounted for 75% of grade 3 AEs.¹⁴¹ One participant in the teplizumab group had a grade 2 (moderate) AE of cytokine release syndrome, which was considered likely related to the study drug; the event resolved and the entire 14-day treatment course was completed by the participant without dose reduction.^{141,142} DKA events did not occur in any people with Stage 2 T1D in the teplizumab or placebo groups.¹⁵³ Data from other individuals treated with teplizumab show similar safety profiles (Section B.2.10.1.4).¹⁴¹

Table 19. Incidence of AEs^a by category during active follow-up (TN-10; safety population; primary analysis)

AE category, n (%)	Teplizumab (n=44)	Placebo (n=32)
Blood or bone marrow ^b	33 (75)	2 (6)
Dermatologic or skin ^b	16 (36)	1 (3)
Pain	5 (11)	3 (9)
Infection	5 (11)	3 (9)
Gastrointestinal	4 (9)	3 (9)
Metabolic or laboratory	4 (9)	2 (6)
Pulmonary or upper respiratory	4 (9)	0
Constitutional symptoms	2 (5)	0
Allergy or immunologic	2 (5)	0
Cardiac, general	1 (2)	1 (3)
Endocrine	0	2 (6)
Vascular	1 (2)	1 (3)
Neurologic	1 (2)	0
Ocular or visual	1 (2)	0
Musculoskeletal or soft tissue	1 (2)	0
Hepatobiliary or pancreatic	0	1 (3)
Cytokine release syndrome	1 (2)	0
Haemorrhage or bleeding	1 (2)	0

^a Events listed were attributed as possibly, probably, or definitely related to the trial agent by the trial-site investigator

^b p<0.001 between treatment arms

AE = adverse event

Source: Herold 2019.¹⁴¹

B.2.10.1.4 AEs from other teplizumab trials

An integrated safety analysis from five clinical trials of teplizumab in 1,018 people with Stage 2 T1D (TN-10) or Stage 3 T1D (AbATE, Protégé, Encore and Delay) included assessments of AEs, mechanism-related AEs and serious AEs (SAEs).¹⁴⁴ Participants in the integrated safety population included all people receiving one of three dosing regimens (full 14-day, 6-day and one-third dose 14-day regimens) who received at least one dose of teplizumab (n=773) or were randomised to placebo or standard of care (n=245).¹⁴⁴ The majority of AEs were grade 1 or 2 in severity, mostly occurring during and after the first few weeks of teplizumab administration, and were resolved without intervention (Section B.3.4.3).¹⁴⁴ Additionally, the rates of cytokine release syndrome were 5.8% and 1.2% for participants treated with teplizumab or control, respectively.¹⁴⁴

B.2.11 Ongoing studies

A summary of all other known completed studies of teplizumab in T1D and ongoing studies that should provide additional clinical evidence in the next 12 months are shown in Table 20.

Table 20. Studies evaluating teplizumab in individuals with T1D

Study	Primary objective	Phase	N	Trial dates
PETITE-T1D ¹⁵⁴	To assess the safety and PK of teplizumab in children aged <8 years with Stage 2 T1D	IV	20 (estimated)	July 2023 to October 2026 (estimated primary completion)
TN-10 extension-phase ¹⁵⁵	To assess the safety and tolerability of teplizumab in participants from the TN-10 trial who progressed to Stage 3 T1D	II	6	March 2020 to January 2024
PROTECT ¹⁴⁵	To assess if beta-cell function and clinical outcomes are maintained with two courses of teplizumab in children aged 8 to 17 years with onset of Stage 3 T1D	III	328 (teplizumab: 217; placebo: 111)	March 2019 to May 2023

PK = pharmacokinetics; T1D = type 1 diabetes

Sources: ClinicalTrials.gov NCT05757713;¹⁵⁴ ClinicalTrials.gov NCT04270942;¹⁵⁵ Ramos 2023¹⁴⁵

B.2.12 Interpretation of clinical effectiveness and safety evidence

Teplizumab will be the first and only disease-modifying therapy to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D in the UK offering a step change in treating individuals with Stage 2 T1D.

In an advisory board convened by Sanofi in May 2024, UK clinical experts indicated that they expect extended time in Stage 2 to provide more time to understand the diagnosis, prepare and more thoroughly learn how to manage Stage 3 T1D, which ultimately may lead to improved outcomes and compliance.⁸ The benefits of education and monitoring interventions in children who do not yet have Stage 3 T1D may extend to reducing the economic burden associated with Stage 3 T1D, as was shown in Italy (reduced hospitalisations due to DKA and lower costs) and in the US (reduced hospitalisations due to DKA).¹⁵⁶⁻¹⁵⁸

B.2.12.1 Direct evidence: TN-10

The phase II, randomised, placebo-controlled, double-blind TN-10 trial provides direct evidence supporting the efficacy and safety of teplizumab in delaying the progression to Stage 3 T1D in people with Stage 2 T1D (≥8 years old).¹⁴¹

B.2.12.1.1 TN-10 efficacy analysis

Individuals treated with teplizumab had a statistically significantly longer median time to onset of Stage 3 T1D of 5.0 years compared to 2.3 years in the placebo arm (2.7-year difference), while also preserving the C-peptide response, in people with Stage 2 T1D aged ≥8 years.¹⁴³ A single course of teplizumab IV infusion administered once daily for 14 consecutive days, significantly delayed the median time to onset of Stage 3 T1D by 2 years vs. placebo at the primary analysis with a median follow-up of 745 days (49.5 vs. 24.9

months, respectively; HR: 0.41; $p=0.0066$);¹⁴² the difference increased to 2.7 years in an extended follow-up analysis after participants had been followed for a median of 923 days (59.6 vs. 27.1 months; HR: 0.457; $p=0.01$).¹⁴³

In addition, further efficacy analysis of the TN-10 trial was published as part of mechanistic analyses in August 2024 (after the clinical SLR searches were run in June 2024). The publication objective was to understand the mechanistic effects of teplizumab on peripheral immune cells to identify cellular signatures that may be associated with long-term response in delaying the onset of Stage 3 T1D.¹⁵⁹ The publication provided an ad hoc update on the median time to Stage 3 T1D onset as it was relevant to the immunological analyses; the difference in the median time to onset of Stage 3 T1D with teplizumab compared with placebo was 2.1 years with a median follow-up of 80.46 months (52.2 vs. 27.3 months, respectively; $p=0.0026$).¹⁵⁹ By year 5, 39% ($n=17/44$) of teplizumab-treated individuals had not progressed to Stage 3 T1D, compared with 19% ($n=6/32$) of placebo-treated individuals.¹⁵⁹ By year 7.5, all individuals in the placebo group had progressed to Stage 3 T1D, and 5 teplizumab-treated individuals had not progressed to Stage 3 T1D, with 1 individual remaining Stage 3 T1D-free at 10 years.¹⁵⁹ The efficacy findings from this paper were supplemental to the primary objectives of the publication¹⁵⁹, therefore the response rate reported at 5 years was arbitrary. Sanofi is exploring the possibility of further follow-up focusing on the efficacy analysis with the study authors.

Teplizumab treatment also led to improvements in beta-cell function as demonstrated by preserved C-peptide responses and insulin secretion.¹⁴³ Through its effects on preserving C-peptide levels, teplizumab may prolong the benefits associated with endogenous C-peptide production in reducing the burden of Stage 3 T1D¹⁴³, including the potential for better glycaemic control²⁸⁻³¹ and lower rates of longer-term complications.^{29,32,33} It has been shown that the retention of C-peptide in individuals with T1D leads to improved glycaemic control (including a higher mean glucose time in the normoglycaemic range, lower glucose variability, lower HbA1c, lower daily exogenous insulin requirements), reduced rates of hypoglycaemia and severe hypoglycaemia, and lower rates of longer-term complications (e.g., retinopathy and nephropathy).^{28-33,160} In the TN-10 study, C-peptide AUC preservation for the 24-month analysis was statistically significant compared with placebo for all teplizumab participants (██████) and in those who progressed to Stage 3 T1D during the study (██████).¹⁴² In addition, an integrated efficacy analysis of C-peptide AUC data pooled from five clinical studies in individuals with Stage 3 T1D showed significant preservation of C-peptide AUC levels in teplizumab-treated individuals at both 1 and 2 years of follow-up compared with controls ($p<0.0001$).¹⁴⁴

B.2.12.1.2 TN-10 safety analysis

Teplizumab has been studied for more than 20 years in approximately 1,000 children and adults,^{144,145} and has demonstrated an acceptable safety profile in TN-10 consistent with other clinical trials of teplizumab.^{141,144}

Results from the primary analysis of TN-10 determined that AEs associated with teplizumab were similar to those reported in previous clinical trials of teplizumab in Stage 3 T1D.¹⁴¹ AEs occurred more frequently in the teplizumab group vs. the placebo group (112 vs. 23 AEs, respectively).¹⁴¹ The incidence of infections was similar between treatment groups.¹⁴¹ In the teplizumab group, lymphopenia accounted for 75% of grade 3 AEs.¹⁴¹

B.2.12.2 Strengths and limitations of clinical evidence

TN-10 was an international trial with an appropriate design involving randomisation of participants to double-blinded treatment.¹⁴¹ Overall, the risk of bias for TN-10 was considered to be low, indicating that the collected evidence is considered robust.

TN-10 was the first trial to successfully demonstrate delayed onset of Stage 3 T1D with immune therapy in individuals with Stage 2 T1D who were relatives of people with Stage 3 T1D. Data from the Fr1da study demonstrated that the risk of progression in individuals with presymptomatic T1D is not significantly associated with having a first-degree relative.⁴³ In line with this, UK clinical experts indicated at an advisory board convened by Sanofi in May 2024 that they believe the disease mechanism of T1D to be similar between individuals with Stage 2 T1D who have a relative with Stage 3 T1D and those who do not.⁸ Based on this, outcomes with teplizumab treatment would be expected to be the same between the two groups.

The TN-10 trial had a sample size of 76 participants, which largely reflects the population of people identified with Stage 2 T1D in the UK in the current clinical landscape.^{58,141} In addition, although the trial evaluated important clinical, safety and laboratory outcomes to monitor the progression to Stage 3 T1D and the loss of beta-cell function over time, QoL measures were not included in TN-10. However, an ongoing vignette-based utility elicitation study is being conducted to support disease-specific utilities in Stage 2 and Stage 3 T1D using EQ-5D-5L.

Although there were no participants in the TN-10 trial from the UK, the variety of sites, together with findings from the expert advisory board convened by Sanofi confirms generalisability of TN-10 to the UK clinical practice. Furthermore, data comparing Fr1da

European cohort rates of progression from Stage 2 to Stage 3 T1D to the placebo arm of TN-10 showed a comparable rate of progression over 5 years indicating similar disease progression and decline of beta-cell mass.⁵²

B.2.12.3 Summary

The current standard of care in T1D is limited to lifelong replacement of insulin following the onset of Stage 3 T1D.¹ Teplizumab is a pivotal advancement in T1D, providing the first and only disease-modifying treatment that targets one of the underlying causes of T1D. Individuals treated with teplizumab had a statistically significantly longer median time to onset of Stage 3 T1D of 5.0 years compared to 2.3 years in the placebo arm (2.7-year difference) with an acceptable safety profile, while also preserving the C-peptide response and postponing the need for insulin replacement.^{141,143} Through its effects on preserving C-peptide levels, teplizumab may prolong the benefits associated with endogenous C-peptide production in reducing the burden of Stage 3 T1D¹⁴³, including the potential for better glycaemic control²⁸⁻³¹ and lower rates of longer-term complications.^{29,32,33} Delaying the onset of Stage 3 T1D also provides more time for people with Stage 2 T1D to prepare for the onset and management of symptomatic disease, potentially minimising disruptions to school and employment due to poor glycaemic control and complications.

There is a willingness among individuals in the UK to have treatments for T1D that can delay the need for insulin.²⁶ The general population, people with Stage 3 T1D and their carers/parents recognise the large treatment burden associated with current standard of care and preferences from these groups suggest a great need for new treatments to delay exogenous insulin dependence and progression to Stage 3 T1D.^{26,130} This suggests that a disease-modifying therapy such as teplizumab would be accepted among individuals with Stage 2 T1D.

B.3 Cost-effectiveness

Model overview

- A cost-effectiveness analysis was conducted to evaluate teplizumab in comparison to established clinical management from the perspective of the NHS and Personal Social Services in England for delaying the onset of Stage 3 T1D in individuals aged 8 years and older with Stage 2 T1D.
- A review of the literature and preceding relevant technology appraisals was conducted.
- The outcomes of the review were used to develop a cohort model comprising three mutually exclusive and collectively exhaustive health states: Stage 2 Type 1 Diabetes (T1D), Stage 3 T1D, and death. The model, which employs a 6-month cycle and a lifetime horizon, compares outcomes for individuals receiving teplizumab with those under established clinical management.
- Since the key benefit of teplizumab for individuals with Stage 2 T1D is the delay of onset of Stage 3 T1D, the model captures this benefit upfront, using time-to-event data directly informed by the TN-10 study, processed through parametric survival analysis.
- Model inputs for the base case analysis include:
 - Baseline characteristics and clinical efficacy data from TN-10 (time to onset of Stage 3 T1D)
 - Other clinical inputs (risk of DKA at onset of Stage 3 T1D and mortality rates) and utility estimates informed by European studies reporting appropriate inputs
 - Inputs for treatment administration and related resource use (e.g., confirmatory tests and pre-medication) informed by requirements and recommendations for teplizumab use, published literature, and UK cost sources (e.g., NICE British National Formulary [BNF] and National Schedule of NHS Costs)
 - Inputs for AE management and DKA management costs informed by clinical trial experience with teplizumab and the National Schedule of NHS Costs
 - HCRU costs informed by a previous NICE appraisal and expert opinion for Stage 2 T1D, and relevant published literature for Stage 3 T1D

Results

- Teplizumab was cost-effective when compared with established clinical management, with an incremental quality-adjusted life year (QALY) gain of [REDACTED] and an incremental cost-effectiveness ratio (ICER) of £29,602 per QALY using a deterministic approach ([REDACTED] and £28,400, respectively, using a probabilistic approach).

Benefits not captured in the QALY calculation

- Teplizumab offers benefits to people with Stage 2 T1D, their carers/parents and society that are unlikely to be captured in the QALY calculation. These include increased time for people with Stage 2 T1D to prepare for the onset and management of symptomatic Stage 3 T1D, prolonged benefits associated with endogenous C-peptide production, value of improving long-term outcomes in people with lower SES and positive impacts on education and employment.

Validation

- UK health economic experts attending an advisory board convened by Sanofi considered the model appropriate for modelling the delay of Stage 3 T1D onset.
- An external technical validation of the model concluded that the chosen modelling approach is reasonable and appropriate. Discrepancies between the outputs of the Sanofi model when compared with other relevant published models did not appear to be substantial and may be explained by different approaches to mortality.

Conclusions

- Teplizumab represents a cost-effective use of NHS resource for delaying the onset of Stage 3 T1D compared with established clinical management and would address a considerable unmet need for a disease-modifying therapy in this setting.

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify economic evaluations and studies assessing the costs and HCRU of treatments for Stage 2 or 3 T1D to understand the economic burden of T1D in children (≥ 8 years old) and adults. There was no lower limit on time horizon for database searches and the cut-off date for articles included in the economic SLR was 27th June 2024. The lower limit on time horizon for grey literature searches was 2021 for conference proceedings and 2018 for submission documents from selected health technology assessment/regulatory agency websites. Full details of the economic SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix G.

The SLR identified only one economic evaluation that was carried out in Stage 2 T1D, Mital et al. (2020).¹⁶¹ The analysis used a hybrid decision tree/Markov microsimulation model to estimate the cost-effectiveness of teplizumab in a hypothetical cohort of 10,000 individuals with Stage 2 T1D in the US (Table 21).¹⁶¹ The economic SLR also identified economic evaluations carried out in Stage 3 T1D; however, these models were not considered to be relevant for this economic analysis since they modelled individual Stage 3 T1D-related complications, and did not capture outcomes from individuals with Stage 2 T1D, the target population (see Section B.3.2.2 for more details on the model structure).

Table 21. Summary list of published cost-effectiveness studies in Stage 2 T1D

Study	Year	Summary of model	Population	Intervention	Comparator	Outcomes
Mital et al.	2020	Cost-effectiveness analysis that applied a hybrid decision tree/ Markov microsimulation model to evaluate the use of teplizumab compared with no teplizumab from the US health system perspective over a lifetime horizon with a 1-year cycle length; cost-effectiveness estimates assumed teplizumab costs of US\$100,000	Individuals who had Stage 2 T1D: • 66% of participants were <18 years of age (mean/median age NR) • 49% of participants were female • The mean HbA1c level at baseline was 7.6%	Teplizumab (efficacy data based on the TN-10 trial as reported in Herold et al. [2019])	No treatment	• Incremental QALY of teplizumab vs. no treatment: 0.07 • Incremental cost of teplizumab vs. no treatment: US\$19,180 • ICER (per QALY gained): US\$271,793

HbA1c = glycosylated haemoglobin; ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life year; T1D = type 1 diabetes; US = United States

Source: Mital 2020¹⁶¹

B.3.2 Economic analysis

B.3.2.1 Population

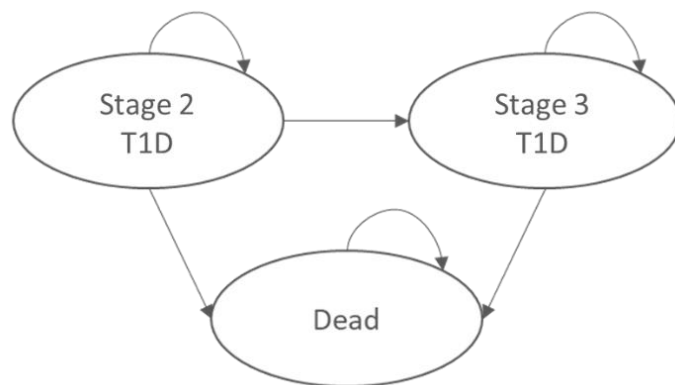
The target population for the economic evaluation was those with Stage 2 T1D (i.e., those individuals with two or more islet autoantibodies and dysglycaemia, who are at risk of progression to Stage 3 T1D), in line with the anticipated license and the final NICE scope.^{34,141} Baseline characteristics of the target population were derived from the TN-10 study, which was conducted in individuals aged 8 years and older.¹⁴¹

B.3.2.2 Model structure

B.3.2.2.1 Overview

A cohort model was developed in Microsoft Excel® from the perspective of the NHS and Personal Social Services in England to assess the cost-effectiveness of teplizumab vs. established clinical management. The cohort model consisted of three mutually exclusive, collectively exhaustive health states: (1) Stage 2 T1D (2) Stage 3 T1D, and (3) dead. Figure 5 illustrates the model structure.

Figure 5. Model structure



T1D = type 1 diabetes

A *de novo* modelling approach was taken to account for Stage 3 T1D-related outcomes in an aggregated manner. This is unlike prior models that captured the frequency and long-term consequences of individual diabetes-complications (see Section B.3.2.2.2 for additional details regarding the approach).

The model captured the treatment benefit of teplizumab compared with established clinical management. In line with the pivotal clinical study, TN-10 (Section B.2.6.1), individuals with Stage 2 T1D receiving a treatment course of teplizumab are expected to stay in Stage 2 T1D

(without progressing to Stage 3) for a longer time on average compared with those who receive established clinical management only.¹⁴³ Therefore, it was hypothesised that the model would find that this treatment-specific benefit would translate into improvements in total life years (LYs) and QALYs for individuals treated with teplizumab.

At the start of the model, all individuals were in the Stage 2 T1D health state, in which general population mortality was assumed to apply (Section B.3.3.2.3). In subsequent model cycles, individuals either remained in the Stage 2 T1D health state or transitioned to the Stage 3 T1D or the dead health states. Once individuals transitioned to the Stage 3 T1D health state, they either remained in this health state or transitioned to the dead health state. The mortality rate in the Stage 3 T1D health state was higher than that of the general population, capturing the excess mortality associated with Stage 3 T1D. The excess mortality was stratified by the age of onset of Stage 3 T1D (Section B.3.3.2.4).

Teplizumab acquisition and administration costs were accrued at the start of the model as one-off costs. Disease management costs and utilities depended on the time since onset of Stage 3 T1D and were assigned over time depending on the individual's health state. Costs and utilities also depended on the time since onset of Stage 3 T1D and were accrued and summarised for each cycle of the model, with increased costs and higher disutility applied to the Stage 3 T1D health state. The difference in cumulative cost and utilities could be calculated and compared between teplizumab and established clinical management.

The time horizon for the base-case cost-effectiveness analysis was assumed to be lifetime (i.e., individuals were simulated to a maximum age of 100 years). A cycle length of 6 months was used with half-cycle correction.

An annual discount rate of 3.5% was applied to both costs and health benefits occurring beyond the first year, as per NICE guidance.¹⁶² A scenario analysis was explored with a 1.5% discount rate.

Inputs for the base-case analysis of the cost-effectiveness model are described in Sections B.3.3, B.3.4 and B.3.5, and also summarised in Table 48.

B.3.2.2.2 *Justification for modelling approach*

In order to determine an appropriate modelling approach for the cost-effectiveness analysis, existing model structures in T1D were assessed based on a review of published literature and grey literature sources (including health technology assessment reports) relevant to the UK identified by the economic SLR. In general, individual patient simulation and Markov

models have been used to model disease progression in Stage 3 T1D,^{163,164} including the hybrid decision tree/ Markov microsimulation model developed for Stage 2 T1D (Mital et al. [2020]).¹⁶¹ It should be noted that most previous T1D models focused on individuals who were already in Stage 3 of the disease. In these models, Stage 3 T1D-related complications are modelled individually, and the transition probabilities (i.e., the risk that individuals would develop these complications over time) are typically based on risk equations that model the relationship between key risk factors (e.g., HbA1c level, age, time since onset of Stage 3 T1D) and disease complications.^{163,164} Translating the delay of Stage 3 T1D onset into measurable risk reductions for individual T1D-related complications would have required capturing improvement in HbA1c levels associated with teplizumab, which was not an available outcome of the TN-10 trial. Therefore, it would have not been possible to use a model structure that directly captured the relationship between key risk factors (such as HbA1c level, age of onset or time since onset of Stage 3 T1D) and the occurrence of Stage 3 T1D-related complications without introducing considerable uncertainty.

In addition to modelling complications individually, Mital et al. (2020) evaluated subgroups of individuals with Stage 2 T1D based on HLA-DR3 status, HLA-DR4 status, and ZnT8 autoantibody status based on the TN-10 trial to inform an annual risk of progressing to Stage 3 T1D.¹⁶¹ This approach was not taken in the submission model because HLA testing is not currently used in routine clinical practice (confirmatory testing for Stage 2 T1D prior to initiation of teplizumab is based on autoantibody status only³⁴). In addition, the very small sample sizes of the HLA subgroups in the TN-10 trial increases uncertainty of long-term projections for any of the subgroups.

Furthermore, there are other key limitations associated with microsimulation models, including the reliance on surrogate measures (i.e., HbA1c), which inform the risk equations that, in turn, are used to predict long-term outcomes and mortality associated with T1D. Evidence gathered by Daly et al. (2022) suggests that the accuracy of HbA1c as a predictor of macrovascular complications or mortality is strongly disputed and, therefore, further validation of this surrogate endpoint is required, especially because small changes in risk factors could have a big impact on the results.¹⁶⁴ In general, the projection of surrogate outcome measures over the longer term introduces uncertainty and this can limit the external validity of the models, especially over a lifetime horizon.

The model for this economic analysis differed from prior models, starting with the need to capture outcomes from individuals with Stage 2 T1D at risk of progressing to Stage 3 T1D, and not only the disease progression once individuals have reached Stage 3 T1D.

Teplizumab's key benefit for individuals with Stage 2 T1D is captured directly through a delay in the onset of Stage 3 T1D. It was assumed that after onset of Stage 3 T1D, individuals would progress at the same rate for a given age of onset, regardless of whether they had previously received teplizumab or established clinical management. By delaying onset of Stage 3 T1D, teplizumab has the potential to reduce the amount of time an individual must live with Stage 3 T1D during their lifetime. Thus, after capturing the delay of onset upfront (i.e., the primary effect of teplizumab), modelling Stage 3 T1D-related outcomes in an aggregated manner in a *de novo* model was deemed more appropriate than modelling individual complications using an existing model structure based on risk equations. The use of risk equations for modelling Stage 3 T1D can introduce uncertainty in predicting long-term outcomes if the data that informs the risk equations is not of high quality (e.g., small sample size) or does not reflect current clinical practice. Previous NICE submission models in diabetes have been criticised for using risk equations to predict long-term outcomes.¹⁶⁴

The model captures the benefit upfront, using time-to-event data directly informed by the TN-10 study, processed through parametric survival analysis. For this population with Stage 2 T1D, the treatment benefit offered by teplizumab is not assumed to be captured through improved HbA1c control, which is a key covariate within the risk equations used by previous models in Stage 3 T1D.^{163,164} This is one of the reasons why a *de novo* model was required.

A lifetime time horizon was considered necessary for the current model to capture the entirety of the costs and benefits of teplizumab.

A cycle length of one year was used in the majority of models reviewed, including Mital et al. 2020 and the NICE appraisal for HCLs.^{70,161} A 6-month cycle was used in this model. This was appropriate because it allowed the impact of the delay in time to onset of Stage 3 T1D associated with teplizumab to be modelled accurately and also reflected data collection in the TN-10 trial which was at 6-month intervals.¹⁴¹ Furthermore, this cycle length also corresponded more closely to the anticipated frequency of testing for progression to Stage 3 T1D for adults and children in the UK following initial diagnosis (every 6 months and every ≥3 months, respectively).²¹

B.3.2.3 Intervention technology and comparators

The intervention in the model was teplizumab. Teplizumab is delivered as a 2 mg per 2 mL clear colourless solution for injection in a single-dose vial and is available as a single-vial

pack. On each day of the 14-day course, the total daily infusion dose is calculated on the basis of BSA as follows:³⁴

- Day 1: 65 mcg/m²
- Day 2: 125 mcg/m²
- Day 3: 250 mcg/m²
- Day 4: 500 mcg/m²
- Days 5 through 14: 1,030 mcg/m²

This dosing regimen is aligned with that recommended for administration of the commercial product in the SmPC (discussed in Section B.2.3.4.1).³⁴

There are currently no interventional comparators of teplizumab for the treatment of Stage 2 T1D. Therefore, the model included established clinical management as the comparator.

B.3.2.4 Summary of key model assumptions and inputs

An overview of the key assumptions and inputs used in the cost-effectiveness model are presented in Table 22.

Table 22. Key model assumptions and inputs

Input (cross reference)	Source/assumption	Justification
Time to onset of Stage 3 T1D (Section B.3.3.2.1)	Time to onset of Stage 3 T1D of the ITT population reported by Sims et al. (2021) (TN-10 study extended follow-up analysis) was extrapolated to inform individuals' transition from Stage 2 to Stage 3 T1D through independent parametric fits (log-normal and exponential distributions fitted to the teplizumab arm and established clinical management arm, respectively)	Sims et al. (2021) reported the outcomes of the TN-10 trial with an extended follow-up period (median 923 days). ¹⁴³ Following recommendations in NICE Decision Support Unit Report 14 on survival data extrapolation, exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma distributions were fitted to model time to Stage 3 T1D. ¹⁶⁵
Mortality for Stage 2 T1D (Section B.3.3.2.3)	Risk of death was assumed to be the same as the general population and was therefore derived from the UK general population life tables ¹⁶⁶	No published data have been identified indicating that individuals with Stage 2 T1D have an increased risk of death compared to the general population.
Mortality for Stage 3 T1D (Section B.3.3.2.4)	Potential survival gains from delaying progression to Stage 3 T1D were captured by applying a HR by age categories at onset of Stage 3 T1D to the UK general population life tables	No UK-specific literature providing excess risk of death compared with the general population stratified by age of onset of Stage 3 T1D was identified. The HR for children (<18 years) was sourced from an analysis of the Swedish National Diabetes Register; the analysis included data for 15,188 individuals with Stage 3 T1D and 74,210 controls from between 2000 and 2019 and is thus expected to reflect current standard of care (in the absence of recent UK-specific data). ⁸¹ This source was selected as it was the most recent publication identified and thus is expected to provide the most accurate representation of the current clinical landscape. The mortality for adults with Stage 3 T1D (>18 years) was assumed to be 50% of the mortality estimate for children with Stage 3 T1D (<18 years). This assumption was made based on a 2014 meta-analysis that found that the pooled mortality estimate for adults diagnosed with Stage 3 T1D was approximately half that of children diagnosed with Stage 3 T1D. ¹⁶⁷
Disutilities for Stage 2 T1D (Section B.3.4.2.2)	No decrement in utility was expected for Stage 2 T1D (prior to teplizumab administration), as disutility was assumed to be the same as the general population.	Expert advice from UK diabetes clinicians indicated that no substantive decrement in utility is observed in individuals with presymptomatic T1D (Stage 1 or Stage 2 T1D) compared with the general population. ⁸
Disutilities for teplizumab administration in Stage 2 T1D (Section B.3.4.2.2)	Infusion-related disutilities were applied for the duration of treatment (i.e., 14 days) to the utility estimates of the general population as a one-off treatment-related burden for people receiving teplizumab.	The value was sourced from a UK study reporting the disutility associated with various treatment modalities for cancer with bone metastases, including IV infusion, as evaluated by individuals from the general population. ¹⁶⁸ The disutility for a 30-minute infusion was used as a proxy in the model to estimate the disutility for people with Stage 2 T1D receiving teplizumab, given that there were no published disutility values for people with Stage 2 T1D identified.
Disutility for onset of Stage 3 T1D (Section B.3.4.2.3)	Stage 3 T1D-related disutilities were applied to the utility estimates of the general population as a one-off when onset of Stage 3 T1D occurs (i.e., for the first cycle only)	The values for onset of Stage 3 T1D were sourced from Sparring et al. (2013) which analysed HRQoL in registered individuals from the Diabetes Incidence Study in Sweden with onset of Stage 3 T1D at the age of 15 to 34 years and with a disease duration of 8, 15 and

Input (cross reference)	Source/assumption	Justification
		24 years compared with control individuals from the general population matched for age, sex and county of residence. ¹² This study was considered the most appropriate available input source because HRQoL for Swedish individuals with Stage T1D 3 was reported based on disease duration, which aligned with the needs for the model.
Disutility for Stage 3 T1D vs. general population (Section B.3.4.2.3)	Disutilities for Stage 3 T1D vs. the general population were applied in the model to account for additional QoL loss due to Stage 3 T1D	The baseline utility for a person with Stage 3 T1D may be lower than that of the general population, even in the absence of Stage 3 T1D–related complications. The values for Stage 3 T1D vs. the general population were sourced from Sullivan et al. (2011), which reports nationally representative preference-based HRQoL scores for having diabetes without complications in the UK, based on the EQ-5D (NICE's preferred measure). ¹⁶⁹
Disutility for Stage 3 T1D based on time since onset of Stage 3 (Section B.3.4.2.3)	Disutilities were based on time since onset of Stage 3 T1D	Disutilities based on Stage 3 T1D disease duration were also obtained from Sparring et al. (2013). ¹² The study used one year outcomes as a point of reference (given that they are captured relatively soon after onset of Stage 3 T1D and it was expected that individuals will not have developed T1D-related complications within this timeframe), and then provided the disutility for years 8, 15 and 24 of disease duration. ¹² The values from this study were selected because the model applies T1D-related disutilities subtracted from a reference utility value. A linear regression model was applied to the disutility values from Sparring et al. (2013) to calculate the disutility for each cycle depending on the number of years since the onset of Stage 3 T1D.
Carer/parent disutility (Section B.3.4.2.4)	Carer/parent disutilities were only applied for individuals <18 years old in the Stage 3 T1D health state and assumed 1.76 carers/parents take care of each child after onset of Stage 3 T1D, up to when the child reaches 18 years of age	The carer/parent disutility was based on a publication by López-Bastida et al. (2019), who studied carers' self-reported HRQoL for children with Stage 3 T1D receiving outpatient care at paediatric endocrinology specialised centres in Spain. ⁸⁹ The study reported a carer EQ-5D-5L score of 0.92 which was subtracted from the general population mean utility of 0.96. ⁸⁹ This study was considered the most appropriate available input source because UK data were not identified from published literature from the past 10 years. The number of carers/parents was calculated as a weighted average of number of carers/parents in families with dependent children using 2023 data on families and children in the UK by family type from the ONS. ¹⁷⁰
AE disutilities (Section B.3.4.3)	AE disutilities were applied for the five most common AEs reported during treatment with teplizumab	The five most common AEs reported in ≥10% of participants treated with teplizumab and occurring at a higher frequency with teplizumab vs. placebo were identified from a pooled analysis of data from five clinical trials of teplizumab, including TN-10. ¹⁴⁴ These five AEs were included in the model (lymphopenia, leukopenia, neutropenia, decreased blood bicarbonate and rash). The duration for each AE was based on TN-10 ¹⁴¹ and the pooled analysis. ¹⁴⁴ Disutility values for AEs were obtained from Sullivan et al. (2011), described above. ^{169,171}
Teplizumab acquisition and administration cost (Section B.3.5.1.1)	The drug acquisition cost for teplizumab was based on a 14-vial treatment course; the administration cost was calculated based on the expected proportion of individuals who will receive the full treatment in hospital vs. those who will receive Days 1 to 5 of treatment in hospital and Days 6 to 14 in a closer-to-home setting	Teplizumab will be available as 14-day treatment course that uses single-vial packs. For the administration cost of teplizumab, it was assumed that uptake for care in a closer-to-home setting will be 90% and hospital only will be 10%, among paediatrics and adults. The administration cost was calculated as the weighted average between closer-to-home and hospital settings. The prices were obtained from the National Schedule of NHS Costs. ¹⁷²

Input (cross reference)	Source/assumption	Justification
Teplizumab-related resource use costs (Section B.3.5.1.2)	Costs were included for confirmatory tests, pre-medication prior to teplizumab dosing to avoid CRS, laboratory evaluations and infusion-related resources	Resource use was based on requirements from the teplizumab SmPC ³⁴ and recommendations on teplizumab use from the Pediatric Society for Endocrinology ¹⁷³ . Costs were derived from published literature and UK sources (e.g., NICE BNF, NHS).
Disease management costs for Stage 2 T1D (Section B.3.5.2.1)	Costs accounted for monitoring touchpoints every 6 months for adults and every 3 months for children	Assumptions for resource use were based on international monitoring guidelines and expert advice from UK diabetes clinicians that recommend glycaemic monitoring and education/psychological support via consultations every 6 months for adults, with more frequent monitoring for children (at least every 3 months). ^{20,21} Costs were based on monitoring touchpoints that include CGM, HbA1c testing and either an MDT consultation or telephone consultation by a diabetologist consultant. ²¹
Disease management costs for Stage 3 T1D (Section B.3.5.2.2)	Costs were based on an initial cost at the onset of Stage 3 T1D followed by estimated HCRU costs per cycle (i.e., 6 months) after onset of Stage 3 T1D	Initial costs incurred at the onset of Stage 3 T1D were based on data from Hex et al. (2024), which estimated total annual direct healthcare costs of Stage 3 T1D in the UK. ¹¹⁹ HCRU costs per person per cycle after onset of Stage 3 T1D were estimated based on trends derived from regression models fitted to observed total healthcare cost data from a longitudinal cohort of people with newly diagnosed T1D followed for 14 years since onset, constructed from Taiwan's National Health Insurance Research Database covering the period 1999 to 2012. ¹⁷⁴ No UK-specific literature was identified that reported appropriate aggregate costing information for Stage 3 T1D that showed the cost changes over time.
AE management costs (Section B.3.5.3)	Costs were based on the frequencies and duration of the five most common AEs reported during treatment with teplizumab	AE management costs were obtained from the National Schedule of NHS Costs and inflated to 2023 costs, ^{172,175} assuming the cost of a general practitioner visit. AE management costs were included as one-off costs.

AE = adverse event; BNF = British National Formulary; CGM = continuous glucose monitoring; CI = confidence interval; CRS = cytokine release syndrome; DKA = diabetic ketoacidosis; HbA1c = glycosylated haemoglobin; HCRU = healthcare resource utilisation; HR = hazard ratio; HRQoL = health-related quality of life; ITT = intention-to-treat; MDT = multidisciplinary team; NIHR = National Institute for Health and Care Research; ONS = Office of National Statistics; PAS = patient access scheme; SmPC = summary of product characteristics; T1D = type 1 diabetes

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

Baseline characteristics were based on the TN-10 study.¹⁴¹ The mean age and proportion of female participants of the TN-10 study population are presented in Table 23.

Table 23. Baseline Characteristics

Characteristic	Value
Mean age, years	13.58
Female, %	44.68

Source: Herold 2019.¹⁴¹

B.3.3.2 Clinical parameters and variables

Clinical parameters which were included in the model are as follows:

- Time to onset of Stage 3 T1D
- Risk of developing DKA at onset of Stage 3 T1D
- Mortality for Stage 2 and Stage 3 T1D

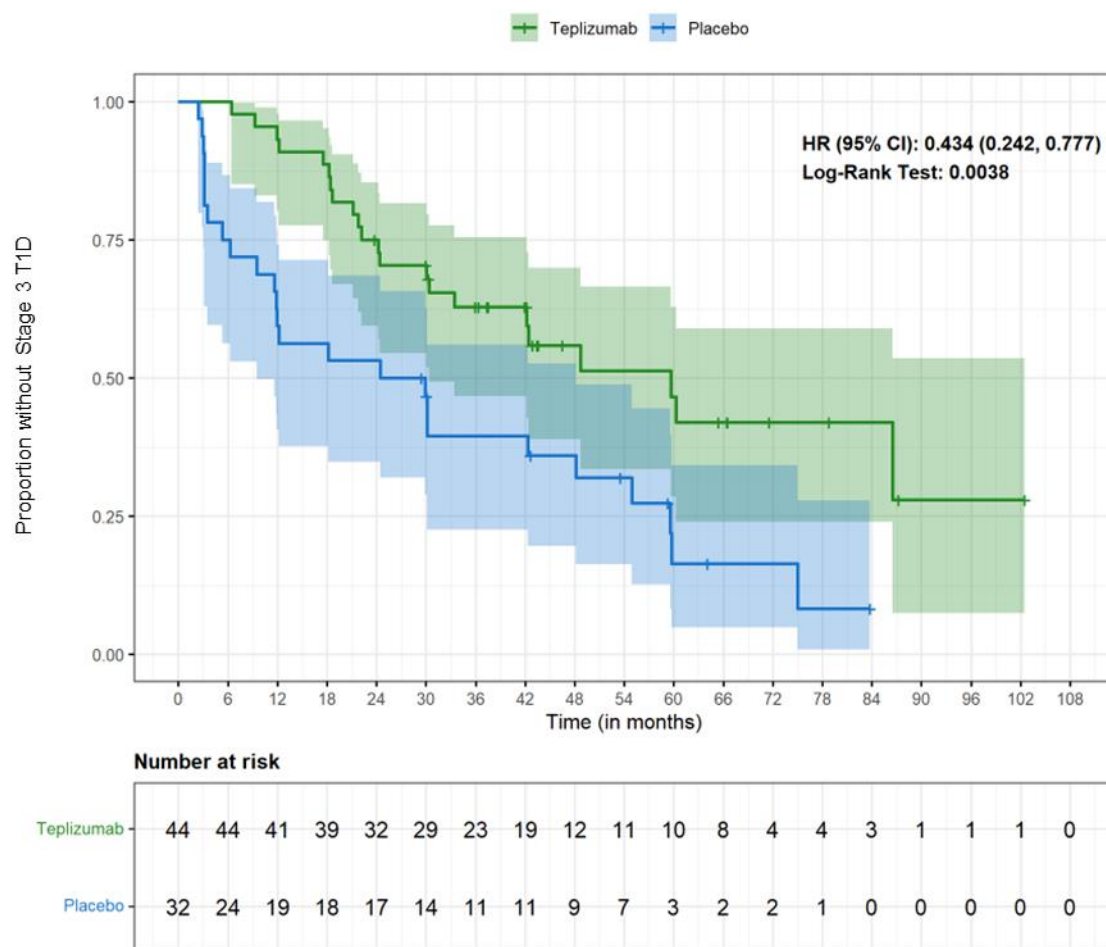
B.3.3.2.1 Time to onset of Stage 3 T1D

Transition probabilities from the Stage 2 to Stage 3 T1D health state at each model cycle were based on parametric distributions fitted to treatment-specific KM curves derived from participant-level data from the TN-10 study.

In the base case, time to onset of Stage 3 T1D of the ITT population reported by Sims et al. (2021) was extrapolated to inform individuals' transition from Stage 2 to Stage 3 T1D.¹⁴³ Sims et al. (2021) reported the outcomes of the TN-10 trial with an extended follow-up period (median 923 days).¹⁴³ Following recommendations in NICE Decision Support Unit Report 14 on survival data extrapolation, exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma distributions were fitted to model time to Stage 3 T1D.¹⁶⁵

KM plots for teplizumab and placebo are shown in Figure 6.

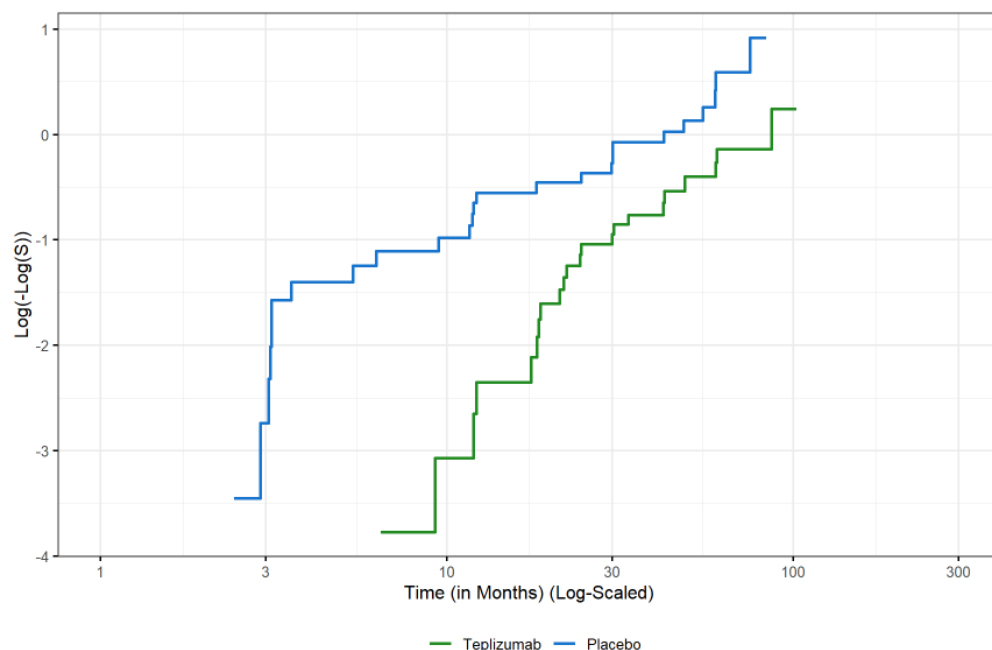
Figure 6. Observed KM curves (ITT population)



CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

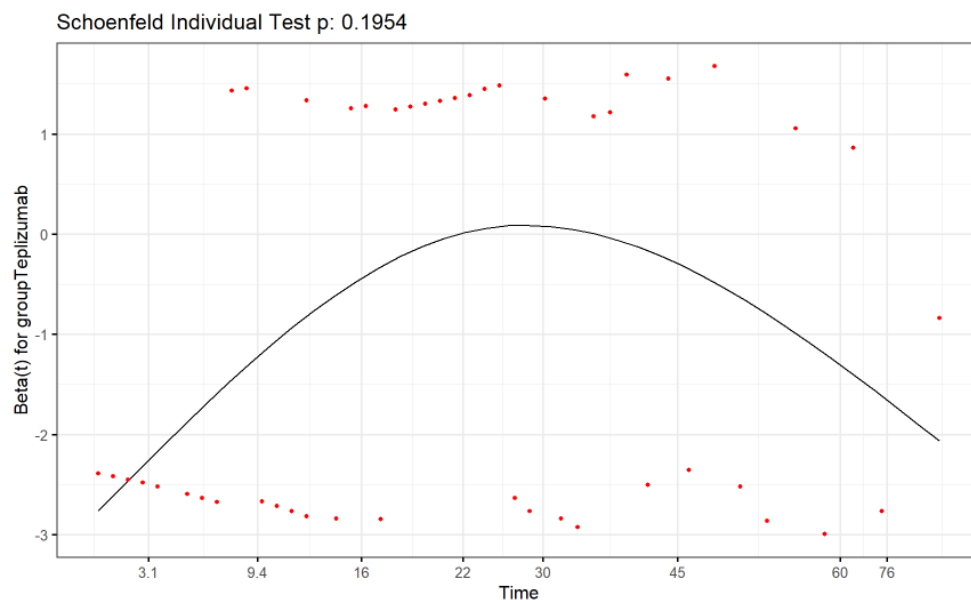
The nonparallel nature of the log-cumulative hazard plots displayed in Figure 7 suggested that the PH assumption was not appropriate. Furthermore, the Schoenfeld residual (Figure 8) implied that the PH assumption may not be reasonable; the line fitted to the Schoenfeld residuals was not parallel in relation to 0. Thus, independent parametric fits were recommended in the analysis for the ITT population (Sims et al., 2021).

Figure 7 Log-cumulative hazard plot (ITT population)



ITT = intention-to-treat

Figure 8. Schoenfeld residuals plot (ITT population)



ITT = intention-to-treat

Parametric fitting using individual curves

Statistical fit estimates using individual curves based on modified Burnham/Anderson Akaike information criterion (AIC)¹⁷⁶⁻¹⁷⁸ and Kass/Raftery criteria for Bayesian information criterion

(BIC)^{179,180}, respectively, are summarised in Table 24. Statistical goodness-of-fit classifications based on modified Burnham/Anderson and Kass/Raftery criteria for AIC and BIC criterion, respectively, are summarised in Table 25.

For teplizumab, the log-normal distribution produced the best statistical fit with the lowest AIC and BIC. All other distributions produced a good relative statistical fit for AIC (<4-point difference)¹⁷⁶⁻¹⁷⁸ and a good (<2-point difference) or reasonable (2-6-point difference) fit for BIC.^{179,180}

For placebo, the log-normal distribution produced the best statistical fit with the lowest AIC, while the exponential distribution produced the best statistical fit based on the second lowest BIC. All other distributions produced a good statistical fit for AIC (<4-point difference)¹⁷⁶⁻¹⁷⁸ and a good (<2-point difference) or reasonable (2-6-point difference) fit for BIC.^{179,180}

Table 24. AIC and BIC estimates using individual curves (ITT population)

Distribution	Teplizumab		Placebo	
	AIC	BIC	AIC	BIC
Exponential	239.6	241.4	232.5	234.0
Weibull	239.0	242.6	234.0	237.0
Gompertz	241.0	244.6	234.2	237.2
Log-logistic	237.3	240.9	234.2	237.1
Log-normal	236.0	239.5	232.3	235.2
Gamma	238.2	241.8	234.2	237.1
Generalised gamma	237.1	242.5	233.9	238.3

AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat

Table 25. AIC and BIC goodness-of-fit for each distribution using individual curves relative to the distribution with the lowest AIC and BIC (ITT population)

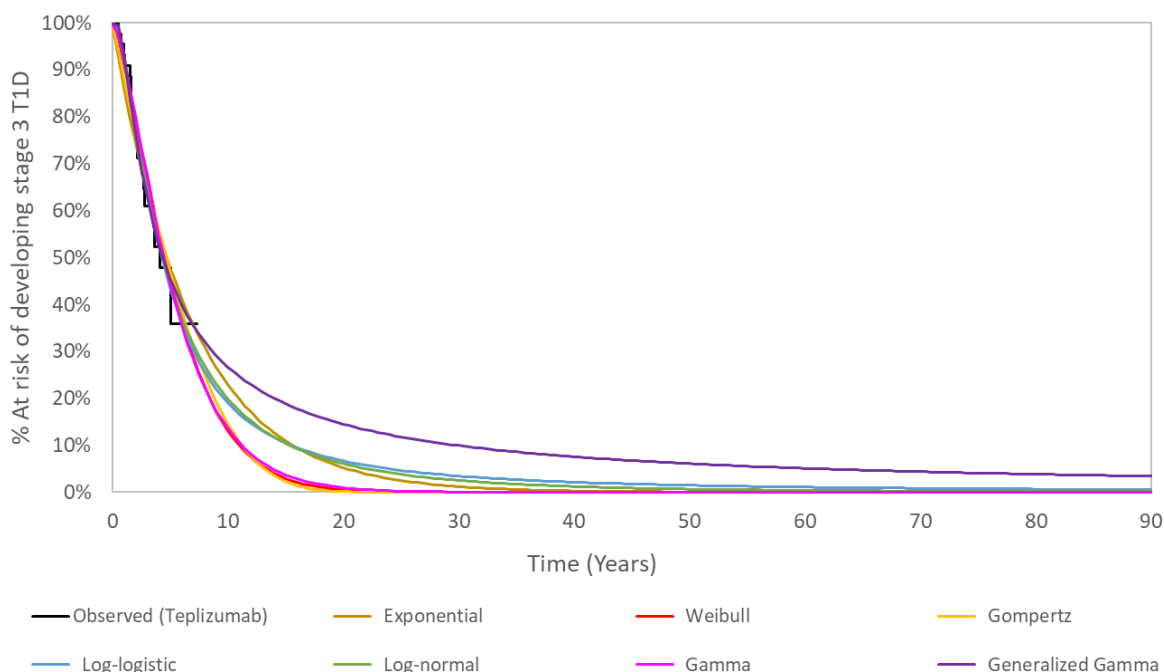
Distribution	Difference From Lowest AIC	AIC Relative Goodness-of-Fit Classification ¹⁷⁶⁻¹⁷⁸	Difference From Lowest BIC	BIC Relative Goodness-of-Fit Classification ^{179,180}
Teplizumab				
Exponential	3.6	Good (0-4 difference)	1.9	Good (0-2 difference)
Weibull	3	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Gompertz	5	Reasonable (4-7 difference)	5.1	Reasonable (2-6 difference)
Log-logistic	1.3	Good (0-4 difference)	1.4	Good (0-2 difference)
Log-normal	Lowest AIC	Reference	Lowest BIC	Reference
Gamma	2.2	Good (0-4 difference)	2.3	Reasonable (2-6 difference)
Generalised gamma	1.1	Good (0-4 difference)	3	Reasonable (2-6 difference)
Placebo				
Exponential	0.2	Good (0-4 difference)	Lowest BIC	Reference

Distribution	Difference From Lowest AIC	AIC Relative Goodness-of-Fit Classification ¹⁷⁶⁻¹⁷⁸	Difference From Lowest BIC	BIC Relative Goodness-of-Fit Classification ^{179,180}
Weibull	1.7	Good (0-4 difference)	3.0	Reasonable (2-6 difference)
Gompertz	1.9	Good (0-4 difference)	3.2	Reasonable (2-6 difference)
Log-logistic	1.9	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Log-normal	Lowest AIC	Reference	1.2	Good (0-2 difference)
Gamma	1.9	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Generalised gamma	1.6	Good (0-4 difference)	4.3	Reasonable (2-6 difference)

AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat
Source: Burnham 2002;¹⁷⁶ Burnham 2004;¹⁷⁷ Burnham 2011;¹⁷⁸ Kass 1995;¹⁷⁹ Raftery 1995.¹⁸⁰

An overlay of the parametric curves on the KM curve for the ITT population (Sims et al. [2021]) on teplizumab and the parametric curves in the long term are presented in Figure 9. All distributions produced relatively similar visual fits to the observed data up to the tail of the KM curve. The clinical plausibility of generalised gamma model may be challenged given the plateau of the curve in the long term.

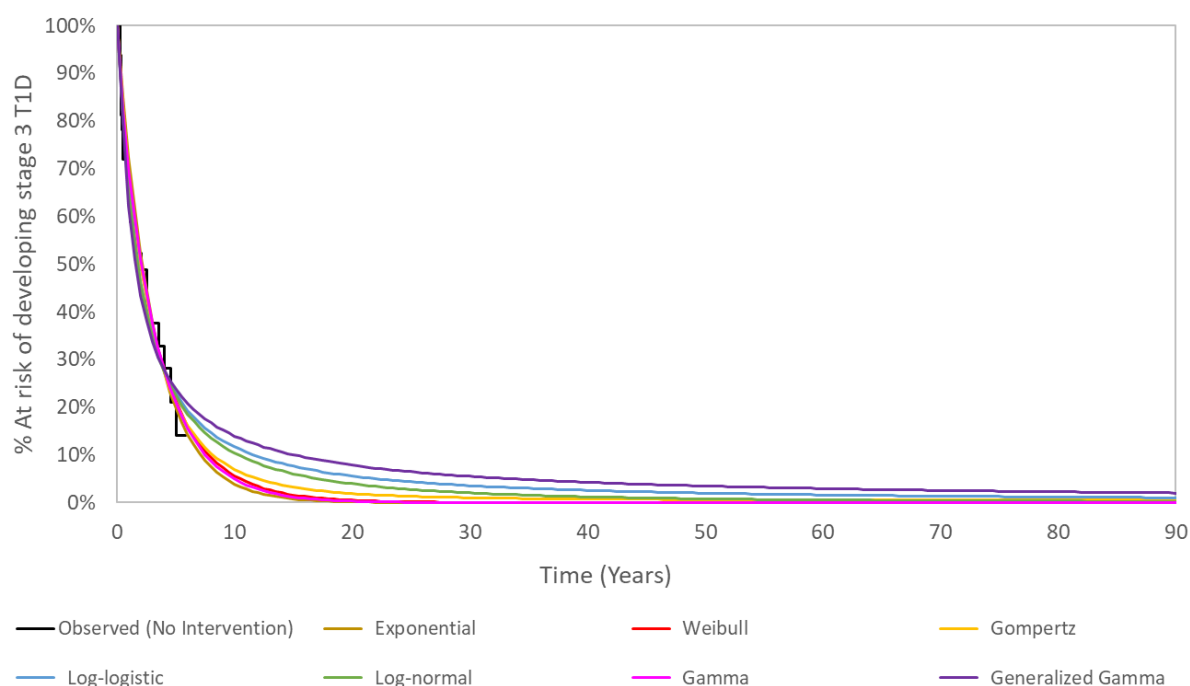
Figure 9 Time to Stage 3 T1D parametric fits for individuals on teplizumab using individual curves (ITT population)



ITT = intention-to-treat; T1D = type 1 diabetes

An overlay of the parametric curves on the KM curve for the ITT population (Sims et al. [2021]) receiving placebo and the parametric curves in the long term are presented in Figure 10. All models provided reasonable overall visual fits, although the generalised gamma model also appeared to somewhat overpredict the tail.

Figure 10 Time to Stage 3 T1D parametric fits for individuals receiving placebo using individual curves (ITT population)



ITT = intention-to-treat; T1D = type 1 diabetes

For individuals receiving teplizumab, the log-normal distribution was considered the most appropriate distribution because it generated the best visual fit to the KM curve and the best fit (i.e., lowest AIC and BIC). For individuals receiving established clinical management, the log-normal distribution produced clinically unrealistic estimates of the proportion of individuals who will not have progressed to Stage 3 T1D in the long term (Table 26). The exponential distribution was therefore selected for individuals receiving established clinical management in the base case because it provided the best overall visual fit to the observed KM curve, with the second lowest AIC and lowest BIC.

Table 26. Proportion of individuals in Stage 2 T1D receiving established clinical management by parametric fitting

Time (years)	Proportion of Individuals in Stage 2 T1D	
	Exponential distribution ^a	Log-normal distribution
0	██████	██████
5	██████	██████
10	██████	██████
15	██████	██████

^a Selected for individuals receiving established clinical management in the base case
T1D = type 1 diabetes

Parametric fitting using a joint distribution

Statistical fit estimates using a joint parametric distribution based on modified Burnham/Anderson AIC¹⁷⁶⁻¹⁷⁸ and Kass/Raftery criteria for BIC^{179,180}, respectively, are summarised in Table 27. Statistical fit classifications based on modified Burnham/Anderson and Kass/Raftery criteria for AIC and BIC, respectively, summarised in Table 28.

Table 27 AIC and BIC estimates using a joint parametric distribution (ITT population)

Distribution	AIC	BIC
Exponential	472.2	476.8
Weibull	474.0	481.0
Gompertz	474.1	481.1
Log-logistic	472.0	479.0
Log-normal	468.6	475.6
Gamma	473.7	480.7
Generalised gamma	467.8	477.1

AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat

Table 28 AIC and BIC goodness-of-fit for each distribution using a joint parametric distribution relative to the distribution with the lowest AIC and BIC (ITT population)

Distribution	Difference from Lowest AIC	AIC Relative goodness-of-fit Classification ¹⁷⁶⁻¹⁷⁸	Difference from Lowest BIC	BIC Relative goodness-of-fit Classification ^{179,180}
Exponential	4.4	Reasonable (4-7 difference)	1.2	Good (0-2 difference)
Weibull	6.2	Reasonable (4-7 difference)	5.4	Reasonable (2-6 difference)
Gompertz	6.3	Reasonable (4-7 difference)	5.5	Reasonable (2-6 difference)
Log-logistic	4.2	Reasonable (4-7 difference)	3.4	Reasonable (2-6 difference)
Log-normal	0.8	Good (0-4 difference)	Lowest BIC	Reference
Gamma	5.9	Reasonable (4-7 difference)	5.1	Reasonable (2-6 difference)
Generalised gamma	Lowest AIC	Reference	1.5	Good (0-2 difference)

AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat

Source: Burnham 2002;¹⁷⁶ Burnham 2004;¹⁷⁷ Burnham 2011;¹⁷⁸ Kass 1995;¹⁷⁹ Raftery 1995.¹⁸⁰

An overlay of the parametric curves on the KM curve along with the parametric curves in the long term for the ITT population (Sims et al. [2021]) on teplizumab and placebo are presented in Figure 11 and Figure 12, respectively. The generalised gamma model clearly overpredicted the KM curve from year 5 onward. All other distributions produced reasonable overall visual fits to the observed data up to the tail of the KM curve.

Figure 11 Time to Stage 3 T1D parametric fits for individuals on teplizumab using a joint parametric distribution (ITT population)

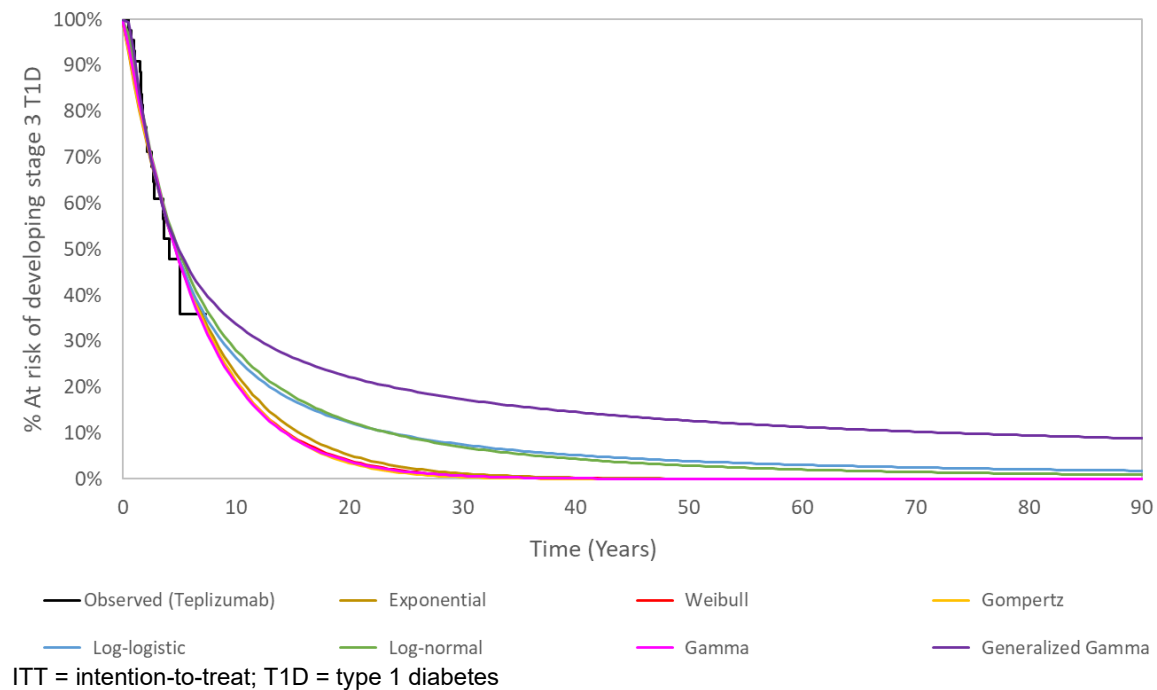
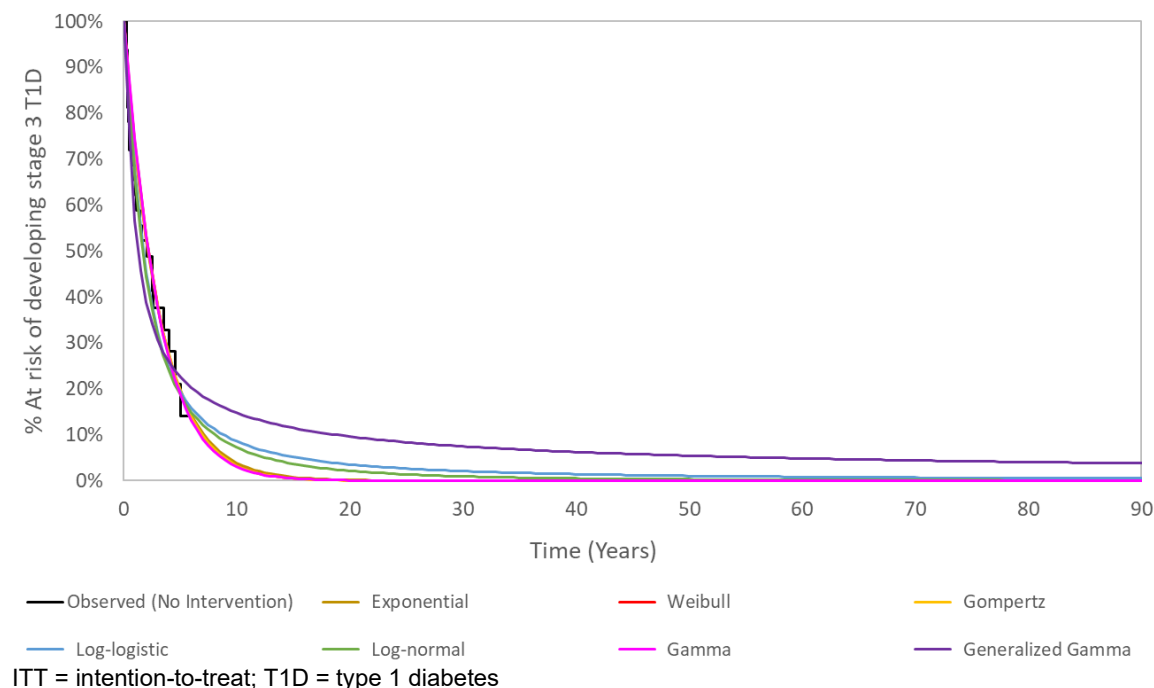


Figure 12 Time to Stage 3 T1D parametric fits for individuals on placebo using a joint parametric distribution (ITT population)



If adopting a joint fits approach, the log-normal distribution was considered the most appropriate distribution, given that it generated the best visual fit to the KM curve and the best fit (i.e., lowest BIC and second lowest AIC). However, as discussed previously, independent parametric fits were recommended in the analysis for the ITT population (Sims et al., 2021) based on analyses suggesting that the PH assumption was not appropriate.

B.3.3.2.2 DKA risk at onset of Stage 3 T1D

DKA events can occur at the time of onset of Stage 3 T1D. These events are known to be costly and potentially life threatening (Section B.1.3.3.1).²⁵ A review article by Besser et al. (2022) estimated that, in the UK, approximately a quarter of individuals with Stage 3 T1D present with DKA.⁵⁶ However, identifying and monitoring individuals with Stage 2 T1D before onset of Stage 3 T1D is assumed to reduce the risk of DKA by 90%.⁵⁶ Thus, the proportion with DKA at onset of Stage 3 T1D was estimated to be 2.5% for individuals with Stage 2 T1D receiving established clinical management or teplizumab in the model (i.e., a 90% reduction in the DKA incidence rate at onset of Stage 3 T1D [25%] results in a DKA incidence rate of 2.5%).⁵⁶

DKA events were only considered at onset of Stage 3 T1D, and it was assumed that there were no differences in the risk of an event between treated (teplizumab) and untreated individuals.

B.3.3.2.3 *Mortality for Stage 2 T1D*

For individuals with Stage 2 T1D, the risk of death was assumed to be the same as the general population and was therefore derived from the UK general population life tables.¹⁶⁶ This assumption was made because no published data have been identified indicating that individuals with Stage 2 T1D have an increased risk of death compared with the general population.

The UK general population life tables used in the base case were based on 2020-2022 data.¹⁶⁶ Given that this time period was concurrent with the Coronavirus disease 2019 (COVID-19) pandemic, life tables based on an earlier time period (2017-2018) were tested in scenario analyses (Section B.3.11.3).

B.3.3.2.4 *Mortality for Stage 3 T1D*

The TN-10 trial could not be used to inform mortality for Stage 3 T1D in the model as there were no deaths in the study.¹⁴²

Stage 3 T1D is associated with an increased mortality risk compared with the general population¹¹ and this was captured in the model by assigning an increased risk of death to individuals in the Stage 3 T1D health state based on age of onset. For individuals who received teplizumab in the model, delaying the onset of Stage 3 T1D led to developing the disease later in life and therefore an increase in total life years.

In line with the model structure, aggregated mortality estimates were applied in the model when individuals transitioned to Stage 3 T1D (see Section B.3.2.2.2 for justification of the aggregate modelling approach). The impact of individual Stage 3 T1D complications on mortality was not directly quantified. This approach was considered valid by UK experts during a May 2024 advisory board convened by Sanofi.⁸

Base case analysis: excess mortality by age bracket

The mortality rate in the Stage 3 T1D health state was higher than that of the general population, capturing the excess mortality associated with Stage 3 T1D. Potential survival gains from delaying progression to Stage 3 T1D were captured by applying a HR by age categories at onset of Stage 3 T1D (Table 29) to the UK general population life tables.

- The HR for children (<18 years) was sourced from an analysis of the Swedish National Diabetes Register (Samuelsson et al. [2024]). The analysis included data for 15,188 individuals with Stage 3 T1D and 74,210 controls from between 2000 and 2019 and is thus expected to reflect current standard of care (in the

absence of recent UK-specific data).⁸¹ This source was selected as it was the most recent publication identified and thus is expected to provide the most accurate representation of the current clinical landscape.

- Although the Samuelsson et al. (2024) study provides the most up-to-date mortality data for Stage 3 T1D, it did not provide a mortality HR for adults. A second publication was identified, Lung et al. (2014), which provided pooled mortality estimates for adults and children with Stage 3 T1D based on meta-analyses of studies reporting these data.¹⁶⁷ Although these data were considered outdated and were not used for the base case, the mortality estimates for adults and children were used to inform the mortality estimate for adults in the base case. Given that the mortality for individuals diagnosed after 18 years of age was reported to be approximately half of the mortality estimate for individuals diagnosed before 18 years of age (2.41 vs. 4.93, respectively),¹⁶⁷ the mortality for adults with Stage 3 T1D (>18 years) in the base case was assumed to be 50% of the mortality estimate for children with Stage 3 T1D (<18 years). This assumption was made based on published evidence demonstrating excess mortality among individuals with Stage 3 T1D relative to the general population in Sweden.⁸⁰

No UK-specific literature providing excess risk of death compared with the general population stratified by age of onset of Stage 3 T1D was identified. Mortality rates for T1D in general may still be available. Therefore, the study by Samuelsson et al. (2024) is the best source currently available.

Table 29. HRs stratified by age at onset of Stage 3 T1D

Age at Onset of Stage 3 T1D	HR (95% CI)	Source
Before 18 years	1.57 (1.16, 2.12)	Swedish registry ⁸¹
After 18 years	1.285 (NA)	Assumption (50% of the mortality estimate for children) ¹⁶⁷

CI = confidence interval; HR = hazard ratio; 1D = type 1 diabetes

Scenario analysis: meta-regression of excess mortality

An alternative approach to the estimation of mortality in Stage 3 T1D was tested in scenario analyses. Rawshani et al. (2018) reported excess risk of all-cause mortality based on an analysis including 27,195 persons with Stage 3 T1D in the Swedish National Diabetes Registry and 135,178 matched control subjects from the general population (1998 to 2012).⁸⁰ This study found that Stage 3 T1D was associated with an increased risk of mortality vs. the general population, and this excess mortality decreases as individuals with Stage 3 T1D age.⁸⁰ The Rawshani et al. (2018) study shares commonalities with the Samuelsson et al. (2024) study given that it is also a Swedish data source that provides an estimation of excess mortality of individuals with Stage 3 T1D compared with the general population in the absence of a UK-specific data source. However, the study period for

Rawshani et al. (2018) is older than that of Samuelsson et al. (2024) (1998 to 2012 vs. 2000 to 2019, respectively),^{80,81} therefore Samuelsson et al. (2024) was considered a better option for the base case analysis. Rawshani et al. (2018) was included in the model as a scenario analysis to allow for more granularity in capturing the mortality HR as it reports estimates based on age of onset of Stage 3 T1D (Table 30).

Table 30. Adjusted HRs for all-cause mortality stratified by age at onset of Stage 3 T1D

Age	HR (95% CI)
0 to 10 years	4.11 (3.24, 5.22)
11 to 15 years	3.21 (2.58, 4.00)
16 to 20 years	3.02 (2.44, 3.73)
21 to 25 years	2.90 (2.41, 3.50)
26 to 30 years	2.83 (2.38, 3.37)

CI = confidence interval
Source: Rawshani 2018⁸⁰

A meta-regression was conducted on the data points reported in Rawshani et al. (2018), using the following general equation form:

$$\text{Log(HR)} = \text{Intercept} + B1 \times \text{log(age)},$$

where HR is the excess mortality ratio vs. the general population, age is the age of onset of Stage 3 T1D, and *B1* is the coefficient of the Log(age) term. The intercept and coefficient are presented in Table 31.

Table 31. Meta-regression model for excess mortality

Input	Estimate (95% CI)	SE
Intercept	1.74 (1.28 to 2.21)	0.24
<i>B1</i>	-0.22 (-0.38 to -0.06)	0.08

CI = confidence interval; SE = standard error

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life studies

A humanistic SLR conducted on 02 May 2023 and updated on 27 June 2024 identified 98 sources reporting on 94 studies assessing HRQoL and/or utilities in T1D, none of which were conducted in people with Stage 2 T1D. A clinical SLR was conducted on the same date and identified five sources reporting on the TN-10 trial in people with Stage 2 T1D; however, none of the sources reported HRQoL or utility data. Note that HRQoL was not collected in the TN-10 trial. Full details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix D and Appendix H. Overall, the

humanistic and clinical SLRs did not identify any HRQoL or utility studies that reported appropriate information for the model. For this reason, targeted searches were conducted to identify sources with the appropriate information for the model.

B.3.4.2 Health-related quality of life data used in the cost-effectiveness analysis

B.3.4.2.1 General population utility

Age-specific utility estimates of the UK general population were applied to individuals with Stage 2 T1D. This allows the model to account for the decline in QoL as individuals age. General population norms were based on a regression model from a 2022 NICE Decision Support Unit report (Table 32) that fitted an adjusted limited dependent variable mixture model to the most recent available Health Survey for England data set (2014) for EQ-5D-3L.¹⁸¹ The last column in the table represents the population utilities factoring in the distribution of female/male individuals (population characteristics from Table 23).

Table 32. EQ-5D-3L utilities for the UK general population

Age Bracket (years)	Utilities		Utilities Weighted (by sex)
	Female	Male	
0 – 9	NR	NR	0.994 ^a
10 – 19	0.9103	0.9446	0.929
20 – 29	0.9101	0.9332	0.923
30 – 39	0.8981	0.9158	0.908
40 – 49	0.8764	0.8943	0.886
50 – 59	0.8464	0.8684	0.859
60 – 69	0.8082	0.8379	0.825
70 – 79	0.7613	0.8027	0.784
80 – 89	0.7045	0.7634	0.737
90 – 100	0.6376	0.7208	0.684

^a Utility for the 0 to 9 years age bracket was estimated using a linear regression based on the utilities for the other age brackets.

NR = not reported

Source: Hernández-Alava 2022.¹⁸¹

B.3.4.2.2 Utility estimates for Stage 2 T1D

Individuals with Stage 2 T1D were assumed to have the same QoL as the UK general population because they do not present with symptoms.¹⁻³ Expert advice from UK diabetes clinicians indicated that no substantive decrement in utility is observed in individuals with presymptomatic T1D (Stage 1 or Stage 2 T1D) compared with the general population.⁸

In the teplizumab arm, infusion-related disutilities were applied for the duration of treatment (i.e., 14 days) to the utility estimates of the general population (Section B.3.4.2.1) as a one-

off treatment-related burden for people receiving teplizumab. Table 33 shows the disutility values and duration.

The value was sourced from a UK study by Matza et al. (2013) reporting the disutility associated with various treatment modalities for cancer with bone metastases, including IV infusion, as evaluated by individuals from the general population.¹⁶⁸ The disutility for a 30-minute infusion was used as a proxy in the model to estimate the disutility for people with Stage 2 T1D receiving teplizumab, given that there were no published disutility values for people with Stage 2 T1D identified in the clinical or humanistic SLRs.

Table 33. Infusion-related disutility for people with Stage 2 T1D

Person with Stage 2 T1D	Value	Duration (days)
Person with Stage 2 T1D	-0.023	14

Source: Matza 2013¹⁶⁸

B.3.4.2.3 Utility estimates for Stage 3 T1D

Stage 3 T1D–related disutilities were applied to the utility estimates of the general population (Section B.3.4.2.1) after onset of Stage 3 T1D. Disutilities associated with the onset of Stage 3 T1D and with Stage 3 T1D vs. the general population were applied in the model to account for additional QoL loss due to Stage 3 T1D. The rationale for the latter was that the baseline utility for a person with Stage 3 T1D may be lower than that of the general population, even in the absence of Stage 3 T1D–related complications. Disutilities associated with the onset of Stage 3 T1D were applied at the time of onset and for a duration of one model cycle (i.e., 6 months).

Table 34 shows the disutility values for each age category at onset of Stage 3 T1D and relative to the general population. The values for onset of Stage 3 T1D were sourced from a study by Sparring et al. (2013) that analysed HRQoL in registered individuals from the Diabetes Incidence Study in Sweden with onset of Stage 3 T1D at the age of 15 to 34 years and with a disease duration of 8, 15 and 24 years compared with control individuals from the general population matched for age, sex and county of residence.¹² This study was considered the most appropriate available input source because HRQoL for Swedish individuals with Stage T1D 3 was reported based on disease duration, which aligned with the needs for the model. The values for Stage 3 T1D vs. the general population were sourced from Sullivan et al. (2011), which reports nationally representative preference-based HRQoL scores for having diabetes without complications in the UK, based on the EQ-5D (NICE’s preferred measure).¹⁶⁹

Table 34. Disutilities for Stage 3 T1D

Disutility	0-17 years	≥18 years
Onset of Stage 3 T1D ¹²	-0.025	-0.025
Stage 3 T1D vs. general population ¹⁶⁹	-0.0621	-0.0621

T1D = type 1 diabetes

Source: Sparring 2013;¹² Sullivan 2011.¹⁶⁹

Disutilities based on Stage 3 T1D disease duration (Table 35) were also obtained from Sparring et al. (2013).¹² The study used one year outcomes as a point of reference (given that they are captured relatively soon after onset of Stage 3 T1D and it was expected that individuals will not have developed T1D-related complications within this timeframe), and then provided the disutility for years 8, 15 and 24 of disease duration.¹² The values from this study were selected for the model because the model applies T1D-related disutilities subtracted from a reference utility value.

Table 35. Disutility values for people with Stage 3 T1D based on time since onset of Stage 3

Time from onset of Stage 3 T1D	Disutility
8 years	-0.023
15 years	-0.055
24 years	-0.074

T1D = type 1 diabetes

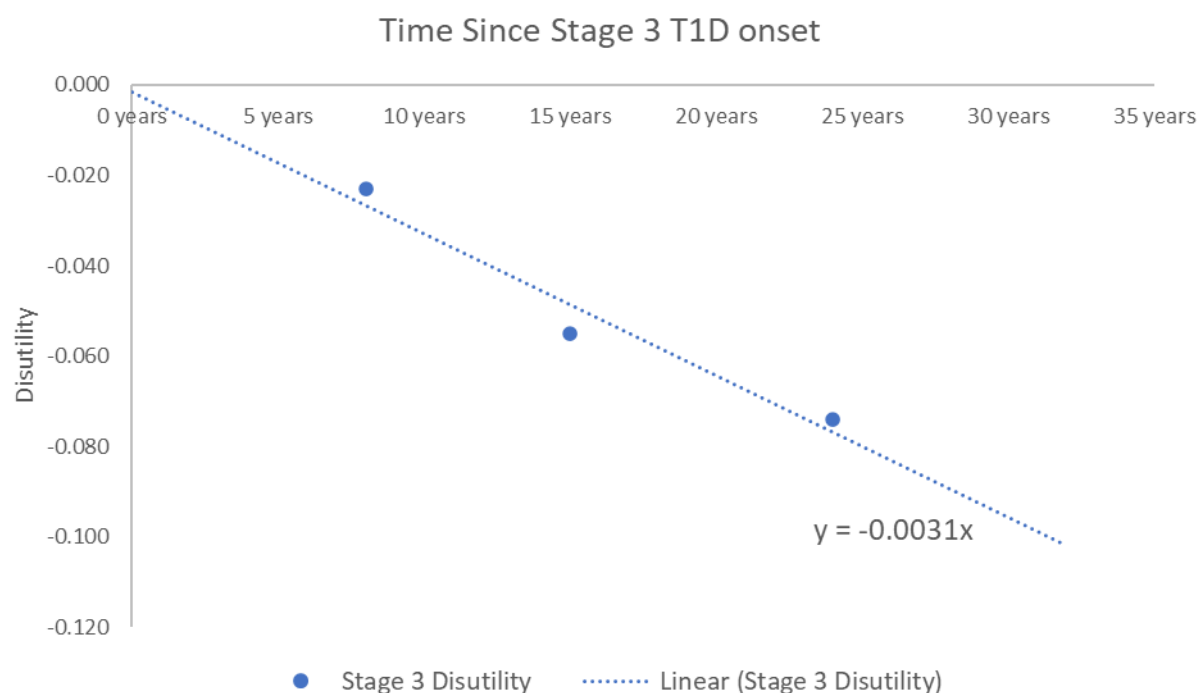
Source: Sparring 2013.¹²

A linear regression model was applied to the disutility values from Sparring et al. (2013) to calculate the disutility for each cycle depending on the number of years since the onset of Stage 3 T1D. The linear regression model (Figure 13) was fitted to the data presented in Table 35 to estimate the disutility value for Stage 3 T1D after a given number of years since onset of Stage 3 T1D:

$$y = -0.0031x,$$

where x represents the years from onset of Stage 3 T1D and y represents the disutility values.

Figure 13. Linear regression model for Stage 3 T1D disutilities according to time from onset



T1D = type 1 diabetes

B.3.4.2.4 Carer/parent utility for Stage 3 T1D

Disutility for carer/parental burden was applied in the model to capture the negative impacts of Stage 3 T1D and its management on parents and siblings of children with Stage 3 T1D, such as constant worry, social isolation, disruption to family life and routines and psychosocial maladjustment (Section B.1.3.3.2).^{99,114} Carers/parent disutilities were only applied for individuals <18 years old in the Stage 3 T1D health state. The carer/parent disutility was estimated to be -0.040 based on a publication by López-Bastida et al. (2019), who studied carers' self-reported HRQoL for children with Stage 3 T1D receiving outpatient care at paediatric endocrinology specialised centres in Spain.⁸⁹ The study reported a carer EQ-5D-5L score of 0.92 which was subtracted from the general population mean utility of 0.96 to obtain the disutility of -0.040.⁸⁹ This study was considered the most appropriate available input source because UK data were not identified from published literature from the past 10 years.

The economic model assumes 1.76 carers/parents take care of each child after onset of Stage 3 T1D, up to when the child reaches 18 years of age. The number of carers/parents was calculated as a weighted average of number of carers/parents in families with dependent children using 2023 data on families and children in the UK by family type from the Office of National Statistics (ONS).¹⁷⁰

Table 36 Number of carers/parents in families with dependent children in the UK

	Number of families with children (thousands)	Source	Proportion out of total number of families with children	Number of parents with children	Weighted average
Couple family ^a	6,278	ONS ¹⁷⁰	76%	2	1.76
Lone parent family ^b	2,024		24%	1	
Total	8,302		100%	N/A	

^a Includes couple families with parents who were married, civil partners, opposite-sex cohabiting, or same-sex cohabiting; assumes 2 parents per family

^b Assumes 1 parent per family

B.3.4.3 Adverse reactions

AE frequencies were obtained from Herold et al. (2023), who listed the most common AEs reported in $\geq 10\%$ of participants treated with teplizumab based on pooled data from five clinical trials of teplizumab, including TN-10.¹⁴⁴ Among these AEs, the five most common AEs, which also occurred at a higher frequency in the teplizumab group vs. the control group, were lymphopenia, leukopenia, neutropenia, decreased blood bicarbonate and rash.¹⁴⁴ These five most common AEs reported with teplizumab identified from the pooled analysis were therefore included in the model. The model assumes no AEs for individuals receiving established clinical management. Lymphopenia was reported to have resolved by day 45 in TN-10 trial.¹⁴¹ Most AEs were grade 1 or 2 in severity and a majority of them resolved without intervention.¹⁴⁴ Therefore, the duration of the other AEs was assumed to be 7 days.

The pooled analysis also reported rates for other AEs experienced by individuals who were treated with teplizumab, including cytokine release syndrome (CRS; 5.8% of participants treated with teplizumab, of which 88% were grade 1 or 2 and treated with non-prescription medications); however, these other AEs did not meet the established threshold of $\geq 10\%$ to be considered as 'common' in the Herold et al. (2023) analysis, and were therefore not included in the model.¹⁴⁴

Disutility values for AEs were obtained from Sullivan et al. (2011) (Table 37), which reports nationally representative preference-based HRQoL scores for the relevant AEs in the UK, based on the EQ-5D (NICE's preferred measure).^{169,171} AE disutilities were applied as a one-off, accounting for the specified duration of the AE.

Table 37. AE disutility

Adverse Event	Excess proportion ^a (%) (vs. placebo)	Source	Duration (days)	Source	Disutility	Source
Lymphopenia	63.2%	Integrated safety analysis ¹⁴⁴	45	TN-10 ¹⁴¹	-0.0722	Sullivan et al. (2011) ¹⁶⁹
Leukopenia	36.8%		7	Assumption based on integrated safety analysis ¹⁴⁴	-0.0722	
Neutropenia	18.0%		7		-0.0722	
Blood bicarbonate decreased	11.0%		7		-0.0722	
Rash	24.3%		7		-0.0006	

^a Calculated as the difference between the incidence rate in the teplizumab and control arms in the integrated safety analysis

AE = adverse event

Source: Herold 2019;¹⁴¹ Herold 2023;¹⁴⁴ Sullivan 2011¹⁶⁹

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

As described in Section B.3.1, an economic SLR was conducted to identify studies assessing the costs and HCRU of treatments for Stage 2 or 3 T1D to understand the economic burden of T1D in children (≥8 years old) and adults. Full details of the economic SLR methodology, study selection process and inclusion and exclusion criteria are presented in Appendix G; findings regarding costs and HCRU are presented in Appendix I. Sanofi also convened advisory boards in May and July 2024 to gather insights from UK clinical experts on costs and healthcare resource utilisation for T1D in the UK (Appendix M).^{8,21}

B.3.5.1 Intervention costs and resource use

Treatment costs include acquisition and administration costs for teplizumab, as well as teplizumab-related resource use (e.g., tests to confirm eligibility for teplizumab, pre-medications, laboratory evaluations and infusions). Price details of treatments included in the submission are presented in Appendix K.

B.3.5.1.1 Teplizumab acquisition and administration costs

Teplizumab will be available as 14-day treatment course that uses single-vial packs. A patient access scheme (PAS) has been submitted to the Patient Access Scheme Liaison Unit (PASLU). This PAS discounts the price of teplizumab to [REDACTED] (excluding value-added tax [VAT]) per 14-vial treatment course (Table 38).

Table 38. Teplizumab acquisition cost

Cost per Treatment Course	PAS Cost ^a
██████████	██████████

^a The proposed PAS discount is ██████████
PAS = patient access scheme

Teplizumab IV infusions are expected to take place in a tertiary care setting, with most individuals anticipated to be suitable for administration in a closer-to-home setting. This is to offer additional flexibility and to address potential inequalities in access, if deemed acceptable by the individual and their clinician. For those wishing to have care in a closer-to-home setting, it is expected that days 1 to 5 of the infusion will be in a hospital setting, with days 6 to 14 administered closer-to-home. Individuals who undergo treatment in a closer-to-home setting were assumed to have a minimum of 5 days (35.7% of treatment time) in hospital and 9 days (64.3% of treatment time) closer-to-home. For the administration cost of teplizumab, it was assumed that uptake for care in a closer-to-home setting will be 90% and hospital only will be 10%, among paediatrics and adults. The administration cost was calculated as the weighted average between closer-to-home and hospital settings. The prices were obtained from the National Schedule of NHS Costs (Table 39).¹⁷²

Individuals will undergo post-infusion observation by an IV infusion nurse in hospital (1 hour) and by a district nurse in the closer-to-home setting (45 minutes).

Table 39. Teplizumab administration cost

Resource	National Schedule of NHS Costs currency code	National Schedule of NHS Costs currency description	Unit administration cost	Source
Closer-to-home administration (30-minute IV infusion, 45 minutes post-infusion observation, 75 minutes total of nurse time)	N02AF	District Nurse, Adult, Face to face	£139.55 ^a	National Schedule of NHS Costs ¹⁷²
Hospital administration (30 to 60-minute IV infusion, 30-minute nurse time)	SB12Z	Deliver simple parenteral chemotherapy	£217.20	
Hospital post-infusion observation (IV infusion nurse; 1 hour)	NA	NA	£22.40/h	GOV.UK ¹⁸²

^a Assumed 75 minutes for the face-to-face session based on the National Schedule of NHS Costs including 30-60 minutes required for teplizumab infusion.
IV= intravenous; NA = not applicable

B.3.5.1.2 Teplizumab-related resource use

Costs for teplizumab-related resource use were charged as a one-off cost at the start of treatment.

Confirmatory tests

Before teplizumab treatment can be initiated, the diagnosis of Stage 2 T1D must be confirmed by documenting the presence of at least two positive pancreatic islet cell autoantibodies and dysglycaemia without overt hyperglycaemia, as per the requirements in the teplizumab SmPC.³⁴ Table 40 lists the costs associated with confirmatory testing for individuals who will receive teplizumab. Autoantibody testing will involve testing for three autoantibodies (anti-GAD, anti-ZnT8 and anti-IA2) with costs based on an NHS laboratory that is utilised as a referral lab for this assay (Exeter Clinical Laboratory International).¹⁸³ Confirmation of dysglycaemia using an OGTT will involve testing blood glucose at five timepoints (fasting and at 30, 60, 90 and 120 minutes) with costs based on the NICE BNF and National Schedule of NHS Costs.^{172,184}

Table 40. Teplizumab confirmatory test costs

Resource	Frequency	Unit cost	Source	Total cost
Autoantibody tests (anti-GAD, anti-ZnT8 and anti-IA2)	1	£29.04	Exeter Clinical Laboratory International ¹⁸³	£29.04
OGTT – glucose solution	1	£3.98	NICE BNF ¹⁸⁴	£3.98
OGTT – blood glucose tests	5	£7.85	National Schedule of NHS Costs ¹⁷²	£39.25

BNF = British National Formulary; OGTT = oral glucose-tolerance test

Pre-medication

As per the requirements in the teplizumab SmPC, and as recommended by the Pediatric Society for Endocrinology (Mehta et al. [2024]), treating HCPs are required to pre-medicate individuals prior to teplizumab infusion for the first five days of dosing with (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) consider use of an antiemetic, to mitigate CRS.^{34,173} Although the teplizumab SmPC indicates a minimum of five days of pre-medication, expert clinical opinion has recommended covering all 14 days of treatment. The latter assumption has therefore been used as a conservative approach. Pre-medication costs are listed in Table 41.

Table 41. Teplizumab pre-medication costs

Resource	Example medication	Source	Frequency	Unit cost per tablet	Source	Total cost
NSAID or acetaminophen	Ibuprofen 400mg tablet; one tablet three times a day when required	Mehta 2024 ¹⁷³	14	£0.10	Draft SmPC ³⁴ ; NICE BNF ¹⁸⁵	£1.34
Antihistamine	Cetirizine hydrochloride, 10mg tablet; once daily		14	£0.02	Draft SmPC ³⁴ ; NICE BNF ¹⁸⁶	£0.34
Anti-emetics	Ondansetron, 4mg tablet; once daily		14	£0.95	Draft SmPC ³⁴ ; NICE BNF ¹⁸⁷	£13.30

BNF = British National Formulary; NSAID = nonsteroidal anti-inflammatory drug

Laboratory evaluations

As per the teplizumab SmPC, prior to initiating treatment with teplizumab, individuals should undergo complete blood count and liver enzyme tests.³⁴ Individuals who are treated with teplizumab will be monitored for CRS (liver enzymes and bilirubin) and lymphopenia (white blood cell counts) during the 14-day treatment course, and for signs and symptoms of infection during and after treatment.³⁴ Assuming that all individuals would need these laboratory evaluations for all 14 days of treatment is a conservative assumption, given that this will not necessarily be the case for all individuals receiving teplizumab.

Table 42. Teplizumab laboratory evaluation costs

Resource	Frequency	Unit cost	Source
Complete blood count	14	£2.65	Draft SmPC ³⁴ ; Akhtar 2014 ¹⁸⁸
Liver enzyme test	14	£2.78	

Infusion-related resources

A highly specialised pharmacist will prepare each infusion taking an estimated 15 minutes per day (Table 43).

Table 43. Teplizumab infusion-related resource costs

Resource	Hours per treatment course	Unit cost	Source
Infusion preparation (highly specialised pharmacist; 15 minutes)	3.5	£29.60	NHS Jobs ¹⁸⁹

B.3.5.2 Disease management costs and resource use

HCRU costs for disease management per person per cycle (i.e., 6 months) were included before and after onset of Stage 3 T1D.

B.3.5.2.1 Stage 2 T1D Costs

For individuals with Stage 2 T1D, the costs were stratified by age (i.e., 8-18 years and ≥19 years) and were applied to both treatment arms in the model. Assumptions for resource use were based on international monitoring guidelines and expert advice from UK diabetes clinicians that recommend glycaemic monitoring and education/psychological support consultations every 6 months for adults, with more frequent monitoring for children (at least every 3 months).^{20,21} Costs were based on monitoring touchpoints that include CGM, HbA1c testing, and either a multidisciplinary team (MDT) consultation or telephone consultation by a diabetologist consultant.²¹ The NHS defines multidisciplinary attendances as a patient consultation involving a team of multiple HCPs with at least two consultants from different national main specialities;¹⁹⁰ it is expected that the MDT members would be the same at each touchpoint. Annual costs for the monitoring touchpoints are described in Table 44. The cost values can be set for four different time periods before Stage 3 T1D onset (0 to 6 months, 6 to 12 months, 12 to 24 months, and >24 months) to allow for the possibility that Stage 2 T1D costs will vary over time. The monitoring costs are the same with or without teplizumab as the monitoring pathway is expected to be the same for both treatment arms (Figure 2).

Table 45 presents the monthly costs for Stage 2 T1D based on the annual costs from Table 44.

Table 44. Annual HCRU costs for Stage 2 T1D

Resource	Annual frequency		Unit cost	Annual Cost		Sources
	Paediatrics	Adults		Paediatrics	Adults	
CGM	4	2	£43.00 (based on cost of FreeStyle Libre 3 sensor)	£172.0	£86.0	NICE TA943 committee papers ¹⁹¹
HbA1c testing	4	2	£14.00 (based on	£56.0	£28.0	NIHR ¹⁹²

Resource	Annual frequency		Unit cost	Annual Cost		Sources
	Paediatrics	Adults		Paediatrics	Adults	
			cost of single HbA1c test)			
Paediatric MDT	2	-	£242.00 (WF02B – Treatment code 263)	£484.0	£0.0	NHS England ¹⁹³
Adult MDT	-	2	£133.00 (WF02B – Treatment code 307)	£0.0	£266.0	NHS England ¹⁹³
Telephone consultation (diabetologist consultant, 30 minutes)	5	3	£31.60 (based on annual salary)	£158.0	£94.8	NHS England ¹⁹⁴
Total cost			£463.60	£870.00	£474.80	-

CGM = continuous glucose monitoring; HbA1c = glycosylated haemoglobin; HCRU = healthcare resource use; MDT = multidisciplinary team; NIHR = National Institute for Health and Care Research; T1D = type 1 diabetes

Table 45. Monthly HCRU costs for Stage 2 T1D stratified by age and time before onset of Stage 3 T1D^a

Age	0-6 months	6-12 months	12-24 months	>24 months
8-18 years	£72.50	£72.50	£72.50	£72.50
≥19 years	£39.60	£39.60	£39.60	£39.60

^a Monthly costs were based on annual costs from Table 44.

CGM = continuous glucose monitoring; HCRU = healthcare resource use; MDT = multidisciplinary team; NIHR = National Institute for Health and Care Research; T1D = type 1 diabetes

B.3.5.2.2 Stage 3 T1D Costs

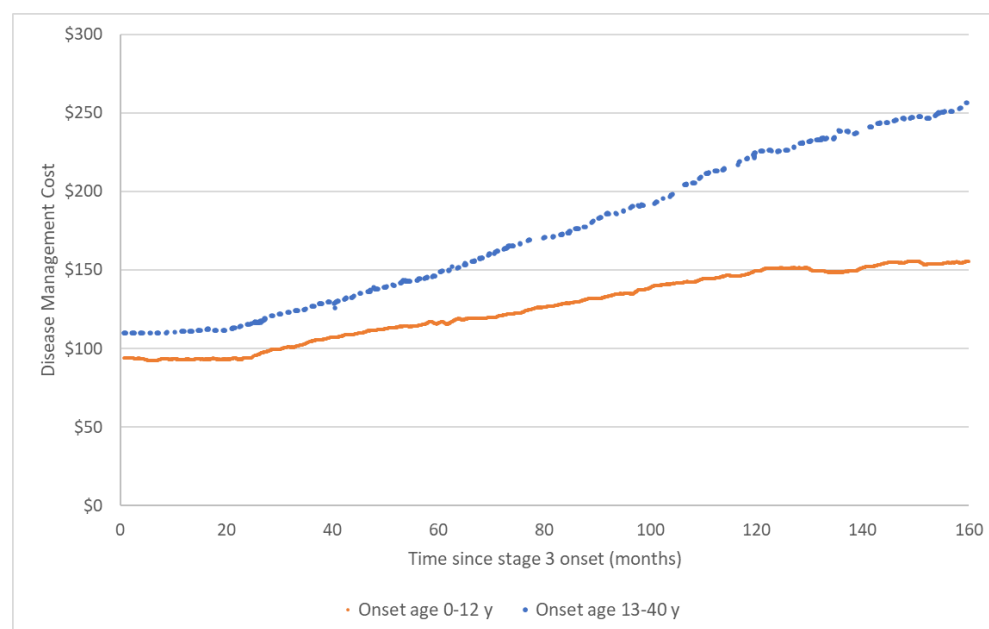
For individuals who progress to Stage 3 T1D, the initial monthly costs incurred at the onset of Stage 3 were estimated to be £415.22 based on data from Hex et al. (2024), which reported current and projected cost estimates for T1D, T2D and gestational diabetes using a cost-of-illness model from an NHS, personal social services (PSS), and societal perspective.¹¹⁹ Hex et al. (2024) reported a total annual direct healthcare cost of Stage 3 T1D in the UK of £1,630,362,000 (2021-2022 costs), which accounted for diagnosis and ongoing management costs, as well as costs related to complications.¹¹⁹ When divided by the total number of people diagnosed with Stage 3 T1D in the UK in 2021-2023 as reported by the Hex et al. (2024) study (327,209), the total annual cost was £4,982.63 per person,¹¹⁹ which is equivalent to £415.22 monthly.

HCRU costs per person per cycle (i.e., 6 months) after onset of Stage 3 T1D were estimated based on trends derived from regression models fitted to observed total healthcare cost data published by Ou et al. (2016).¹⁷⁴ Ou et al. (2016) used a longitudinal cohort of people with newly diagnosed T1D followed for 14 years since onset, constructed from Taiwan's National Health Insurance Research Database covering the period 1999 to 2012.¹⁷⁴ An aggregate

approach was used when quantifying the cost burden of Stage 3 T1D, and the trends from the publication were considered an appropriate source for the increasing disease management costs over time. No UK-specific literature was identified that reported aggregate costing information for Stage 3 T1D that showed the cost changes over time. In general, there appears to be a paucity of relevant costing data using this approach. Therefore, the study by Ou et al. (2016) is the most appropriate source currently available.

The software Digitizeit¹⁹⁵ was used to digitise Figure 2, from Ou et al. (2016). Figure 14 shows the observed average monthly total health care costs for individuals with early (0–12 years old) and late (13–40 years old) onset of Stage 3 T1D, who were followed for 14 years.¹⁷⁴

Figure 14. Disease management cost digitised from Ou et al. (2016)



Note: Costs are in 2012 US dollars.

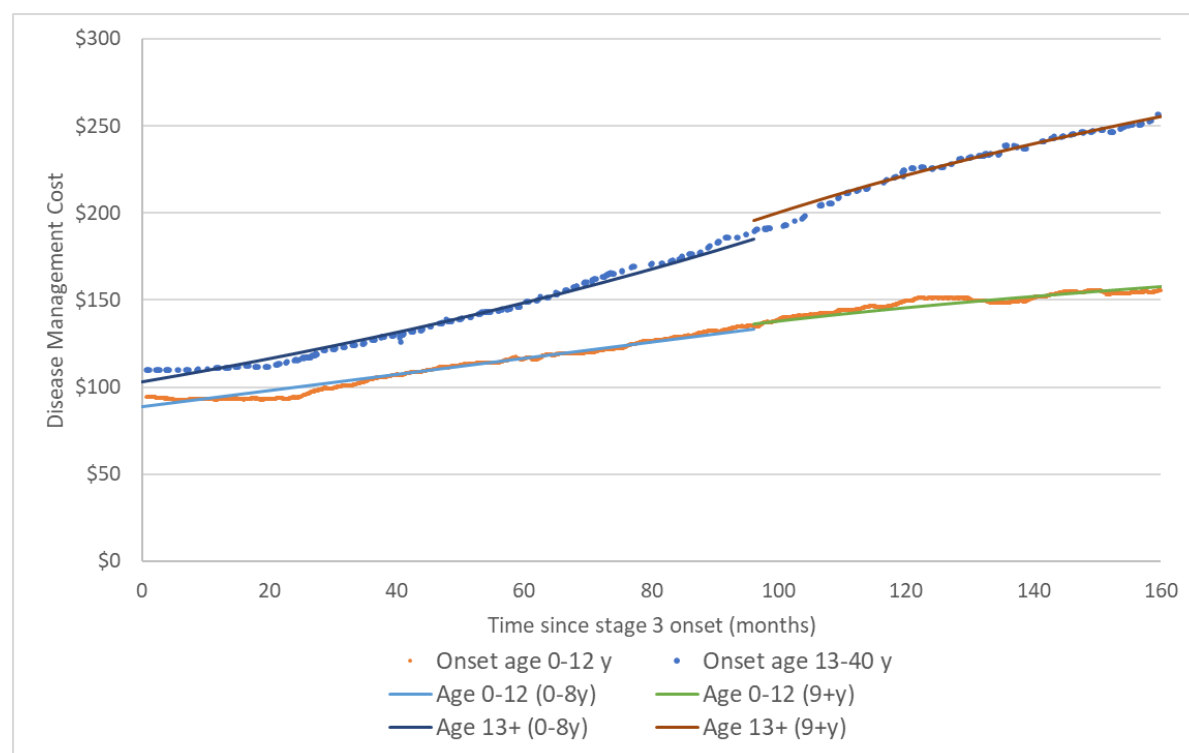
y = years

Adapted from: Ou 2016.¹⁷⁴

A piece-wise regression approach was used to fit models to the observed data, after visual inspection of the observed trends revealed an inflexion point at around 8 to 10 years since disease onset. For example, for the group with Stage 3 T1D onset occurring before the age of 12 years, an early linear trend was observed in costs over time. Therefore, initially a linear model was fitted to extrapolate the monthly costs beyond the 14 years follow-up. However, the linear model alone was not deemed appropriate for long-term projections (beyond the follow-up period), as the projected costs seemed to increase too rapidly. To overcome this issue a piece-wise regression model was adopted. For the first 8 years a linear regression

model was used, whereas after that a non-linear model was fitted (based on the last 7 years of observed data). Figure 15 shows an overlay of the observed data and the fitted regression models.

Figure 15. Regression models vs. observed data from Ou et al. (2016)



Note: Costs are in 2012 US dollars.

y = years

Adapted from: Ou 2016.¹⁷⁴

The regression models' parameters are presented in Table 46. Ordinary least squares regression in Microsoft Excel® was used for both the linear and non-linear regressions.

Table 46. Regression models for Ou et al. (2016)

Regression Parameters (raw data)	Age 0-12 years		Age ≥13 years	
	0-8 Years Since Onset	9+ Years Since Onset	0-8 Years Since Onset	9+ Years Since Onset
Model type	Linear	Logistic	Exponential	Logistic
Intercept	\$88.4 ^a	-\$53.7 ^a	\$103.2 ^a	-\$338.4 ^a
Slope/rate	\$0.47 ^a	\$41.5 ^a	\$0.006 ^a	\$116.9 ^a
R ²	0.98	0.94	0.99	0.98
Regression Parameters (scaled)				
Intercept	£415.22	-£252.29	£415.22	-£1,362.06
Slope/rate	£2.18	£195.64	£0.006	£470.77

Note: linear model, T1D cost = intercept + (slope × time); Logistic model, T1D cost = intercept + [rate × Log(time)]; Exponential model, T1D cost = intercept × Exp(rate × time). The scaling was based on the starting monthly cost of £415.22, representing current starting UK costs.

^a Costs are in 2012 US dollars.

T1D = type 1 diabetes
Source: Ou 2016.¹⁷⁴

B.3.5.3 Adverse reaction management costs and resource use

As discussed in Section B.3.4.3, AE frequencies were obtained from Herold et al. (2023), and the five AEs occurring at a higher frequency in the teplizumab group vs. the control group (i.e., lymphopenia, leukopenia, neutropenia, decreased blood bicarbonate and rash) were included in the model.¹⁴⁴

AE management costs were obtained from the National Schedule of NHS Costs and inflated to 2023 costs,^{172,175} assuming the cost of a general practitioner visit. AE management costs were included as one-off costs. The inputs for AE management costs are presented in Table 47.

Table 47. AE frequency (for teplizumab) and management costs

AE	Management cost per event ^a	Source	Excess proportion ^b (%) (vs. placebo)	Source	Duration (days)	Source
Lymphopenia	£56.00	National Schedule of NHS Costs ¹⁷²	63.2%	Integrated safety analysis ¹⁴⁴	45	TN-10 ¹⁴¹
Leukopenia	£56.00		36.8%		7	Assumption based on integrated safety analysis ¹⁴⁴
Neutropenia	£56.00		18.0%		7	
Blood bicarbonate decreased	£56.00		11.0%		7	
Rash	£56.00		24.3%		7	

^a Unit costs for a general practitioner, per consultation lasting 10 minutes, with qualification

^b Calculated as the difference between the incidence rate in the teplizumab and control arms in the integrated safety analysis

AE = adverse event

Source: NHS 2023;¹⁷² Herold 2023;¹⁴⁴ Herold 2019.¹⁴¹

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 DKA event management cost

The cost for managing a DKA event was calculated from the cost per DKA event combined with the proportion of people who experienced DKA at onset of Stage 3 T1D. The cost per DKA event leading to inpatient care was assumed to be £1,722.32 which was derived based on the weighted average of inpatient costs from the “Non-Elective Admissions” under the code KB02G-K (Diabetes with Hyperglycaemic Disorders) in the National Schedule of NHS Costs.¹⁷²

B.3.6 Severity

The severity modifier is not applicable.

B.3.7 *Uncertainty*

The epidemiology of Stage 2 T1D is poorly understood given that there are no extensive general population early detection programmes for Stage 2 T1D in the UK.⁷ Additionally, there is uncertainty regarding the timing of progression and the typical duration of Stage 2 T1D, as highlighted by UK clinical experts during the advisory board convened by Sanofi in May 2024 (Table 3).⁸

Other uncertainties around the nature of Stage 2 T1D that were identified as limitations of the model were as follows:

- There are limited data capturing the long-term survival gain of delaying Stage 3 T1D onset in individuals with Stage 2 T1D. In the base case, potential survival gains from delaying progression to Stage 3 T1D were captured by applying a HR by age categories at onset of Stage 3 T1D to the UK general population life tables. A long-term follow-up study focused on the UK population would be preferred to properly capture the survival trend.
- The rates of onset of Stage 3 T1D observed in the TN-10 study were based on trial settings, i.e., participants were relatives of people with Stage 3 T1D and had Stage 2 T1D. The generalisability of the trial results to other at-risk populations (e.g., individuals with Stage 2 T1D who do not have a relative with Stage 3 T1D) are assumed to be equivalent, as current clinical opinion indicates that this will not have an impact on the effectiveness of teplizumab in other at-risk populations (Section B.1.3.1.2).

B.3.8 *Managed access proposal*

N/A

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

The inputs and variables used in the cost-effectiveness analysis of the base case are summarised in Table 48.

Table 48. Summary of base-case variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution, SE) ^a	Source(s)/corresponding section in this report
Model characteristics			
Perspective	NHS and Personal Social Services in England	N/A	NICE reference case (Section B.3.2.2)
Population	Full licence population	N/A	N/A (Section B.3.2.1)
Time horizon	Lifetime (up to 100 years)	N/A	Reference case (Section B.3.2.2)
Cost discount rate	3.5% (annual)	N/A	NICE Manual ¹⁶² (Section B.3.2.2)
Health discount rate	3.5% (annual)	N/A	NICE Manual ¹⁶² (Section B.3.2.2)
Baseline characteristics			
Mean age, years	13.58	<i>Normal</i>	TN-10 study ¹⁴¹ (Section B.3.3.1)
Female, %	44.68	<i>Beta</i>	TN-10 study ¹⁴¹ (Section B.3.3.1)
Clinical inputs			
Time to onset of Stage 3 T1D	Log-normal distribution fitted to the teplizumab arm and exponential distribution fitted to the established clinical management arm, derived from participant-level data from the TN-10 study	<i>Multivariate normal (SE from variance/covariance matrix)</i>	TN-10 study extended follow-up analysis ¹⁴³ (Section B.3.3.2.1)
Proportion with DKA at onset of Stage 3 T1D	2.5% (based on the estimation that monitoring individuals with Stage 2 T1D will lead to a 90% reduction in the DKA incidence rate at onset of Stage 3 T1D [25%], resulting in a DKA incidence rate of 2.5%)	<i>Beta</i>	Besser et al. 2022 review ⁵⁶ (Section B.3.3.2.2)
Mortality for Stage 2 T1D	UK general population life tables 2020-2022	N/A	ONS ¹⁶⁶ (Section B.3.3.2.3)
Mortality for Stage 3 T1D, before 18 years, HR	1.57	<i>Log-normal, 0.15</i>	Swedish registry from Samuelsson 2024 ⁸¹ (Section B.3.3.2.4)
Mortality for Stage 3 T1D, after 18 years, HR	1.285	<i>Log-normal, 0.09</i>	Assumption (50% of the mortality estimate for children) ¹⁶⁷ (Section B.3.3.2.4)

Variable	Value	Measurement of uncertainty (distribution, SE) ^a	Source(s)/corresponding section in this report
Utilities			
General population weighted utility (age, years):		<i>Beta</i>	NICE Decision Support Unit report 2022 ¹⁸¹ (Section B.3.4.2.1)
0 – 9	0.994		
10 – 19	0.929		
20 – 29	0.923		
30 – 39	0.908		
40 – 49	0.886		
50 – 59	0.859		
60 – 69	0.825		
70 – 79	0.784		
80 – 89	0.737		
90 – 100	0.684		
Utility estimates for Stage 2 T1D			
Infusion-related disutility for people with Stage 2 T1D	-0.023	<i>Beta, 0.09</i>	Matza et al. 2013 ¹⁶⁸ (Section B.3.4.2.2)
Utility estimates for Stage 3 T1D			
Disutility associated with onset of Stage 3 T1D:		<i>Beta</i>	Sparring et al. 2013 ¹² (Section B.3.4.2.3)
0-17 years	-0.025		
≥18 years	-0.025		
Disutility vs. general population:		<i>Beta, 0.004</i>	Sullivan et al. 2011 ¹⁶⁹ (Section B.3.4.2.3)
0-17 years	-0.0621		
≥18 years	-0.0621		
Disutility based on time from onset of Stage 3 T1D:		<i>Beta</i>	Sparring et al. 2013 ¹² (Section B.3.4.2.3)
8 years	-0.023		
15 years	-0.055		
24 years	-0.074		
Carer/parent disutility for people with Stage 3 T1D <18 years	-0.040	<i>Beta</i>	López-Bastida et al. 2019 ⁸⁹ (Section B.3.4.2.4)

Variable	Value	Measurement of uncertainty (distribution, SE) ^a	Source(s)/corresponding section in this report
AE disutilities			
Lymphopenia	-0.0722	Beta	Sullivan et al. 2011 ¹⁶⁹ (Section B.3.4.3)
Leukopenia	-0.0722	Beta	
Neutropenia	-0.0722	Beta	
Blood bicarbonate decreased	-0.0722	Beta	
Rash	-0.0006	Beta	
Costs			
Teplizumab acquisition and administration cost			
Teplizumab acquisition cost per 14-vial treatment course		N/A	(Section B.3.5.1.1)
Teplizumab administration cost		Gamma	National Schedule of NHS Costs ¹⁷² (Section B.3.5.1.1)
Home (30-minute IV infusion, 45 minutes post-infusion observation, 75 minutes total of nurse time)	£139.55		
Hospital (30-60 minute IV infusion, 30-minute nurse time)	£217.20		
Teplizumab-related resource use			
Costs for confirmatory tests, (frequency)		Gamma	Exeter Clinical Laboratory International ¹⁸³ ; NICE BNF ¹⁸⁴ ; National Schedule of NHS Costs ¹⁷² (Section B.3.5.1.2)
Autoantibody testing	£29.04 (1)		
OGTT – glucose solution	£3.98 (1)		
OGTT – blood glucose tests	£7.85 (5)		
Costs for pre-medication prior to teplizumab dosing to avoid CRS, (frequency)		Gamma	Draft SmPC ³⁴ ; Mehta 2024 ¹⁷³ ; NICE BNF ¹⁸⁵⁻¹⁸⁷ (Section B.3.5.1.2)
NSAID or acetaminophen	£0.10 (14)		
Antihistamine	£0.02 (14)		
Anti-emetics	£0.95 (14)		

Variable	Value	Measurement of uncertainty (distribution, SE) ^a	Source(s)/corresponding section in this report
Costs for laboratory evaluations, (frequency) Complete blood count Liver enzyme test	£2.65 (14) £2.78 (14)	<i>Gamma</i>	Draft SmPC ³⁴ ; Akhtar 2014 ¹⁸⁸ (Section B.3.5.1.2)
Costs for infusion-related resources Hospital post-infusion observation Infusion preparation	£22.40 (1 hour) £29.60 (3.5 hours)	<i>Gamma</i>	GOV.UK ¹⁸² ; NHS Jobs ¹⁸⁹
Disease management costs and HCRU			
Monthly HCRU costs for Stage 2 T1D 0-18 years ≥19 years	£72.50 £39.60	<i>Gamma</i>	NICE TA943 committee papers ¹⁹¹ ; NIHR ¹⁹² ; NHS England ^{193,194} (Section B.3.5.2.1)
HCRU cost per cycle (i.e., 6 months) after onset of Stage 3 T1D Age 0-12 years, 0-8 years since onset Age 0-12 years, 9+ years since onset Age ≥13 years, 0-8 years since onset Age ≥13 years, 9+ years since onset	Intercept: £415.22; slope/rate: £2.18 Intercept: -£252.29; slope/rate: £195.64 Intercept: £415.22; slope/rate: £0.006 Intercept: -£1,362.06; slope/rate: £470.77	<i>Normal</i>	Hex et al. (2024) ¹¹⁹ Taiwan National Health Insurance Research Database 1999-2012 as used in Ou et al. (2016) ¹⁷⁴ (Section B.3.5.2.2)
Adverse reaction management costs			
Lymphopenia	£56.00	<i>Gamma</i>	National Schedule of NHS Costs, ¹⁷² integrated safety analysis ¹⁴⁴ and TN-10 ¹⁴¹ (Section B.3.5.3)
Leukopenia	£56.00	<i>Gamma</i>	
Neutropenia	£56.00	<i>Gamma</i>	
Blood bicarbonate decreased	£56.00	<i>Gamma</i>	
Rash	£56.00	<i>Gamma</i>	

Variable	Value	Measurement of uncertainty (distribution, SE) ^a	Source(s)/corresponding section in this report
Miscellaneous unit costs and resource use			
DKA event management costs	£1,722.32	<i>Gamma</i>	National Schedule of NHS Costs ¹⁷² (Section B.3.5.4.1)

^a Where SE is not reported it was assumed to be 20% of the mean value

AE = adverse event; BNF = British National Formulary; CI = confidence interval; CRS = cytokine release syndrome; DKA = diabetic ketoacidosis; HCRU = healthcare resource utilisation; HR = hazard ratio; IV = intravenous; N/A = not applicable; NIHR = National Institute for Health and Care Research; NSAID = nonsteroidal anti-inflammatory drug; OGTT = oral glucose-tolerance test; SE = standard error; T1D = type 1 diabetes

B.3.9.2 Assumptions

The model was built based on several underlying assumptions, as summarised in Table 49.

Table 49. Model assumptions

Assumption	Rationale
All individuals entering the model have already been diagnosed with Stage 2 T1D	The model assumes that all individuals have already been diagnosed with Stage 2 T1D when they enter the model (being identified through research studies [e.g., ELSA, T1DRA and INNODIA] or ad hoc clinical testing). Therefore, the HCRU and costs associated with identifying individuals as having Stage 2 T1D were not included in the model, since diagnosis would have happened in the past.
Time to onset of Stage 3 T1D was based on parametric distributions fitted to participant-level data from the TN-10 study	The long-term estimation of time to onset of Stage 3 T1D for teplizumab was based on extrapolations of the parametric distributions.
Long-term T1D-related complications expected to occur while people are in the Stage 3 T1D health state were not modelled individually	The model captures aggregated disease-duration-dependent costs and QoL outcomes associated with living with Stage 3 T1D.
There is an indirect effect of treatment on survival	Published literature has shown that survival for people with Stage 3 T1D correlates with the age of disease onset. ⁸⁰ Since teplizumab delays the onset of Stage 3 T1D, it indirectly impacts the survival for people receiving teplizumab.
The utility estimates of people with Stage 3 T1D over time were based on a linear extrapolation of data obtained from the literature	QoL was expected to be driven by the complications and comorbidities associated with Stage 3 T1D. However, detailed modelling of the timing of these comorbidities and complications was not included in the model. Instead, the model captures aggregated disease-duration-dependent QoL outcomes.

HCRU = healthcare resource use; QoL = quality of life; T1D = type 1 diabetes

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case results were calculated based on the key parameters listed in Table 48 above. Base-case incremental cost-effectiveness analysis results are presented in Table 50. Clinical outcomes and disaggregated results from the model are presented in Appendix J.

At the PAS price, individuals receiving a course of teplizumab accrued an incremental cost of [REDACTED] (deterministic approach) or [REDACTED] (probabilistic approach) over a lifetime, compared with those receiving established clinical management. The delay in onset of Stage 3 T1D onset derived from treatment translates into [REDACTED] discounted incremental QALYs ([REDACTED] using a probabilistic approach); without discounting, the incremental QALYs were [REDACTED] using a deterministic approach. The ICER was within the range considered cost-effective at £29,602 per QALY (£28,400 using a probabilistic approach).

Table 50. Discounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
Established clinical management								
Teplizumab							N/A	£29,602
Probabilistic results								
Established clinical management								
Teplizumab							N/A	£28,400

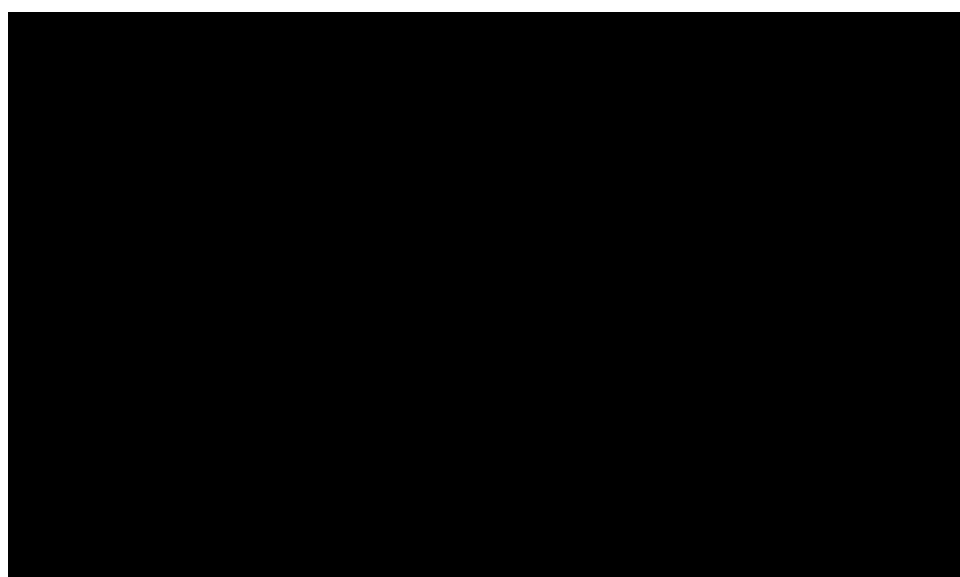
ICER = incremental cost-effectiveness ratio; LYG = life years gained; N/A = not applicable; QALY = quality-adjusted life year

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probability distributions and analysed using Monte Carlo simulation. In the PSA, the uncertainty around parameters was estimated as shown in Table 48. For each PSA iteration, a new set of input parameter values was randomly sampled, assuming the probability distributions specified. 400 PSA iterations were selected after running a convergence test based on the ICER (Figure 16).

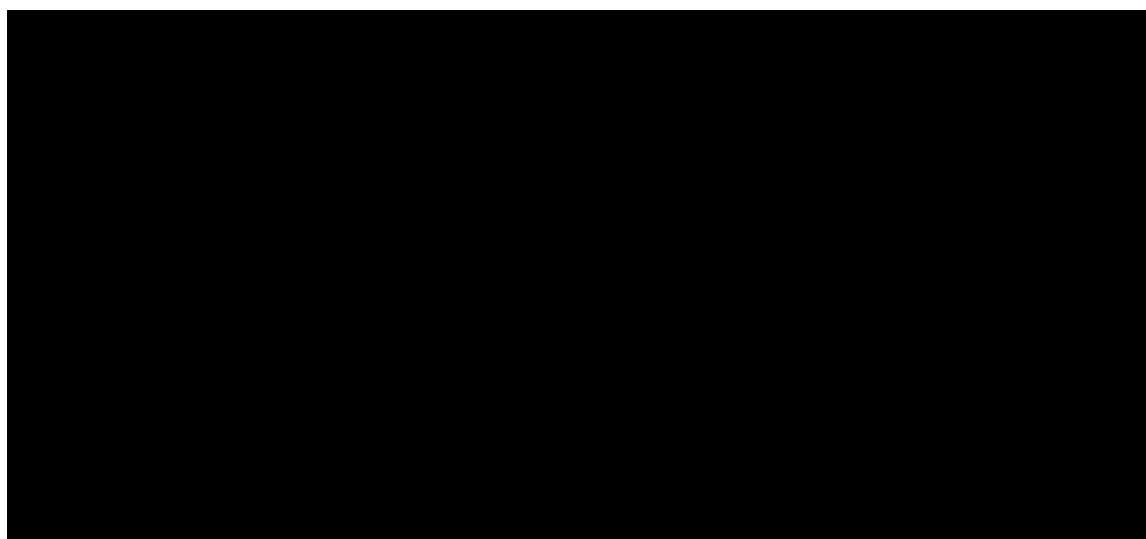
Figure 16. PSA convergence test



ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis

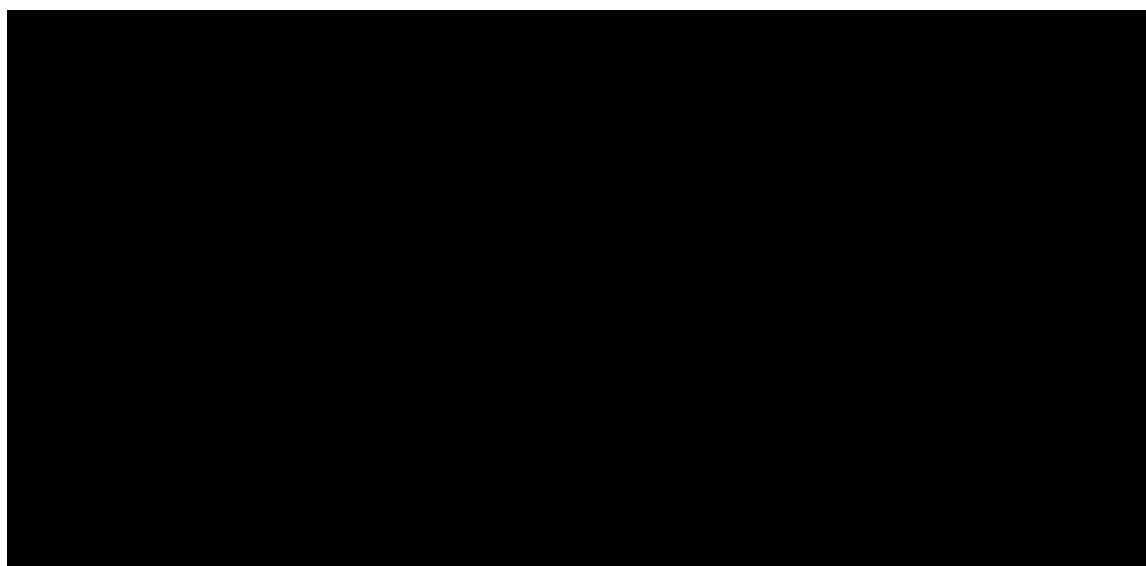
The incremental health outcomes in terms of QALYs gained were plotted against the incremental cost of teplizumab vs. established clinical management on the cost-effectiveness plane shown in Figure 17. The results of the 400 PSA simulations show that the mean incremental costs and QALYs were [REDACTED] and [REDACTED], respectively, resulting in an average ICER of £28,400. Teplizumab was cost-effective in [REDACTED]% of the iterations compared with established clinical management based on a cost-effectiveness threshold of £30,000/QALY (Figure 18). Teplizumab had a greater probability of being cost-effective vs. established clinical management at a willingness-to-pay threshold of [REDACTED] per QALY or higher (Figure 18).

Figure 17. PSA scatterplot



PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 18. Cost-effectiveness acceptability curve



QALY = quality-adjusted life year

B.3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) was conducted by systematically varying parameters, one at a time, from their assumed base-case values. This allows for the evaluation of the robustness of key model outcomes to changes in any single parameter and helps to determine the main drivers of the model's results. The analysis evaluated a lower and upper bound for each model parameter considered. The model parameters that were varied and their ranges are presented in Table 51. Ranges were based on the 95% CI if available; otherwise a +/-20% variation from the mean was assumed.

Table 51. DSA settings

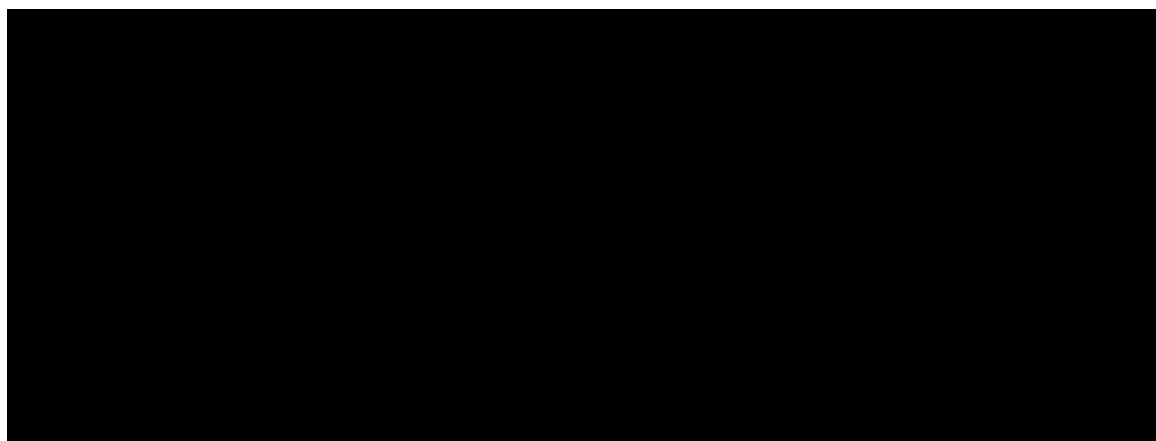
Parameters	Base-case Value	Lower Bound	Upper Bound	Source
DKA risk at onset of Stage 3 T1D	2.5%	-20%	+20%	Assumption
AE management cost	£56.00	-20%	+20%	Assumption
AE incidence	Various (Table 47)	-20%	+20%	Assumption
AE duration	Various (Table 47)	-20%	+20%	Assumption
AE disutility	Various (Table 47)	-20%	+20%	Assumption
HR risk of death Stage 3 onset under 17 years	1.57	1.16	2.12	95% CI, Samuelsson
General population utilities	Various (Table 32)	-20%	+20%	Assumption
Infusion related disutility	-0.023	-20%	+20%	Assumption
Stage 3 diagnosis-related disutility	-0.025	-20%	+20%	Assumption
Stage 3 disutility vs. general population	-0.0621	-20%	+20%	Assumption
Stage 3 disutility based on disease duration (linear slope)	-0.0031	-20%	+20%	Assumption
Carer/parent disutility	-0.04	-20%	+20%	Assumption
Teplizumab's administration cost	Various (Table 39)	-20%	+20%	Assumption
Treatment-related resource use	Various (Table 40, Table 41, Table 42, Table 43)	-20%	+20%	Assumption
Treatment-related resource unit costs	Various (Table 40, Table 41, Table 42, Table 43)	-20%	+20%	Assumption
DKA event management cost	£1,722	-20%	+20%	Assumption
Stage 2 disease management costs	Various (Table 44, Table 45)	-20%	+20%	Assumption
Stage 3 disease management costs	Various (Table 46)	-20%	+20%	Assumption

ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY =, quality-adjusted life year

Results from the DSA are presented as tornado diagrams for incremental costs, incremental QALYs, and ICER. Parameters were ranked according to their impact on the results (i.e., the most influential variables are displayed at the top of the tornado diagrams). The incremental

cost for teplizumab vs. established clinical management was most sensitive to the disease management cost during Stage 3 T1D, the excess risk of death during Stage 3 T1D, and the administration costs of teplizumab (Figure 19).

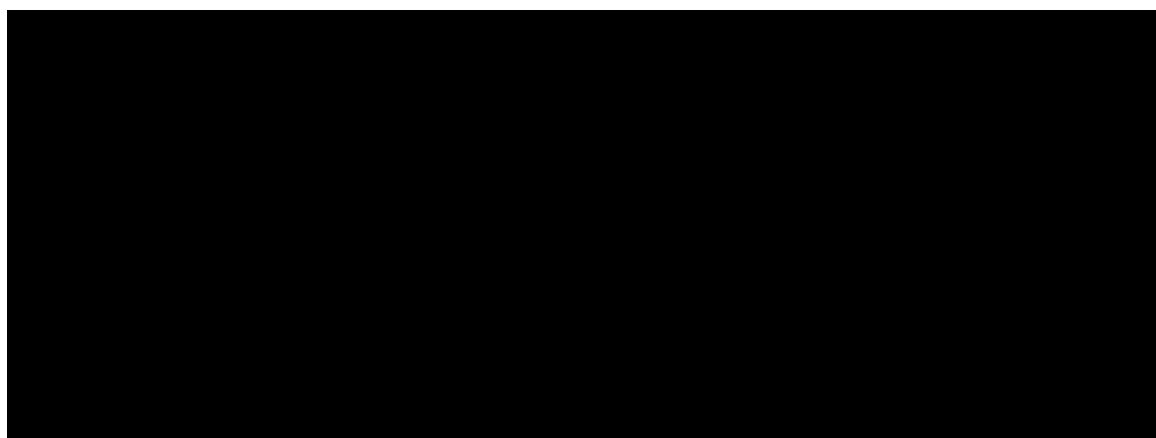
Figure 19. Tornado diagram: incremental cost



AE =adverse event; T1D = type 1 diabetes

The key drivers for incremental QALYs included: the Stage 3 T1D disutilities based on disease duration; the excess risk of death during Stage 3 T1D; the Stage 3 T1D disutilities vs. the general population, the utilities for the general population; and the carer/parent disutility while tending to individuals with Stage 3 T1D (Figure 20).

Figure 20. Tornado diagram: incremental QALYs



AE = adverse event; QALY = quality-adjusted life year; T1D = type 1 diabetes

The ICERs were most sensitive to variations in the following: the disease management cost during Stage 3 T1D; the Stage 3 T1D disutilities based on disease duration; the Stage 3 T1D disutilities vs. the general population; and the administration cost of teplizumab (Figure 21).

Figure 21. Tornado diagram: ICER



ICER = incremental cost-effectiveness ratio; T1D = type 1 diabetes

B.3.11.3 Scenario analysis

Results of the scenario analyses (based on a probabilistic approach) are shown in Table 52.

The first three scenarios tested resulted in a modest impact to the ICER compared with the base case. These included testing the following options:

- Scenario 1: Uptake for the closer-to-home option will be 70% and hospital will be 30%, among paediatrics and adults to receive teplizumab.
- Scenario 2: All individuals would receive the full treatment course of teplizumab (14 days) in hospital
- Scenario 3: The excess risk of death during Stage 3 T1D is informed by Rawshani et al. (2018),⁸⁰ which is based on a regression equation and, thus, allows for more granularity when assigning the excess risk of death (Section B.3.3.2.4)
- Scenario 4: Using a life table from pre-COVID years (2017-2018)

The model results are not sensitive to the treatment delivery setting or the changes to risk of death, based on the results of the first four scenarios.

Scenarios testing a threshold for the transition to Stage 3 T1D among individuals in the established clinical management group (scenarios 5 and 6) resulted in lower ICERs than the base case, as expected. It could be argued that, without treatment, most individuals with Stage 2 T1D will transition to Stage 3 T1D within a maximum number of years (e.g., 10 years, 15 years), whereas the parametric models informing the time to onset of Stage 3 T1D would allow for some individuals to remain in Stage 2 T1D for a relatively longer period.

Finally, the scenario with the largest impact on the ICER was the use of a 1.5% discount rate for both costs and health outcomes (scenario 7). This was expected as a lower discount rate increases the impact of long-term outcomes.

Table 52 Scenario analysis (based on a probabilistic approach)

	Scenario description	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base case
0	Base case			£28,400	NA
1	30% of individuals receive treatment at a hospital (increased from 10% in base case)			£29,574	4.1%
2	No closer-to-home administration which assumes 100% of individuals receive all 14 days of treatment in hospital <i>In practice (and in the base case), a proportion of individuals were expected to use the closer-to-home option.</i>			£29,681	4.5%
3	Stage 3 T1D excess risk of death informed by Rawshani et al. (2018), testing more granularity when defining the impact of age of onset of Stage 3 T1D on survival <i>The base case uses a more recent data source.</i>			£29,328	3.3%
4	UK life tables from pre-COVID years (2017-2018). <i>The life tables used in the base case (2020-2022) include effects of COVID in overall survival, hence why the scenario tests an earlier data source.</i>			£28,222	-0.6%
5	Maximum time to Stage 3 T1D onset for established clinical management set to 10 years <i>A maximum number of years was not set in the base case.</i>			£24,764	-12.8%
6	Maximum time to Stage 3 T1D onset for established clinical management set to 15 years <i>A maximum number of years was not set in the base case.</i>			£27,626	-2.7%

	Scenario description	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base case
7	Discount rates for both cost and health benefits set to 1.5% <i>The base case uses a discount rate of 3.5%, per NICE guidance.¹⁶²</i>			Teplizumab is dominant	NA

COVID-19 = Coronavirus disease 2019; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life year; T1D = type 1 diabetes

B.3.12 Subgroup analysis

Given the small number of people diagnosed with Stage 2 T1D and the limited evidence on patient subgroups, the entire eligible patient population has been considered in the cost-effectiveness analysis.

B.3.13 Benefits not captured in the QALY calculation

There are several benefits that are unlikely to be included in the QALY calculation, as no data quantifying these impacts are available. These are, however, of high relevance to individuals with Stage 2 T1D, their carers/parents and the broader healthcare system, and include:

- *Increased time for people with Stage 2 T1D to prepare for the onset and management of symptomatic Stage 3 T1D:* As noted by UK clinical experts at an advisory board convened by Sanofi in May 2024, delaying onset of Stage 3 T1D in people with Stage 2 T1D would be expected to delay the onset of complications and increase life expectancy; extend the time for individuals to cognitively prepare for the onset of Stage 3 T1D (also from a developmental perspective in younger children) and to slowly learn about the condition and how to manage it, which may ultimately lead to improved outcomes and compliance; and postpone the constant mental burden associated with having Stage 3 T1D.⁸
- *Prolonged benefits associated with endogenous C-peptide production:* Through its effects on preserving C-peptide levels, teplizumab may prolong the benefits associated with endogenous C-peptide production (see Section B.2.12).
- *Improving long-term outcomes in people with lower SES:* Among people with Stage 3 T1D, low SES is frequently associated with poorer outcomes in terms of morbidity and mortality, as well as with aspects of diabetes management.¹³⁵ It is possible that delaying the onset of symptomatic Stage 3 T1D among people with

Stage 2 T1D could provide valuable additional time for individuals of low SES to prepare for diabetes management with more flexibility, and for HCPs to engage with these individuals and establish support systems before the urgencies of managing hyperglycaemia set in.

- *Full impact on carers/parents and siblings:* Carers/parents of children with Stage 3 T1D are negatively impacted by the disease and its management.⁹⁹ Several factors have been found to impact parents of children with Stage 3 T1D, including constant worry, disruption to family life and routines and social isolation.⁹⁹ Additional impacts are experienced by other family members, including emotional and behavioural problems in siblings of children with Stage 3 T1D and burdens affected through transactional interaction within the family unit.^{114,115} Interventions that improve awareness of hypoglycaemia and/or glycaemic control in people with Stage 3 T1D have been found to result in improvements in QoL in parents of children with Stage 3 T1D.¹¹⁸ Teplizumab has the potential to delay the need for initiation of insulin replacement therapy and the burden associated with management of Stage 3 T1D, thereby delaying the additional burden imposed on carers/parents of children with Stage 3 T1D.
- *Impact on education and employment:* Stage 3 T1D can have a negative impact on education and participation in the labour market.¹⁹⁶⁻¹⁹⁸ Poor glycaemic control,^{196,197} serious hypoglycaemic events,¹⁹⁷ fewer blood glucose measurements¹⁹⁶ and post-onset DKA¹⁹⁶ have been associated with worse educational achievement. In Sweden, both men and women with Stage 3 T1D had fewer years of schooling, were less likely to be employed and had lower expected earnings in their occupational field.¹⁹⁸ Delaying onset of Stage 3 T1D in people with Stage 2 T1D could allow individuals to better prepare for diabetes management, potentially minimising disruptions to school and employment due to poor glycaemic control and complications.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

B.3.14.1.1 UK health economic expert validation

UK health economic and clinical experts attending a May 2024 advisory board convened by Sanofi considered the three-state Markov model structure appropriate for modelling the

delay of onset of Stage 3 T1D, and similar to the approach taken for the economic evaluation of the DiRECT trial in T2D.⁸ The experts noted that the outcomes in the model are the standard outcomes expected in the economic evaluation, and the granularity with which the outcomes are estimated is appropriate.⁸ The experts also stated that an exponential model for extrapolating treatment efficacy data was considered reasonable as a conservative estimate of outcomes in current clinical practice.⁸ The aggregate approach to modelling all-cause mortality rather than the mortality associated with individual complications of Stage 3 T1D using HbA1c was accepted by experts, as they noted that the treatment is expected to delay rather than prevent onset of Stage 3 T1D.⁸

B.3.14.1.2 Technical validation

The technical validation process for the model examined the extent to which the mathematical calculations were performing correctly and were consistent with the model's specifications. These steps were followed to ensure the model's technical validity:

- Extreme-value analyses
- Technical review
- Input verification

Following the verification, corrections of identified errors were incorporated into a revised model, which was rechecked by the validator.

Extreme-value testing

Extreme-value analyses tested the functionality of the model by inputting extreme values into the model inputs and checking whether the model yielded the expected results.

Key input parameters were varied to extreme values (e.g., their highest and lowest possible values) to identify any inconsistencies in model behaviour. The results were reviewed, corrections identified, and the final model provided results for this exercise that were consistent with expected model behaviour.

Technical review

The model programming was reviewed by a senior modeller who was not a member of the project team who developed the model. This technical review involved the use of different settings to examine the model formulas to make sure they yielded the expected calculations and translated the model structure correctly. Additionally, links between worksheets were checked to ensure the correct cells were referenced in all formulas. Mathematical formulas

and the sequence of calculations for inputs and parameters were also checked. Any errors identified and clarification questions were discussed by the project team and validator; changes were made as required and checked by the validator.

Input verification

All parameters included in the model were checked against source documents (e.g., published sources or internal reports); any inconsistencies were corrected. The model outputs were also compared against the inputs and source data to ensure these were as expected.

B.3.14.1.3 Secondary technical validation

Sanofi engaged York Health Economics Consortium (YHEC) to provide a critique of the model and to assess whether the modelling approach is robust. Overall, the external validation reported that the chosen modelling approach appears reasonable and appropriate, given the clinical efficacy data that are available for teplizumab, and the nature of long-term outcomes with Stage 3 T1D. The external validation report did provide feedback in relation to a small number of limitations associated with the model, particularly in relation to certain input parameters. These were addressed by Sanofi where feasible/possible.

The outputs from the current model (described as the 'Sanofi model' henceforth) were compared with other relevant published UK T1D models. Several economic models assessing the cost-effectiveness of diagnostic processes were identified. However, there was a paucity of previous health technology assessments of treatments for delaying the onset of Stage 3 T1D. An economic model that estimated the cost-effectiveness of teplizumab for Stage 3 T1D prevention in different groups was identified and considered especially relevant, given that a different modelling approach to the one implemented by the model in this submission was adopted.¹⁶¹ In particular, this model estimated long-term outcomes by adopting a microsimulation approach,¹⁶¹ as opposed to the approach used by the model in this submission which models long-term outcomes in an aggregate manner. The current model structure used in this submission is considered to be appropriate based on the external validation given that there is no data to directly translate the delay of treatment onset into a specific risk reduction for T1D-related complications and the model structure allows the TN-10 primary endpoint, the elapsed time from randomisation to the onset of Stage 3 T1D, to be used directly through the application of the KM curves.

The clinical outcomes from the Sanofi model were compared against published UK Stage 3 T1D models^{70,199} and the Mital et al. (2020) preventative diabetes model¹⁶¹ to ensure the

results had face validity. These comparisons are discussed individually below. The HRs for mortality were informed by Samuelsson et al. (2024) in the comparisons (in line with the submission base case).⁸¹

Comparison with NICE TA943

The age in the teplizumab model was changed to 43.4 years to align with the EAG model from the NICE appraisal of HCL systems for managing blood glucose levels in T1D (TA943)⁷⁰ to allow for direct comparison with the UK Stage 3 T1D population (as presented in Table 53). The ‘established clinical management’ arm of the Sanofi model should be reflective of current standard care in the UK and, therefore, the results should be comparable to the models reviewed. The QALYs and LYs were relatively consistent across the two models but they were slightly higher in the ‘established clinical management’ arm of the Sanofi model. This may be partially explained by the inclusion of people with Stage 2 T1D in the Sanofi model (as opposed to Stage 3 T1D in TA943), who would be expected to have higher remaining QALYs and LYs compared to people with Stage 3 T1D of the disease. The results may also imply lower mortality rates are being applied in the Sanofi model, reflecting more recent data on T1D.

Table 53. Comparison of Sanofi model with NICE TA943 EAG Stage 3 T1D model

Model	Population	Starting age	Time horizon	QALYs	Undiscounted LYs
Sanofi teplizumab model	At risk of progressing to Stage 3 T1D	43.4 years	Lifetime	Established clinical management: [REDACTED] Teplizumab: [REDACTED]	Established clinical management: [REDACTED] Teplizumab: [REDACTED]
NICE TA943 (EAG base case) ⁷⁰	Stage 3 T1D	43.4 years	Lifetime	CSII: 14.232 PLGS: 14.291 HCL: 14.392	CSII: 32.499 PLGS: 32.685 HCL: 32.957

CSII = continuous subcutaneous insulin infusion; EAG = external assessment group; HCL = hybrid closed loop; LY = life year; PLGS = predictive low-glucose suspend; QALY = quality-adjusted life year; T1D = type 1 diabetes

Comparison with Roze et al. (2021) model

The age in the teplizumab model was then changed to align with a UK-based economic model estimating the cost-effectiveness of continuous subcutaneous insulin infusion (CSII) and the Minimed 670G system in the diagnosed T1D population (Roze et al. [2021]¹⁹⁹) (as presented in Table 54). The QALYs were considerably higher in the Sanofi model. As alluded to above, this may be due to lower mortality in the Sanofi model. The longer life expectancy in the Sanofi model is likely the reason for the QALYs in the ‘established clinical management’ arm of the Sanofi model being higher than what was seen in the Roze et al. (2021) model.

Table 54 Comparison of Sanofi model with published Stage 3 T1D model

Model	Population	Starting age	Time horizon	QALYs	Undiscounted LYs
Sanofi teplizumab model	At risk of progressing to Stage 3 T1D	37.8 years	Lifetime	Established clinical management: [REDACTED] Teplizumab: [REDACTED]	Established clinical management: [REDACTED] Teplizumab: [REDACTED]
Roze (2021) ¹⁹⁹	Stage 3 T1D	37.8 years	Lifetime	CSII: 12.36 MiniMed 670G system: 14.09	Not reported

CSII = continuous subcutaneous insulin infusion; LY = life year; QALY = quality-adjusted life year; SAP+LGS = sensor-augmented pump therapy + low glucose suspend

Comparison with Mital et al. (2020) model

Finally, the results of the Sanofi model were compared with the aforementioned Mital et al. (2020) model, which was also informed by the phase II TN-10 trial of teplizumab ¹⁶¹ (as presented in Table 55). The starting age in the Sanofi model was set to 13.58 years to align with the baseline characteristics of the trial population. The QALYs for both no treatment and teplizumab were larger in the Sanofi model, but the differences do not appear substantial.

Table 55 Comparison of Sanofi model with the Mital et al. (2020) model

Model	Population	Starting age	Time horizon	QALYs	Undiscounted LYs
Sanofi teplizumab model	At risk of progressing to Stage 3 T1D	13.58 years	Lifetime	Established clinical management: [REDACTED] Teplizumab: [REDACTED]	Established clinical management: [REDACTED] Teplizumab: [REDACTED]
Mital (2020) ¹⁶¹	At risk of progressing to Stage 3 T1D	8 to 49 years	Lifetime	Established clinical management: 18.72 Teplizumab: 19.26	Not reported

LY = life year; QALY = quality-adjusted life year

Overall, there are differences between the modelled clinical outputs of the Sanofi model when compared with other relevant published models, but these may be explained by differences in the starting patient populations (Stage 2 vs. Stage 3 T1D) and different approaches to modelling mortality.

YHEC also completed a validation checklist and did not identify any major calculation errors. The model functioned as expected, and the outcomes of both the DSA and PSA were explainable when compared with the deterministic base case outcomes.

B.3.15 Interpretation and conclusions of economic evidence

Teplizumab is cost-effective for delaying the onset of Stage 3 T1D compared with established clinical management in adults and paediatric individuals aged 8 years and older with Stage 2 T1D.

T1D is a chronic autoimmune disease affecting both children and adults,¹⁻³ which can lead to serious complications (e.g., kidney disease, eye disease, nerve damage and cardiovascular disease)⁴⁻⁶ and a substantial impact on everyday lives.¹ Most people with T1D are diagnosed at Stage 3 due to the onset of symptoms relating to hyperglycaemia.¹ The management of Stage 3 T1D with insulin replacement therapy, BGM, carbohydrate counting and exercise can be complex and burdensome.²² The act of continuously managing their own blood glucose can make people feel worn down or depressed,^{23,24} and when not adequately managed can lead to hypoglycaemia and hyperglycaemia, as well as DKA which is a life-threatening condition.^{5,25} Even with the availability of HCL systems that can improve the amount of time spent within normoglycaemic levels (i.e., time in range), widespread uptake in the UK is expected to take time, and the recommendations for use of HCL systems introduce the potential for inequality in adults.^{70,72}

There is currently no treatment available in the UK to delay the onset of Stage 3 T1D for people with Stage 2 T1D, and there is a substantial unmet need for disease-modifying therapies in this setting. In the absence of pharmacological treatments in the UK, management of Stage 2 T1D focuses on metabolic monitoring for progression to Stage 3 T1D, as well as education and psychosocial support for those with Stage 2 T1D and their family members.^{1,20,21}

Worldwide, teplizumab is the first and only therapy approved to delay the onset of Stage 3 T1D in people with Stage 2 T1D.¹⁶⁻¹⁸ Since its approval in the US, teplizumab has been incorporated into the ADA standards of care, offering for the first time a step change in management of individuals with Stage 2 T1D.¹⁹ Individuals treated with teplizumab had a statistically significantly longer median time to onset of Stage 3 T1D of 5.0 years compared to 2.3 years in the placebo arm (2.7-year difference) with an acceptable safety profile, while also preserving the C-peptide response.^{141,143} Some people treated with teplizumab may remain free of the burden of Stage 3 T1D for more than 10 years.¹⁵⁹ Teplizumab has the potential to delay the need for initiation of insulin replacement therapy and the burden associated with management of Stage 3 T1D, thereby improving long-term outcomes and reducing the risk of complications.

The economic analysis described in this section presents a robust case for the value of teplizumab for delaying the onset of Stage 3 T1D in adults and paediatric individuals aged 8 years and older with Stage 2 T1D. Teplizumab was cost-effective at the PAS price when compared with established clinical management, with an incremental QALY gain of [REDACTED] and an ICER of £29,602 per QALY using a deterministic approach ([REDACTED] and £28,400, respectively, using a probabilistic approach).

The *de novo* economic model designed and implemented to evaluate teplizumab has several strengths. Given the key benefit of teplizumab in delaying the onset of Stage 3 T1D, the model is fit for purpose as it captures up front the delay of Stage 3 T1D onset (whereas traditional approaches model the progression of patients through Stage 3 T1D). It is simpler compared with prior models that focused on evaluating treatment options during Stage 3 T1D, hence it should allow for reviewers to better understand the model's logic, making the model more transparent. Results from the *de novo* model were compared with those from relevant published references; findings from this exercise indicate that the *de novo* model produces comparable outcomes to relevant cost-effectiveness models.

The *de novo* model also faced some challenges. Given that teplizumab is the first and only disease-modifying therapy to delay the onset of Stage 3 T1D, there is a paucity of data for key model inputs, e.g., QoL estimates that capture the impact of the disease as individuals experience it in the long term, or long-term disease management costs that take into account the increased risk for additional T1D-related complications over time. However, these were explored in scenario and sensitivity analyses leading to robust results. Additionally, every effort was taken to identify the most appropriate data sources in the model.

Teplizumab represents a cost-effective use of NHS resources for delaying the onset of Stage 3 T1D compared with established clinical management and would address a considerable unmet need for a disease-modifying therapy in this setting.

B.4 References

1. Besser REJ, Bell KJ, Couper JJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1175-1187. doi:10.1111/pedi.13410
2. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care*. Jan 1 2023;46(Suppl 1):S19-s40. doi:10.2337/dc23-S002
3. Libman I, Haynes A, Lyons S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1160-1174. doi:10.1111/pedi.13454
4. Juvenile Diabetes Research Foundation (JDRF). Type 1 diabetes and complications. Accessed 4 December 2023, <https://jdrf.org.uk/knowledge-support/guide-to-type-1-complications/>
5. Diabetes UK. Complications of diabetes. Accessed December 2023, <https://www.diabetes.org.uk/guide-to-diabetes/complications>
6. NHS. Type 1 diabetes - Avoiding complications. Updated 9 August 2021. <https://www.nhs.uk/conditions/type-1-diabetes/living-with-type-1-diabetes/avoiding-complications/>
7. Diabetes UK. Type 1 Diabetes Screening. Accessed June, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1/type-1-diabetes-screening>
8. Sanofi (Data on File). *UK Advisory Board for teplizumab in Stage 2 aT1D (NICE): Conducted in May 2024*. 2024. *Summary Report*. Date of preparation: November 2024.
9. Insel RA, Dunne JL, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974. doi:10.2337/dc15-1419
10. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. Jun 19 2013;309(23):2473-9. doi:10.1001/jama.2013.6285
11. NHS Digital. National Diabetes Audit Complications and Mortality Dashboard (Core Report 2 - Outcomes Dashboard). Accessed 22 May, 2024. <https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit/dashboards>
12. Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish population-based study using EQ-5D. *BMC Public Health*. Apr 22 2013;13:377. doi:10.1186/1471-2458-13-377
13. Bronner MB, Peeters MAC, Sattoe JNT, van Staa A. The impact of type 1 diabetes on young adults' health-related quality of life. *Health Qual Life Outcomes*. May 12 2020;18(1):137. doi:10.1186/s12955-020-01370-8
14. Rechenberg K, Koerner Ms R. General Anxiety, Diabetes-Specific Anxiety, and Quality of Life in Adolescents With Type 1 Diabetes. *Sci Diabetes Self Manag Care*. Dec 2022;48(6):469-475. doi:10.1177/26350106221125689
15. Stedman M, Lunt M, Davies M, et al. Cost of hospital treatment of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) compared to the non-diabetes population: a detailed economic evaluation. *BMJ Open*. May 5 2020;10(5):e033231. doi:10.1136/bmjopen-2019-033231
16. US Food & Drug Administration (FDA). FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes. Updated November 17. Accessed November 3, 2023. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-can-delay-onset-type-1-diabetes>
17. Sanofi (Data on File). *TZIELD 2024 אישור עקרוני*.

18. Sanofi (Data on File). *Sanofi (Data on File) 2024 TZIELD-TeudatRishum-37817_07.24. 2024.*
19. ElSayed NA, Aleppo G, Aroda VR, et al. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes-2023. *Diabetes Care*. Jan 1 2023;46(Suppl 1):S41-s48. doi:10.2337/dc23-S003
20. Phillip M, Achenbach P, Addala A, et al. Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes. *Diabetes Care*. Jun 24 2024;doi:10.2337/dci24-0042
21. Sanofi (Data on File). *Sanofi Pre-symptomatic Type 1 Diabetes Care Pathway July 2024 Advisory Board Meeting Report v1.0 (MAT-XU-2402985)*. 2024. 19 July.
22. Holt RIG, DeVries JH, Hess-Fischl A, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Nov 2021;44(11):2589-2625. doi:10.2337/dci21-0043
23. Svedbo Engström M, Leksell J, Johansson UB, Gudbjörnsdóttir S. What is important for you? A qualitative interview study of living with diabetes and experiences of diabetes care to establish a basis for a tailored Patient-Reported Outcome Measure for the Swedish National Diabetes Register. *BMJ Open*. Mar 24 2016;6(3):e010249. doi:10.1136/bmjopen-2015-010249
24. Carlsund Å, Söderberg S. Living with type 1 diabetes as experienced by young adults. *Nurs Open*. Apr 2019;6(2):418-425. doi:10.1002/nop2.222
25. Rewers A. Acute Metabolic Complications in Diabetes. In: Cowie CC, Casagrande SS, Menke A, et al, eds. *Diabetes in America*. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018.
26. Lloyd A, Swinburn P, Boye KS, et al. A valuation of infusion therapy to preserve islet function in type 1 diabetes. *Value Health*. Aug 2010;13(5):636-42. doi:10.1111/j.1524-4733.2010.00705.x
27. National Institute for Health and Care Excellence (NICE). Type 1 diabetes. Updated 2023. Accessed November 6, 2023. <https://bnfc.nice.org.uk/treatment-summaries/type-1-diabetes/>
28. Rickels MR, Evans-Molina C, Bahnson HT, et al. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. *J Clin Invest*. Apr 1 2020;130(4):1850-1862. doi:10.1172/jci134057
29. Harsunen M, Haukka J, Harjutsalo V, et al. Residual insulin secretion in individuals with type 1 diabetes in Finland: longitudinal and cross-sectional analyses. *Lancet Diabetes Endocrinol*. Jul 2023;11(7):465-473. doi:10.1016/s2213-8587(23)00123-7
30. Kurpiewska E, Cieżki S, Jamiolkowska-Sztabkowska M, et al. Excessive BMI is associated with higher C-peptide level at recognition but also with its greater loss in two years clinical observation in children with new onset type 1 diabetes. *Front Immunol*. 2023;14:1176403. doi:10.3389/fimmu.2023.1176403
31. Gubitosi-Klug RA, Braffett BH, Hitt S, et al. Residual β cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. *J Clin Invest*. Feb 1 2021;131(3)doi:10.1172/jci143011
32. Fuhri Snethlage CM, McDonald TJ, Oram RD, et al. Residual β -Cell Function Is Associated With Longer Time in Range in Individuals With Type 1 Diabetes. *Diabetes Care*. Aug 3 2023;doi:10.2337/dc23-0776
33. Jeyam A, Colhoun H, McGurnaghan S, et al. Clinical Impact of Residual C-Peptide Secretion in Type 1 Diabetes on Glycemia and Microvascular Complications. *Diabetes Care*. Feb 2021;44(2):390-398. doi:10.2337/dc20-0567
34. Sanofi (Data on File). *Draft Summary of Product Characteristics (Tzield)*. 2024.
35. National Institute for Health and Care Excellence (NICE). *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]. Final scope*. 2024. <https://www.nice.org.uk/guidance/gid-ta10981/documents/final-scope>

36. Besser REJ, Griffin KJ. Transitioning to stage 3 type 1 diabetes: when to start insulin. *The Lancet Diabetes & Endocrinology*. 2024/10/01/ 2024;12(10):692-694. doi:[https://doi.org/10.1016/S2213-8587\(24\)00238-9](https://doi.org/10.1016/S2213-8587(24)00238-9)
37. Shubrook JH, Brannan GD, Wapner A, Klein G, Schwartz FL. Time Needed for Diabetes Self-Care: Nationwide Survey of Certified Diabetes Educators. *Diabetes Spectrum*. 2018/08/01 2018;31(3):267-271. doi:10.2337/ds17-0077
38. French R, Kneale D, Warner JT, et al. Educational Attainment and Childhood-Onset Type 1 Diabetes. *Diabetes Care*. 2022/12/01 2022;45(12):2852-2861. doi:10.2337/dc21-0693
39. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med*. Jul 2012;29(7):855-62. doi:10.1111/j.1464-5491.2012.03698.x
40. Hakkarainen P, Moilanen L, Hänninen V, Heikkinen J, Räsänen K. Work-related diabetes distress among Finnish workers with type 1 diabetes: a national cross-sectional survey. *Journal of Occupational Medicine and Toxicology*. 2016/03/21 2016;11(1)doi:10.1186/s12995-016-0099-4
41. Azimi T, Johnson J, Campbell SM, Montesanti S. Caregiver burden among parents of children with type 1 diabetes: A qualitative scoping review. *Heliyon*. 2024/03 2024;10(6):e27539. doi:10.1016/j.heliyon.2024.e27539
42. Elkon K, Casali P. Nature and functions of autoantibodies. *Nat Rev Rheumatol*. 2008/09/01 2008;4(9):491-498. doi:10.1038/ncprheum0895
43. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. *JAMA*. Jan 28 2020;323(4):339-351. doi:10.1001/jama.2019.21565
44. van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev*. Jan 2011;91(1):79-118. doi:10.1152/physrev.00003.2010
45. Jacobsen LM, Haller MJ, Schatz DA. Understanding Pre-Type 1 Diabetes: The Key to Prevention. *Front Endocrinol (Lausanne)*. 2018;9:70. doi:10.3389/fendo.2018.00070
46. American Diabetes Association Professional Practice Committee. Diabetes Care. 2022;45(S1):S17-S38.
47. McCall AL, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinol*. Jun 2013;38(2):145-63.
48. Juvenile Diabetes Research Foundation (JDRF). The stages of type 1 diabetes. Accessed October, 2024. <https://jdrf.org.au/stages-of-type-1-diabetes/>
49. Diabetes UK. Type 1 Diabetes Symptoms. Accessed June, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1/symptoms>
50. Sanofi (Data on File). *Assessment of Generalizability of TN-10 Trial Results to a European Population (Population from the Fr1da Study)*. 2024. 5 September.
51. Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. *Diabetes Care*. Sep 2009;32(9):1603-7. doi:10.2337/dc08-2140
52. Koeger M, Hummel S, Weiss A, et al. Abstract #413: Use of teplizumab to delay stage 3 type 1 diabetes: generalisability of the TN-10 trial to a European population. . 2024. IDS 2024. 4-8 November.
53. Weiss A, Zapardiel-Gonzalo J, Voss F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. *Diabetologia*. Dec 2022;65(12):2121-2131. doi:10.1007/s00125-022-05780-9
54. Krischer JP. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. *Diabetologia*. Sep 2013;56(9):1919-24. doi:10.1007/s00125-013-2960-7
55. Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. May 30 2002;346(22):1685-91. doi:10.1056/NEJMoa012350

56. Besser REJ, Ng SM, Gregory JW, Dayan CM, Randell T, Barrett T. General population screening for childhood type 1 diabetes: is it time for a UK strategy? *Arch Dis Child*. Sep 2022;107(9):790-795. doi:10.1136/archdischild-2021-321864
57. INNODIA.org. INNODIA. Accessed August, 2024. <https://www.innodia.eu/>
58. Swaby R, Randell T, Martin R, et al. How many children are out there? A BSPED survey of children and young people with early-stage type 1 diabetes. presented at: 51st Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes; 08 Oct 2024 - 10 Oct 2024 2024; Glasgow, UK.
59. University of Birmingham. Launch of new international medical code for presymptomatic type 1 diabetes. Accessed September, 2024. <https://www.birmingham.ac.uk/news/2024/launch-of-new-international-medical-code-for-presymptomatic-type-1-diabetes>
60. Breakthrough T1D. New ICD-10 Codes Will Help the T1D Community. Updated October 9, 2024. Accessed November 19, 2024. <https://www.breakthrough1d.org/news-and-updates/icd-10/>
61. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics – ICD-10-CM. Updated October 1, 2024. Accessed November 19, 2024. <https://icd10cmtool.cdc.gov/?fy=FY2025>
62. National Institute for Health and Care Excellence (NICE). *Type 1 diabetes in adults: diagnosis and management [NG17]*. 2022. <https://www.nice.org.uk/guidance/ng17/evidence/economic-model-report-on-insulin-therapy-pdf-11376462925>
63. National Institute for Health and Care Excellence (NICE). *Diabetes (type 1 and type 2) in children and young people: diagnosis and management [NG18]*. 2023. <https://www.nice.org.uk/guidance/ng18/resources/diabetes-type-1-and-type-2-in-children-and-young-people-diagnosis-and-management-pdf-1837278149317>
64. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. 2006;
65. Quinn LM, Dias RP, Bidder C, et al. Presentation and characteristics of children with screen-detected type 1 diabetes: learnings from the ELSA general population pediatric screening study. *BMJ Open Diabetes Research & Care*. 2024;12(5):e004480. doi:10.1136/bmjdr-2024-004480
66. NHS Digital. *National Diabetes Audit 2021-22, Report 1: Care Processes and Treatment Targets, Detailed Analysis Report*. 2023. 12 October. <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2021-22-full-report>
67. NHS Digital. *National Diabetes Audit, 2019-20 Type 1 Diabetes*. 2021. 12 August. <https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FAC%2F6F045A%2FNDNA%25202019-20%2520Type%25201%2520Diabetes%2520Report.pptx&wdOrigin=BROWSELINK>
68. Diabetes UK. Open for recruitment: UK-first ELSA study to screen 20,000 children for type 1 diabetes. Accessed October, 2024. <https://www.diabetes.org.uk/about-us/news-and-views/elsa-trial-screen-children-type-1-diabetes>
69. Swediabkids (Swedish Diabetes Registry). *Annual report 2020*. DOI:10.18158/S1t0tko3K. Available at: https://www.ndr.nu/pdfs/Annual_Report_Swediabkids_2020.pdf. Accessed November 2023. 2020.
70. National Institute for Health and Care Excellence (NICE). *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes [TA943]*. 2023. <https://www.nice.org.uk/guidance/ta943/resources/hybrid-closed-loop-systems-for-managing-blood-glucose-levels-in-type-1-diabetes-pdf-82615666856389>
71. NHS England. *Hybrid closed loop technologies: 5-year implementation strategy*. 2024. <https://www.england.nhs.uk/long-read/hybrid-closed-loop-technologies-5-year->

[implementation-](#)

[strategy/#:~:text=Nq%2C%20et%20al%202022\).,over%20a%205%2Dyear%20period](#)

72. Crabtree TSJ, Griffin TP, Yap YW, et al. Hybrid Closed-Loop Therapy in Adults With Type 1 Diabetes and Above-Target HbA1c: A Real-world Observational Study. *Diabetes Care*. Oct 1 2023;46(10):1831-1838. doi:10.2337/dc23-0635
73. Royal College of Paediatrics and Child Health (RCPCH). *National Paediatric Diabetes Audit (NPDA) Report on Care and Outcomes 2022/23*. 2024. April 2024.
74. Fleming M, Fitton CA, Steiner MFC, et al. Educational and Health Outcomes of Children Treated for Type 1 Diabetes: Scotland-Wide Record Linkage Study of 766,047 Children. *Diabetes Care*. Sep 2019;42(9):1700-1707. doi:10.2337/dc18-2423
75. Rafferty J, Owens DR, Luzio SD, Watts P, Akbari A, Thomas RL. Risk factors for having diabetic retinopathy at first screening in persons with type 1 diabetes diagnosed under 18 years of age. *Eye*. 2021/10/01 2021;35(10):2840-2847. doi:10.1038/s41433-020-01326-8
76. Chiang JL, Kirkman MS, Laffel LM, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care*. Jul 2014;37(7):2034-54. doi:10.2337/dc14-1140
77. NHS Digital. *National Diabetes Inpatient Audit (NaDIA) 2016*. 2017. 8 March. <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-inpatient-audit/national-diabetes-inpatient-audit-nadia-2016>
78. AbuHammad GAR, Naser AY, Hassouneh LKM. Diabetes mellitus-related hospital admissions and prescriptions of antidiabetic agents in England and Wales: an ecological study. *BMC Endocr Disord*. May 6 2023;23(1):102. doi:10.1186/s12902-023-01352-z
79. NHS Digital. *National Diabetes Audit, 2017-18 Report 2a: Complications and Mortality (complications of diabetes), England and Wales*. 2019.
80. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. Aug 11 2018;392(10146):477-486. doi:10.1016/s0140-6736(18)31506-x
81. Samuelsson J, Bertilsson R, Bülow E, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. *Diabetologia*. Apr 2024;67(4):679-689. doi:10.1007/s00125-024-06086-8
82. Lawrence JM, Reynolds K, Saydah SH, et al. Demographic Correlates of Short-Term Mortality Among Youth and Young Adults With Youth-Onset Diabetes Diagnosed From 2002 to 2015: The SEARCH for Diabetes in Youth Study. *Diabetes Care*. Dec 2021;44(12):2691-2698. doi:10.2337/dc21-0728
83. Samuelsson J, Samuelsson U, Hanberger L, Bladh M, Åkesson K. Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age-A population-based cohort study. *Pediatr Diabetes*. May 2020;21(3):479-485. doi:10.1111/pedi.12980
84. Rawshani A, Rawshani A, Franzén S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *N Engl J Med*. Apr 13 2017;376(15):1407-1418. doi:10.1056/NEJMoa1608664
85. Tran-Duy A, Knight J, Clarke PM, Svensson AM, Eliasson B, Palmer AJ. Development of a life expectancy table for individuals with type 1 diabetes. *Diabetologia*. Oct 2021;64(10):2228-2236. doi:10.1007/s00125-021-05503-6
86. Eliasson B, Lyngfelt L, Strömblad SO, Franzén S, Eeg-Olofsson K. The significance of chronic kidney disease, heart failure and cardiovascular disease for mortality in type 1 diabetes: nationwide observational study. *Sci Rep*. Oct 26 2022;12(1):17950. doi:10.1038/s41598-022-22932-4
87. Bjerg L, Gudbjörnsdóttir S, Franzén S, et al. Duration of diabetes-related complications and mortality in type 1 diabetes: a national cohort study. *Int J Epidemiol*. Aug 30 2021;50(4):1250-1259. doi:10.1093/ije/dyaa290

88. Diabetes UK. Easing the burden for people with diabetes. Accessed November, 2024. <https://www.diabetes.org.uk/about-us/news-and-views/easing-burden-people-diabetes>
89. López-Bastida J, López-Siguero JP, Oliva-Moreno J, et al. Health-related quality of life in type 1 diabetes mellitus pediatric patients and their caregivers in Spain: an observational cross-sectional study. *Curr Med Res Opin.* Sep 2019;35(9):1589-1595. doi:10.1080/03007995.2019.1605158
90. Lafontaine S, Mok E, Frei J, et al. Associations of Diabetes-related and Health-related Quality of Life With Glycemic Levels in Adolescents With Type 1 Diabetes Preparing to Transition to Adult Care. *Can J Diabetes.* Aug 2023;47(6):525-531. doi:10.1016/j.cjcd.2023.05.002
91. Liu S, Ludvigsson JF, Lichtenstein P, et al. Educational Outcomes in Children and Adolescents With Type 1 Diabetes and Psychiatric Disorders. *JAMA Netw Open.* Apr 3 2023;6(4):e238135. doi:10.1001/jamanetworkopen.2023.8135
92. Forsander G, Bøgelund M, Haas J, Samuelsson U. Adolescent life with diabetes-Gender matters for level of distress. Experiences from the national TODS study. *Pediatr Diabetes.* Nov 2017;18(7):651-659. doi:10.1111/pedi.12478
93. Iturralde E, Weissberg-Benchell J, Hood KK. Avoidant coping and diabetes-related distress: Pathways to adolescents' Type 1 diabetes outcomes. *Health Psychol.* Mar 2017;36(3):236-244. doi:10.1037/hea0000445
94. Iturralde E, Rausch JR, Weissberg-Benchell J, Hood KK. Diabetes-Related Emotional Distress Over Time. *Pediatrics.* Jun 2019;143(6)doi:10.1542/peds.2018-3011
95. Kamody RC, Berlin KS, Rybak TM, et al. Psychological Flexibility Among Youth with Type 1 Diabetes: Relating Patterns of Acceptance, Adherence, and Stress to Adaptation. *Behav Med.* Oct-Dec 2018;44(4):271-279. doi:10.1080/08964289.2017.1297290
96. Weissberg-Benchell J, Antisdel-Lomaglio J. Diabetes-specific emotional distress among adolescents: feasibility, reliability, and validity of the problem areas in diabetes-teen version. *Pediatr Diabetes.* Jun 2011;12(4 Pt 1):341-4. doi:10.1111/j.1399-5448.2010.00720.x
97. Barnard-Kelly K, Marrero D, de Wit M, et al. Towards the standardisation of adult person-reported outcome domains in diabetes research: A Consensus Statement development panel. *Diabet Med.* Aug 2024;41(8):e15332. doi:10.1111/dme.15332
98. Haugstvedt A, Wentzel-Larsen T, Rokne B, Graue M. Perceived family burden and emotional distress: similarities and differences between mothers and fathers of children with type 1 diabetes in a population-based study. *Pediatr Diabetes.* Mar 2011;12(2):107-14. doi:10.1111/j.1399-5448.2010.00661.x
99. Whittemore R, Jaser S, Chao A, Jang M, Grey M. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ.* Jul-Aug 2012;38(4):562-79. doi:10.1177/0145721712445216
100. Chen Z, Wang J, Carru C, Coradduzza D, Li Z. The prevalence of depression among parents of children/adolescents with type 1 diabetes: A systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2023;14:1095729. doi:10.3389/fendo.2023.1095729
101. Fisher L, Hessler D, Polonsky W, Strycker L, Masharani U, Peters A. Diabetes distress in adults with type 1 diabetes: Prevalence, incidence and change over time. *Journal of Diabetes and its Complications.* 2016/08/01/ 2016;30(6):1123-1128. doi:<https://doi.org/10.1016/j.jdiacomp.2016.03.032>
102. Wilmot EG, Close KL, Jurišić-Eržen D, et al. Patient-reported outcomes in adults with type 1 diabetes in global real-world clinical practice: The SAGE study. *Diabetes Obes Metab.* Aug 2021;23(8):1892-1901. doi:10.1111/dom.14416
103. Molvaer AK, Iversen MM, Iglund J, et al. Metabolic predictors of pain, fatigue, depression and quality of life in people with long-term type 1 diabetes-the Dialong study. *Diabet Med.* Mar 2023;40(3):e15009. doi:10.1111/dme.15009
104. Fischer KI, Fischer FH, Barthel D, et al. Trajectories of Health-Related Quality of Life and HbA1c Values of Children and Adolescents With Diabetes Mellitus Type 1 Over 6 Months: A Longitudinal Observational Study. *Front Pediatr.* 2019;7:566. doi:10.3389/fped.2019.00566

105. Jacobson AM, Braffett BH, Cleary PA, Gubitosi-Klug RA, Larkin ME. The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications cohort. *Diabetes Care*. Oct 2013;36(10):3131-8. doi:10.2337/dc12-2109
106. Glocker V, Bachmann S, Hess M, Szinnai G, Burckhardt MA. Fear of hypoglycemia and quality of life in young people with type 1 diabetes and their parents in the era of sensor glucose monitoring. *Front Endocrinol (Lausanne)*. 2022;13:958671. doi:10.3389/fendo.2022.958671
107. Rossi MC, Nicolucci A, Ozzello A, et al. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. *Nutr Metab Cardiovasc Dis*. Jul 2019;29(7):736-743. doi:10.1016/j.numecd.2019.04.009
108. Coolen M, Aalders J, Broadley M, et al. Hypoglycaemia and diabetes-specific quality of life in adolescents with type 1 diabetes. *Diabet Med*. Aug 2021;38(8):e14565. doi:10.1111/dme.14565
109. Beverly EA, Rennie RG, Guseman EH, Rodgers A, Healy AM. High Prevalence of Diabetes Distress in a University Population. *J Am Osteopath Assoc*. Sep 1 2019;119(9):556-568. doi:10.7556/jaoa.2019.099
110. Howarth G, May T. *Type 1 diabetes and disordered eating: Parliamentary Inquiry*. 2024.
111. Hanlan ME, Griffith J, Patel N, Jaser SS. Eating Disorders and Disordered Eating in Type 1 Diabetes: Prevalence, Screening, and Treatment Options. *Curr Diab Rep*. Sep 12 2013;doi:10.1007/s11892-013-0418-4
112. Dahlquist G, Källén B. School performance in children with type 1 diabetes--a population-based register study. *Diabetologia*. May 2007;50(5):957-64. doi:10.1007/s00125-007-0615-2
113. National Institute for Health and Care Excellence (NICE). *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. Comments on the assessment consultation document*. 2023. 23 May <https://www.nice.org.uk/guidance/ta943/documents/1-2>
114. Elhabashy SA, Elhenawy YI, Hassan HA, Abdelmageed RI. Siblings of children with type 1 diabetes mellitus: Psychosocial health, coping. *J Pediatr Nurs*. Oct 27 2023;doi:10.1016/j.pedn.2023.10.024
115. Allen V, Mahieu A, Kasireddy E, et al. Humanistic burden of pediatric type 1 diabetes on children and informal caregivers: systematic literature reviews. *Diabetol Metab Syndr*. Mar 21 2024;16(1):73. doi:10.1186/s13098-024-01310-2
116. Nana M, Moore SL, Ang E, Lee ZX, Bondugulapati LNR. Flash glucose monitoring: Impact on markers of glycaemic control and patient-reported outcomes in individuals with type 1 diabetes mellitus in the real-world setting. *Diabetes Res Clin Pract*. Nov 2019;157:107893. doi:10.1016/j.diabres.2019.107893
117. Speight J, Holmes-Truscott E, Little SA, et al. Satisfaction with the Use of Different Technologies for Insulin Delivery and Glucose Monitoring Among Adults with Long-Standing Type 1 Diabetes and Problematic Hypoglycemia: 2-Year Follow-Up in the HypoCOMPASS Randomized Clinical Trial. *Diabetes Technol Ther*. Nov 2019;21(11):619-626. doi:10.1089/dia.2019.0152
118. D'Souza RS, Ryan M, Hawkes E, et al. Questionnaire-based service evaluation of the efficacy and usefulness of SEREN: a structured education programme for children and young people diagnosed with type 1 diabetes mellitus. *BMJ Open Qual*. Sep 2021;10(3)doi:10.1136/bmjopen-2021-001337
119. Hex N, MacDonald R, Pocock J, et al. Estimation of the direct health and indirect societal costs of diabetes in the UK using a cost of illness model. *Diabet Med*. Sep 2024;41(9):e15326. doi:10.1111/dme.15326

120. Langa KM, Vijan S, Hayward RA, et al. Informal caregiving for diabetes and diabetic complications among elderly americans. *J Gerontol B Psychol Sci Soc Sci*. May 2002;57(3):S177-86. doi:10.1093/geronb/57.3.s177
121. Lawton J, Blackburn M, Allen J, et al. Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocr Disord*. Feb 20 2018;18(1):12. doi:10.1186/s12902-018-0239-1
122. Commissariat PV, Boyle CT, Miller KM, et al. Insulin Pump Use in Young Children with Type 1 Diabetes: Sociodemographic Factors and Parent-Reported Barriers. *Diabetes Technol Ther*. Jun 2017;19(6):363-369. doi:10.1089/dia.2016.0375
123. de Zoysa N, Choudhary P. *Tech ~Master 'v' Slave? Handling tricky responses in clinic*. 2024.
124. Patton SR, Clements MA. Psychological Reactions Associated With Continuous Glucose Monitoring in Youth. *J Diabetes Sci Technol*. May 2016;10(3):656-61. doi:10.1177/1932296816638109
125. Barnard KD, Breton MD. Diabetes Technological Revolution: Winners and Losers? *J Diabetes Sci Technol*. Nov 2018;12(6):1227-1230. doi:10.1177/1932296818788872
126. Juvenile Diabetes Research Foundation (JDRF). *Barriers and drivers to technology*. 2019. November 2019.
127. Giorda CB, Rossi MC, Ozzello O, et al. Healthcare resource use, direct and indirect costs of hypoglycemia in type 1 and type 2 diabetes, and nationwide projections. Results of the HYPOS-1 study. *Nutr Metab Cardiovasc Dis*. Mar 2017;27(3):209-216. doi:10.1016/j.numecd.2016.10.005
128. Jacobsen LM, Schatz DA, Herold KC, Skyler JS. *Prevention of Type 1 Diabetes*. 2023. *Diabetes in America [Internet] Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*. June 6. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK604182/>
129. Tatovic D, Dayan CM. Replacing insulin with immunotherapy: Time for a paradigm change in Type 1 diabetes. *Diabet Med*. Dec 2021;38(12):e14696. doi:10.1111/dme.14696
130. DiSantostefano RL, Sutphin J, Hedrick JA, Klein K, Mansfield C. Parent Preferences for Delaying Insulin Dependence in Children at Risk of Stage III Type 1 Diabetes. *Diabetes Technol Ther*. Aug 2020;22(8):584-593. doi:10.1089/dia.2019.0444
131. National Institute for Health and Care Excellence (NICE). *Diagnostics Assessment Programme. Equality impact assessment – Guidance development: MTA Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes* 2023. <https://www.nice.org.uk/guidance/ta943/documents/equality-impact-assessment-guidance-development>
132. National Institute for Health and Care Excellence (NICE). *NICE guidelines. Equality Impact Assessment: Type 1 diabetes in children and young people: diagnosis and management [NG18]*. 2021. <https://www.nice.org.uk/guidance/ng18/update/ng18-update-2/documents/equality-impact-assessment>
133. National Institute for Health and Care Excellence (NICE). *Equality Impact Assessment. NICE guidelines: Type 1 diabetes in adults: diagnosis and management [NG17]*. 2022. <https://www.nice.org.uk/guidance/ng17/update/ng17-update-2/documents/equality-impact-assessment-3>
134. Mäkimattila S, Harjutsalo V, Forsblom C, Groop PH. Every Fifth Individual With Type 1 Diabetes Suffers From an Additional Autoimmune Disease: A Finnish Nationwide Study. *Diabetes Care*. May 2020;43(5):1041-1047. doi:10.2337/dc19-2429
135. Scott A, Chambers D, Goyder E, O'Cathain A. Socioeconomic inequalities in mortality, morbidity and diabetes management for adults with type 1 diabetes: A systematic review. *PLoS One*. 2017;12(5):e0177210. doi:10.1371/journal.pone.0177210
136. Apperley LJ, Ng SM. Socioeconomic Deprivation, Household Education, and Employment are Associated With Increased Hospital Admissions and Poor Glycemic Control in Children With Type 1 Diabetes Mellitus. *Rev Diabet Stud*. Summer-Fall 2017;14(2-3):295-300. doi:10.1900/rds.2017.14.295

137. Fallon C, Jones E, Oliver N, Reddy M, Avari P. The impact of socio-economic deprivation on access to diabetes technology in adults with type 1 diabetes. *Diabet Med*. Oct 2022;39(10):e14906. doi:10.1111/dme.14906
138. Scott A, O'Cathain A, Goyder E. Socioeconomic disparities in access to intensive insulin regimens for adults with type 1 diabetes: a qualitative study of patient and healthcare professional perspectives. *Int J Equity Health*. Oct 11 2019;18(1):150. doi:10.1186/s12939-019-1061-8
139. Khanolkar AR, Amin R, Taylor-Robinson D, et al. Ethnic differences in early glycemic control in childhood-onset type 1 diabetes. *BMJ Open Diabetes Research & Care*. 2017;5(1):e000423. doi:10.1136/bmjdr-2017-000423
140. NHS RightCare. *Children and young people diabetes toolkit*. 2024. <https://www.england.nhs.uk/wp-content/uploads/2024/07/children-and-young-people-diabetes-toolkit.pdf>
141. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. Aug 15 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
142. Provention Bio Inc. (Data on File). *TN-10 Clinical Study Report Addendum: Anti-CD3 MAP (Teplizumab) for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus. Final Version 1.0*. 2020. September 3.
143. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med*. Mar 3 2021;13(583)doi:10.1126/scitranslmed.abc8980
144. Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β -Cell Function. *Diabetes Care*. 2023;46(10):1848-1856. doi:10.2337/dc23-0675
145. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β -Cell Function in Newly Diagnosed Type 1 Diabetes. *N Engl J Med*. Oct 18 2023;doi:10.1056/NEJMoa2308743
146. ClinicalTrials.gov. TrialNet Pathway to Prevention of T1D. Accessed July 9, 2024. <https://clinicaltrials.gov/study/NCT00097292>
147. ClinicalTrials.gov. Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk". Accessed July 9, 2024. <https://clinicaltrials.gov/study/NCT01030861>
148. CDER Office of Clinical Pharmacology. *CLINICAL PHARMACOLOGY REVIEW(S) (761183Orig1s000)*. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000ClinPharmR.pdf
149. Lebowitz MR, Blumenthal SA. The molar ratio of insulin to C-peptide. An aid to the diagnosis of hypoglycemia due to surreptitious (or inadvertent) insulin administration. *Arch Intern Med*. Mar 8 1993;153(5):650-5.
150. Taylor PN, Collins KS, Lam A, et al. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. *Lancet Diabetes Endocrinol*. Nov 3 2023;doi:10.1016/s2213-8587(23)00267-x
151. Holman N, Knighton P, Wild SH, et al. Cohort profile: National Diabetes Audit for England and Wales. *Diabetic Medicine*. 2021;38(9):e14616. doi:<https://doi.org/10.1111/dme.14616>
152. Provention Bio Inc. TZIELD® (teplizumab-mzwv) injection US Prescribing Information. Dec 2023;
153. Wood Heickman LK. *Clinical Review*. 2022. 17 February.
154. ClinicalTrials.gov. Teplizumab in Pediatric Stage 2 Type 1 Diabetes (PETITE-T1D). Updated April 16, 2024. Accessed July 10, 2024. <https://clinicaltrials.gov/study/NCT05757713>
155. ClinicalTrials.gov. At-Risk for Type 1 Diabetes Extension Study (TN-10 Extension). Updated April 16, 2024. Accessed July 10, 2024. <https://clinicaltrials.gov/study/NCT04270942>

156. Barker JM, Goehrig SH, Barriga K, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care*. Jun 2004;27(6):1399-404. doi:10.2337/diacare.27.6.1399
157. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care*. Jan 1999;22(1):7-9. doi:10.2337/diacare.22.1.7
158. Vanelli M, Chiari G, Lacava S, Iovane B. Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care*. Apr 2007;30(4):e12. doi:10.2337/dc07-0059
159. Lledó-Delgado A, Preston-Hurlburt P, Currie S, et al. Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes. *J Clin Invest*. Aug 13 2024;134(18)doi:10.1172/jci177492
160. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. Mar 2003;26(3):832-6. doi:10.2337/diacare.26.3.832
161. Mital S, Nguyen HV. Cost Effectiveness of Teplizumab for Prevention of Type 1 Diabetes Among Different Target Patient Groups. *Pharmacoeconomics*. Dec 2020;38(12):1359-1372. doi:10.1007/s40273-020-00962-y
162. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013 [PMG9]*. 2013.
<https://www.nice.org.uk/process/pmg9/chapter/foreword>
163. Henriksson M, Jindal R, Sternhufvud C, Bergenheim K, Sörstadius E, Willis M. A Systematic Review of Cost-Effectiveness Models in Type 1 Diabetes Mellitus. *Pharmacoeconomics*. Jun 2016;34(6):569-85. doi:10.1007/s40273-015-0374-8
164. Daly MJ, Elvidge J, Chantler T, Dawoud D. A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for Treatments of T1DM & T2DM. *Front Pharmacol*. 2022;13:887298. doi:10.3389/fphar.2022.887298
165. Latimer N. *Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data (NICE DSU Report)*. 2013.
166. Office for National Statistics. *National life tables – life expectancy in the UK: 2020 to 2022*. 2024.
167. Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PM. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. *PLoS One*. 2014;9(11):e113635. doi:10.1371/journal.pone.0113635
168. Matza LS, Cong Z, Chung K, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence*. 2013;7:855-65. doi:10.2147/ppa.S44947
169. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. Nov-Dec 2011;31(6):800-4. doi:10.1177/0272989x11401031
170. Office for National Statistics. *Families and households*. 2024. May 8.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/datasets/familiesandhouseholds/familiesandhouseholds/current>
171. National Institute for Health and Care Excellence (NICE). *NICE health technology evaluations: the manual*. 2023. <https://www.nice.org.uk/process/pmg36/>
172. National Health Services (NHS). *National Schedule of NHS Costs 2021/22 (V3, updated 19 May 2023)*. 2023. <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>
173. Mehta S, Ryabets-Lienhard A, Patel N, et al. Pediatric Endocrine Society Statement on Considerations for Use of Teplizumab (Tzield™) in Clinical Practice. *Horm Res Paediatr*. Apr 30 2024;1-12. doi:10.1159/000538775
174. Ou HT, Yang CY, Wang JD, Hwang JS, Wu JS. Life Expectancy and Lifetime Health Care Expenditures for Type 1 Diabetes: A Nationwide Longitudinal Cohort of Incident Cases

- Followed for 14 Years. *Value Health*. Dec 2016;19(8):976-984. doi:10.1016/j.jval.2016.05.017
175. Jones K, Weatherly H., Birch S, et al. *Unit Costs of Health and Social Care 2023 Manual (Table 12.1.1: The NHS Inflation Index [NHSCII])*. 2023:98.
 176. Burnham K, Anderson D. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*. Second ed. Springer; 2002.
 177. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research*. 2004;33(2):261-304. doi:10.1177/0049124104268644
 178. Burnham KP, Anderson DR, Huyvaert KP. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behavioral Ecology and Sociobiology*. 2011/01/01 2011;65(1):23-35. doi:10.1007/s00265-010-1029-6
 179. Kass RE, Raftery AE. Bayes Factors. *Journal of the American Statistical Association*. 1995;90(430):773-795. doi:10.2307/2291091
 180. Raftery AE. Bayesian Model Selection in Social Research. *Sociological Methodology*. 1995;25:111-163. doi:10.2307/271063
 181. Hernández-Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by age and sex for the UK (NICE DSU Report)*. 2022.
 182. GOV.UK. Sister/Charge Nurse - Infusion Unit | East Sussex Healthcare NHS Trust. Updated December 11, 2023. Accessed November 4, 2024. <https://findajob.dwp.gov.uk/details/13603257>
 183. Exeter Clinical Laboratory International. Glutamic Acid Decarboxylase (GAD) Antibodies. Accessed 31 October, 2024. <https://www.exeterlaboratory.com/test/gad-antibodies/>
 184. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Glucose Medicinal forms. Accessed 1 November, 2024. <https://bnf.nice.org.uk/drugs/glucose/medicinal-forms/>
 185. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Ibuprofen Medicinal forms. Accessed 1 November, 2024. <https://bnf.nice.org.uk/drugs/ibuprofen/medicinal-forms/#oral-tablet>
 186. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Cetirizine hydrochloride Medicinal forms. Accessed 1 November, 2024. <https://bnf.nice.org.uk/drugs/cetirizine-hydrochloride/medicinal-forms/#oral-tablet>
 187. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Ondansetron Medicinal forms. Accessed 1 November, 2024. <https://bnf.nice.org.uk/drugs/ondansetron/medicinal-forms/#oral-tablet>
 188. Akhtar W, Chung Y. Saving the NHS one blood test at a time. *BMJ Qual Improv Rep*. 2014;2(2)doi:10.1136/bmjquality.u204012.w1749
 189. NHS Jobs. Highly Specialised Pharmacist - Gastroenterology. Updated April 4, 2023. Accessed November 4, 2024. <https://beta.jobs.nhs.uk/candidate/jobadvert/C9279-23-5654>
 190. NHS England. 2023/25 NHS Payment Scheme - Annex B: Guidance on currencies. 2023. 30 March. <https://www.england.nhs.uk/wp-content/uploads/2023/03/23-25NHSPS-Annex-B-Guidance-on-currencies-1.pdf>
 191. National Institute for Health and Care Excellence (NICE). *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. Final appraisal committee papers*. 2023. <https://www.nice.org.uk/guidance/ta943/evidence/final-appraisal-determination-committee-papers-pdf-13254232142>
 192. National Institute for Health and Care Research (NIHR). Comparing blood tests to detect diabetes during NHS health checks. Detection, screening and diagnosis <https://evidence.nihr.ac.uk/alert/comparing-blood-tests-to-detect-diabetes-during-nhs-health-checks/>
 193. NHS England. NHS Payment Scheme: 2024/2025 prices workbook. Accessed 06/05/2024,

[https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.england.nhs.uk%2Fwp-content%2Fuploads%2F2023%2F03%2F23-25NHSPS Annex-A 2024-25.xlsx&wdOrigin=BROWSELINK](https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.england.nhs.uk%2Fwp-content%2Fuploads%2F2023%2F03%2F23-25NHSPS%20Annex-A%2024-25.xlsx&wdOrigin=BROWSELINK)

194. NHS England. NHS Staff Annual Earnings Estimates December 2023, NHS Trusts and other core orgs 2024. Accessed 19/05/2024, <https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FF3%2F0C1ABF%2FNHS%2520Staff%2520Annual%2520Earnings%2520Estimates%2520December%25202023%252C%2520NHS%2520Trusts%2520and%2520other%2520core%2520orgs%252C%2520Tables.xlsx&wdOrigin=BROWSELINK>
195. Digitizelt. Digitizelt software. <https://www.digitizeit.xyz/>
196. Lindkvist EB, Thorsen SU, Paulsrud C, et al. Association of type 1 diabetes and educational achievement in 16-20-year-olds: A Danish nationwide register study. *Diabet Med*. Feb 2022;39(2):e14673. doi:10.1111/dme.14673
197. Milton B, Holland P, Whitehead M. The social and economic consequences of childhood-onset Type 1 diabetes mellitus across the lifecourse: a systematic review. *Diabet Med*. Aug 2006;23(8):821-9. doi:10.1111/j.1464-5491.2006.01796.x
198. Persson S, Dahlquist G, Gerdtham UG, Steen Carlsson K. Why childhood-onset type 1 diabetes impacts labour market outcomes: a mediation analysis. *Diabetologia*. Feb 2018;61(2):342-353. doi:10.1007/s00125-017-4472-3
199. Roze S, Buompiensiere MI, Ozdemir Z, de Portu S, Cohen O. Cost-effectiveness of a novel hybrid closed-loop system compared with continuous subcutaneous insulin infusion in people with type 1 diabetes in the UK. *J Med Econ*. Jan-Dec 2021;24(1):883-890. doi:10.1080/13696998.2021.1939706

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID6259_Teplizumab_SIP_27Nov2024_noCON	1.0	No	27Nov2024

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: Teplizumab

Brand name: Tzield®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

Teplizumab is used to delay the onset of Stage 3 (symptomatic) type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with Stage 2 (presymptomatic) T1D.

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.

Marketing authorisation is pending.

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:

Hands off funding of £52,000 (including VAT) provided to Breakthrough T1D UK in 2024 to support charitable activities. Collaboration has been conducted on disease awareness materials and resources, including payment of £2,013 in consultancy fees.

Hands off funding of £30,000 provided to Diabetes UK in 2024 to support charitable activities.

Hands off funding of £15,000 provided to Diabetes Africa in 2024 to support charitable activities.

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 type 1 diabetes (T1D)?

T1D is a lifelong, autoimmune condition which is characterised by chronic high blood sugar (glucose) levels also known as hyperglycaemia. This can result in several symptoms, including needing to go to the toilet a lot and thirst, needing to urinate at night, inability to control urination, weight loss (possibly accompanied by fatigue and behavioural disturbances) and blurred vision.^{1,2}

T1D progressively worsens over time and specifically involves a person's own immune system (T cells) attacking and damaging healthy beta-cells in the pancreas.^{3,4} Beta-cells are responsible for making insulin, which is a hormone that helps the body to absorb sugar from the blood.³ When too many insulin-producing beta-cells are damaged, the body cannot make enough insulin, ultimately resulting in hyperglycaemia.^{2,3,5,6} Additionally, recurrent hyperglycaemia may lead to diabetic ketoacidosis (DKA; which occurs when there is a severe lack of insulin in the body), long-term complications (e.g., kidney disease, eye disease, nerve damage, cardiovascular disease) and possibly coma and death.^{2,7-9} Therefore, people with T1D whose bodies can no longer make enough insulin require insulin injections to control the high blood sugar levels for the rest of their lives.¹⁰

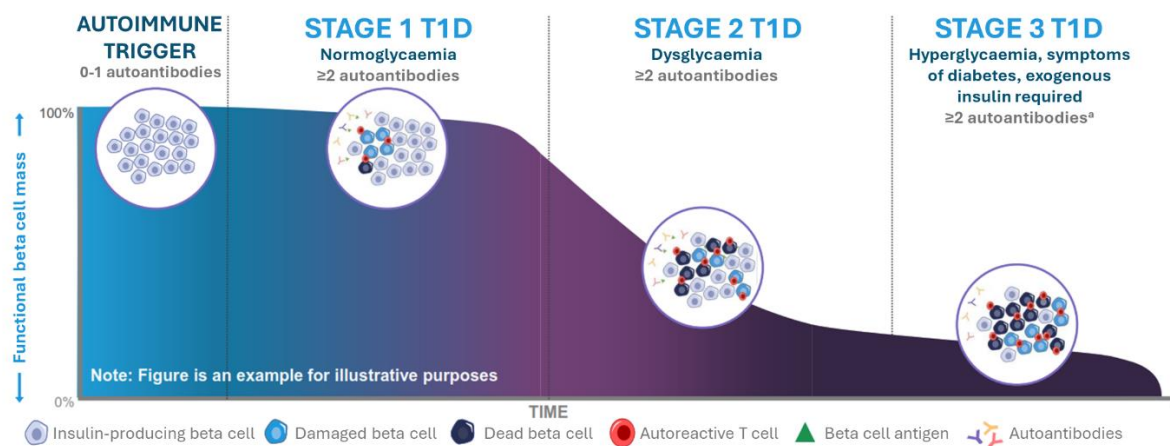
The immune system may produce several antibodies, known as diabetes-related autoantibodies. These can be used as an indicator in diagnosing T1D because these antibodies show up in blood tests when the immune system is attacking beta-cells.^{2,3,6}

T1D progresses across the following 3 stages (Figure 1):^{2,3,5,6}

- **Stage 1 T1D**, blood sugar levels are normal (normoglycaemia) and there are no noticeable symptoms, meaning people have presymptomatic T1D at this stage.

- **Stage 2 T1D**, abnormal blood sugar levels (dysglycaemia); however, there are still no noticeable symptoms, meaning people have presymptomatic T1D at this stage. Insulin injections are not required yet.
- **Stage 3 (clinical) T1D**, the appearance of noticeable symptoms of T1D; as the body can no longer make enough insulin, blood sugar levels are too high (hyperglycaemia). Once in Stage 3, people with T1D will require lifelong insulin treatment (exogenous insulin).

Figure 1. The stages of T1D



^aIn some people, autoantibodies may become absent in Stage 3 T1D.

T1D = type 1 diabetes

Source: Insel 2015;¹¹ van Belle 2022;¹² Jacobsen 2018;¹³ ADA 2022;¹⁴ McCall 2013¹⁵

The *stages* of T1D described above are different from the *types* of diabetes, of which there are two (Type 1 and Type 2 diabetes [T2D]). As described above, T1D is an autoimmune condition,^{2,6} while in contrast, T2D is a non-autoimmune condition in which the body cannot make enough insulin or the insulin being made does not work properly.² People with T2D may be able to manage the condition with lifestyle changes at the beginning when the condition is first diagnosed and do not always require lifelong insulin injections.⁶

How many people have Stage 2 T1D?

The number of people with Stage 2 T1D in England is not well understood because at the moment T1D isn't normally found before people experience symptoms (Stage 3); there are currently no early detection programmes in the general population of the UK,¹⁶ and that clinicians do not usually identify Stage 2 T1D in routine clinical practice.¹⁷

How many people have Stage 3 T1D?

Most people with T1D are diagnosed at Stage 3 due to the onset of symptoms relating to high blood sugar levels.⁵ Between 2021-2022 in England, 9,725 individuals were diagnosed with Stage 3 T1D across all age groups and 4,145 individuals aged below 19 years were diagnosed, as reported by the National Diabetes Audit (NDA).¹⁸ It was estimated that in 2021-2022 there were 270,935 individuals across all ages living with Stage 3 T1D in England.¹⁸

What is the impact of Stage 2 T1D on a person's quality of life?

It is expected that people with Stage 2 T1D will experience some distress and an impact on their emotional wellbeing following diagnosis. Additionally, for children who are diagnosed with Stage 1 or 2 T1D, the diagnosis has been associated with increased psychological distress (generally of low or moderate severity) in the children's mothers.¹⁹

Most people with Stage 2 T1D will eventually progress along the stages of T1D to symptomatic Stage 3 T1D where people's lives are impact the most by T1D, including lifelong daily disease management, risk of acute and long-term complications and increased mortality compared with the general population.⁵

What is the impact of Stage 3 T1D on a person's quality of life?

Once a person progresses to Stage 3 T1D, they and their families and caregivers face a substantial impact on their quality of life and emotional wellbeing due to the disease and the reality of lifelong daily disease management.^{20,21} People with Stage 3 T1D can feel stressed, low and depressed or burned out.²² Children and adolescents with Stage 3 T1D experience impacts on daily activities, pain and discomfort and have a higher number of psychiatric/mental health disorders than peers without T1D.²³⁻²⁵

Further, the negative impact of T1D on health-related wellbeing can be greater in people who have been diagnosed with Stage 3 T1D for a longer time.²⁰ Other factors reported to worsen emotional wellbeing in people with Stage 3 T1D include poor management of diabetes in children, adolescents and adults,^{24,26-30} occurrence of severe hypoglycaemia (low blood sugar levels) or hypoglycaemia requiring assistance in adolescents and adults,^{29,31} fear of hypoglycaemia in children and adolescents^{30,32} and diabetes-related distress in adults.³³

Adults with Stage 3 T1D reported in qualitative interviews that continuously managing their blood sugar levels can make them feel worn down, depressed or embarrassed, and that their condition can seem relentless.^{34,35}

- *“It [fluctuating blood sugar levels] takes a lot of energy... It takes a lot, it’s a great strain... I’d say, it wears me down. It really wears me down.”*
- *“This is a condition that requires CONSTANT monitoring, awareness and cautiousness... it isn’t just a mental load, it’s mentally exhausting and debilitating.”*

Caregivers of children with Stage 3 T1D are also negatively impacted by the disease and its management, with psychological distress reported in many of parents of children with Stage 3 T1D.³⁶ Parents report constant worry, disruption to family life and routines and social isolation, with many parents seeking professional support.³⁶

How many people die from Stage 3 T1D?

Although people with Stage 2 T1D are not expected to have a greater risk of death compared with the general population, the majority of those with Stage 2 will progress to Stage 3 T1D, which is associated with a greater risk of death.³⁷ Diabetes-related causes of death include hypoglycaemia, serious complications such as DKA,³⁸⁻⁴⁰ and chronic complications/comorbidities such as kidney disease and cardiovascular disease.⁴¹⁻⁴⁴

Based on 2015-2016 NDA data for England and Wales, the relative risk of death for people with Stage 3 T1D vs. the general population is increased at all ages, and the risk of death is higher in individuals aged 15 to 34 years compared with individuals aged ≥35 years.⁴⁵ A younger age at onset of Stage 3 T1D may also be associated with an increased risk of early death, as a 2016 Swedish study based on data from 1998 to 2012 reported approximately 16 years lower life expectancy for those diagnosed before the age of 10 years compared with people of the same age without T1D.⁴⁶ Furthermore, children and young adults with Stage 3 T1D had an increased risk of early death compared with the general population, as reported in another Swedish study based on 2000 to 2009 data.⁴⁷

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 Stage 2 T1D diagnosed?

Diagnostic criteria from the International Society for Pediatric and Adolescent Diabetes (ISPAD) note that people with multiple islet autoantibodies, as well as high blood sugar levels despite not eating for a long time, are classified as having Stage 2 T1D.⁵ Glycaemic staging and ongoing monitoring should be offered to those with multiple islet autoantibodies, with the oral glucose tolerance test (OGTT) being recommended as the gold standard for staging T1D. An OGTT involves a blood test before and after consuming sugar and fasting, with the goal being to observe how the body handles sugar that is ingested from food and drinks.⁴⁸

Currently, in the UK some people are identified and diagnosed with Stage 2 T1D through research studies or opportunistic testing.^{2,16,17,49,50}

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 Stage 2 T1D currently treated?

There are no specific UK guidelines on the management of Stage 2 T1D currently published.

However, international consensus guidelines and UK clinical experts have recommended regular checks of blood sugar levels, every three months in children and every six months in adults, to determine if people with Stage 2 T1D have progressed to Stage 3.^{51,52}

Additionally, education and psychosocial support is also recommended for people with Stage 2 T1D and their family members.^{51,52}

How is Stage 3 T1D currently treated?

The main goal of treatment for Stage 3 T1D is achieving ideal blood sugar levels through the use of insulin treatment, to limit the occurrence of hyperglycaemia and hypoglycaemia.⁵³

Insulin

Insulin replacement therapy is the main treatment for Stage 3 T1D. Treatment with insulin aims to reproduce the insulin production usually carried out by the pancreas before the destruction of beta-cells.⁵⁴ Multiple daily injections or insulin pump therapy are recommended by NICE to help achieve healthy blood sugar levels in people with Stage 3 T1D.⁵³

Blood glucose monitoring (BGM)

People with Stage 3 T1D need to check their blood sugar levels frequently to guide insulin dosage, food intake and to prevent hypoglycaemia.^{53,54} The monitoring of blood sugar levels can be managed by the individual manually with finger prick blood glucose monitoring (BGM) tests and automatically with a continuous glucose monitoring (CGM) device.^{53,55,56}

Hybrid closed loop (HCL) systems

The treatment options for Stage 3 T1D have evolved with the introduction of newer technologies, such as hybrid closed loop (HCL) systems. HCL systems use a mathematical algorithm to automatically deliver insulin by continuous infusion through the skin in response to blood sugar levels that are monitored via real-time CGM.⁵⁷

Education and support

NICE and the European Association for the Study of Diabetes (EASD) also recommend diabetes self-management education and support programs, to help people learn more about eating well including the importance of nutrition, carbohydrate counting and physical activity in achieving better management of blood sugar levels.^{53,54}

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.

Limitations of current treatments for Stage 2 T1D

There are currently no treatments for Stage 2 T1D in the UK. International consensus monitoring guidelines from 2024 recommend the monitoring of children every 3 months and every 6 months in adults to confirm glycaemic status in individuals with Stage 2 T1D.⁵¹

Limitations of current treatments for Stage 3 T1D

The current treatment for Stage 3 T1D is insulin injections or insulin pumps.^{5,53,54} This treatment provides replacement insulin once the disease has progressed to the final stage of damage to insulin-producing beta-cells and the body can no longer produce its own insulin.⁵⁸ As a result, this treatment helps manage the symptoms of Stage 3 T1D, but does not target the actual cause or prevent further progression of T1D.⁵⁸ Furthermore, current insulin treatments for Stage 3 T1D are associated with side effects, which negatively impact the emotional wellbeing and daily lives of people with the condition.^{29,31,53,54} The main risk of insulin treatment is hypoglycaemia, which occurs when blood sugar levels drop below the normal range and can often require hospitalisation.^{53,54} For example the National Diabetes Inpatient Audit reported that in England and Wales, 20% of hospital inpatients with Stage 3 T1D had one or more hypoglycaemic episode in the past seven days.⁵⁹ Weight gain can also result with insulin treatment, which may also negatively impact the individual.⁵⁴ Additional side effects are possible with the use of insulin pumps, including technical faults that stop insulin delivery (e.g., hardware/software malfunction, battery failure) and skin-related side effects (e.g., scarring, infections) that may impair how insulin is taken into the body.⁶⁰

The use of diabetes technology in Stage 3 T1D management may also cause some difficulties for people with the condition.^{61,62} Adults with Stage 3 T1D in England who were surveyed about diabetes technologies (e.g., CGM devices) indicated that the bulky devices elicited self-consciousness and were constant reminders of their conditions; one respondent noted “*Change the size of that and how it looks. I would be quite happy to use it if I could go out and nobody would know I was doing it.*”⁶³

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.

What is the mechanism of action of teplizumab?

Teplizumab is a medicine that targets immune system T cells that in T1D attack and damage insulin-producing beta-cells.⁴ While we do not fully understand how teplizumab works, research suggests it might help by turning off the T cells that attack the beta-cells. This means the beta-cells can keep making insulin for a longer time.⁴ As a result, teplizumab is believed to delay the damage to beta-cells and slow down the progression to a more severe stage of T1D (Stage 3). However, people treated with teplizumab are still expected to eventually reach Stage 3.

Where will teplizumab fit into the clinical pathway for T1D?

Teplizumab is the only therapy approved to delay the onset of Stage 3 T1D in people with Stage 2 T1D, with approval currently granted in the United States (US), Israel and United Arab Emirates (UAE).⁶⁴⁻⁶⁶

The proposed position of teplizumab in the clinical pathway of care in England is as a treatment option for individuals with Stage 2 T1D, in order to delay the onset of Stage 3 T1D in adult and paediatric patients 8 years of age and older (the anticipated licensed population for teplizumab).

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.

Is the medicine intended to be used in combination with any other medicines?

No.

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?

Teplizumab is administered by intravenous (IV) infusion (administration directly into or within a vein) over a minimum of 30 minutes once daily for 14 consecutive days in a hospital setting using a dose specific to a person's body surface area (calculated based on weight and height).⁶⁷

- Day 1: 65 mcg/m²
- Day 2: 125 mcg/m²
- Day 3: 250 mcg/m²
- Day 4: 500 mcg/m²
- Days 5 through 14: 1,030 mcg/m²

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.

There is one clinical trial of teplizumab in Stage 2 T1D, the population of interest for this submission. The efficacy and safety of teplizumab in this population was evaluated in the phase II TrialNet (TN)-10 trial.⁶⁸

Full Title: Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus (TN-10)

Location: The trial was conducted in sites in the US, Canada, Australia and Germany.

Population: People with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D.

Patient group size: 76 people randomised in a 1:1 ratio to receive either teplizumab (44 people) or placebo (32 people).

Comparators: Placebo.

Key inclusion and exclusion criteria: People with Stage 2 T1D (including abnormal blood sugar tolerance and the presence of two or more diabetes-related autoantibodies) who were at least 8 years old and relatives of people with Stage 3 T1D. People with a diagnosis of Stage 3 T1D were not eligible to participate in the trial.

There are other clinical trials in Stage 3 T1D patients which informed the pooled safety data referred to in this document.

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.

Based on the results of TN-10, treatment with teplizumab resulted in a delay in the need for insulin injections. Individuals treated with teplizumab had a statistically significantly longer median time to onset of Stage 3 T1D than individuals treated with placebo (5.0 vs. 2.3 years; difference: 2.7 years).⁶⁹ Additionally, treatment with teplizumab resulted in significantly higher C-peptide levels vs. treatment with placebo (mean of 1.94 vs. 1.72 pmol/ml, respectively).⁶⁹

For further information, see Section B.2.6 of submission Document B.

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.

Quality of life data were not collected in the TN-10 trial. The only data on quality of life come from another study of teplizumab in people with newly diagnosed Stage 3 T1D (the PROTECT study).⁷⁰

Preference for treatments to delay the need for insulin injections

A study in the UK published in 2010 found that adults with T1D, parents of children with T1D, and the general public valued reducing or avoiding the need for insulin injections.⁷¹

In a more recent survey in the US, the most important treatment attributes cited by parents, regardless of whether their child had T1D, included delaying insulin dependence and reducing the risk of long-term complications.⁷²

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.

Teplizumab has demonstrated an acceptable safety profile.⁶⁸ A pooled safety analysis looked at the adverse events (AEs) of approximately 1,000 people enrolled into five clinical trials of teplizumab, including TN-10.⁷³ In the clinical trials, 791 people had been given teplizumab, and 245 had been given a control.⁷³ 99.5% (n=787) of individuals treated with teplizumab had at least one AE, whilst 95.1% (n=233) of individuals treated with control had at least one AE.⁷³ The five most common AEs in individuals treated with teplizumab are listed in Table 1.⁷³

Table 1. Five most common adverse events (AEs) occurring in individuals treated with teplizumab

Adverse Event	Description	Teplizumab (n=791)	Control (n=245)
Lymphopenia	Decrease in lymphocytes	632 (79.9%)	41 (16.7%)
Leukopenia	Decrease in white blood cells	501 (63.3%)	65 (26.5%)
Neutropenia	Decrease in neutrophils	313 (39.6%)	53 (21.6%)
Blood bicarbonate decreased	Indication that the blood has too much acid	303 (38.3%)	67 (27.3%)
Rash	-	273 (34.5%)	25 (10.2%)

Source: Herold 2023⁷³

In addition, the rates of cytokine release syndrome (CRS) were 5.8% and 1.2% for participants treated with teplizumab or control, respectively.⁷³

In the TN-10 clinical trial specifically, the proportion of participants who experienced at least one AE during treatment was 97.7% in the teplizumab group and 68.8% in the placebo group.⁷⁴ The majority of participants completed the 14-day treatment course for both teplizumab (97.7%) and placebo (93.8%), with discontinuation rates of 2.3% and 6.3%, respectively.⁷⁴ One participant in the teplizumab group had a grade 2 (moderate

severity) AE of CRS, which was considered likely related to the study drug; the event resolved and the entire 14-day treatment course was completed by the participant without the need to reduce the dose of their treatment.^{68,74}

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

Teplizumab will be the first and only disease-modifying therapy licensed to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D in the UK, offering the opportunity for people to delay the need for daily insulin injections and the challenges of frequent blood sugar level monitoring by a median of 2.7 years.^{69,75}

Additionally, the delayed onset of Stage 3 T1D may also postpone the risk of long-term complications associated with Stage 3 T1D such as DKA. UK clinical expert advice gathered by Sanofi indicated that they expect extended time in Stage 2 would provide more time to understand the diagnosis, prepare and more thoroughly learn how to manage Stage 3 T1D, which ultimately may lead to improved outcomes and compliance.¹⁷

As discussed above, there is a willingness among people with T1D, caregivers and healthcare professionals in the UK to have treatments for T1D that can delay the need for insulin⁷¹, which suggests that a disease-modifying therapy such as teplizumab would be accepted among individuals with Stage 2 T1D. For example, findings from interviews of people with Stage 3 T1D determined that the prospect of being “insulin-free” was associated with a substantially better health state compared with needing insulin injections.⁷¹ Additionally, in a US survey, the most important treatment attributes cited by parents of children with Stage 3 T1D included delaying insulin dependence from 6 months to 4 years (hypothetical timeframe used in the survey) and reducing the risk of long-term complications.⁷²

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

Treatment with teplizumab is an IV infusion for 14 consecutive days that may be difficult for some people with T1D and their caregivers to accommodate. Furthermore, treatment with teplizumab may cause CRS and a decrease in white blood cells.³ The signs of CRS typically occurred during the first 5 days of teplizumab treatment in clinical trials;⁷⁶ these signs include fever, nausea, feeling tired, headache, muscle and joint pain or increased liver enzymes in the blood.³ Therefore, it is very important for people receiving teplizumab treatment to report any of these signs and symptoms of CRS to their healthcare provider.³

3j) 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.

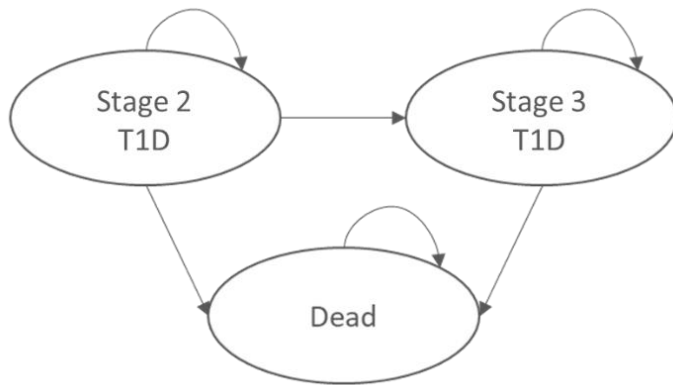
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- 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. How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

A model was developed from the perspective of the NHS in England to assess how treatment with teplizumab may extend life, improve quality of life and reduce the costs of treating Stage 2 T1D compared with no treatment. The model consisted of three health states: (1) Stage 2 T1D (2) Stage 3 T1D, and (3) dead. In the model, individuals could remain in only one health state at any given time and returning to a previous health state was not possible once they have progressed to the next. Figure 2 illustrates the model structure.

Figure 2. Model structure



T1D = type 1 diabetes

The model captured the benefit of treatment with teplizumab compared with no treatment. In line with the clinical study, TN-10, individuals with Stage 2 T1D receiving a treatment course of teplizumab were expected to stay in Stage 2 T1D (without progressing to Stage 3) for a longer time on average compared with those who received no treatment.⁶⁹

In the model, all individuals began in the Stage 2 T1D health state, in which the risk of death was assumed to be similar to the general population. Individuals could either remain in the Stage 2 T1D health state or progress to the Stage 3 T1D or the dead health states. Once individuals progressed to the Stage 3 T1D health state, they could remain in this health state or progress to the dead health state. The mortality rate in the Stage 3 T1D health state was higher than that of the general population, capturing the greater risk of death associated with Stage 3 T1D.³⁷

Uncertainty

There are several uncertainties around the nature of Stage 2 T1D that were identified as limitations of the model, including:

- The number of people who have the condition in the UK is not well understood.
- There are not enough data available to demonstrate how much longer individuals will live if the onset of Stage 3 T1D is delayed.
- The rates of progression to Stage 3 T1D used in the model come from the TN-10 trial population of individuals with relatives with Stage 3 T1D, rather than the general population. However, clinical experts do not expect this to have an effect on how well teplizumab works.¹⁷

Additional factors

Teplizumab offers substantial potential benefits to people living with T1D, their caregivers and society that are unlikely to be captured in the model results, including increased time for people with Stage 2 T1D to prepare for the onset and management of symptomatic Stage 3 T1D, prolonged benefits associated with the body continuing to make its own C-peptide, value of improving long-term outcomes in people with lower socioeconomic status (SES) and positive impacts on education and employment.

3k) 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)

Teplizumab will be the first and only disease-modifying immunotherapy to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D in the UK, offering a major step change in the management of individuals with T1D. Through its effects on preserving C-peptide levels, teplizumab may prolong the benefits associated with the release of C-peptide into the blood in reducing the burden of Stage 3 T1D⁶⁹, including the potential for better control of blood sugar levels⁷⁷⁻⁸⁰ and lower rates of longer-term complications.^{78,81,82}

It is expected that delaying the onset of Stage 3 T1D and extending the time spent in Stage 2 will provide more time to understand the diagnosis, prepare and more thoroughly learn how to manage Stage 3 T1D, which ultimately may lead to improved outcomes and correct use of insulin.¹⁷ Having more time to better prepare for diabetes management could also potentially minimise disruptions to school and employment due to poor blood sugar level control and complications.

3l) 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

Socioeconomic status

Among people with Stage 3 T1D, low socioeconomic (SES) is frequently associated with poorer outcomes in terms of acute and long-term complications (including DKA in some studies) and death.⁸³ People with Stage 3 T1D and lower SES tend to have worse blood sugar level control,⁸⁴ lower participation in structured diabetes education⁸⁵ and reduced attendance at specialist diabetes services than people with higher SES.⁸⁶ In an interview study, individuals with Stage 3 T1D and low SES in the UK highlighted that work commitments are a common barrier to attending specialist services and structured education, both of which are associated with improved outcomes in Stage 3 T1D.⁸⁶

Ethnicity

The National Paediatric Diabetes Audit found that the use of real-time CGM and insulin pumps was higher in White children and young people with Stage 3 T1D in England and Wales in 2022-2023 compared with children and young people of Black, Asian or other ethnicities.⁸⁷ A large US study also found that non-Hispanic Black individuals with Stage 3 T1D have higher HbA1c levels (average blood sugar levels over the past 2 to 3 months) and higher incidence of acute complications, including severe hypoglycaemia and DKA, compared with non-Hispanic White and Hispanic individuals and those of other ethnicities.⁸⁸ Insulin pumps and CGM were used most often by non-Hispanic White individuals and least often by non-Hispanic Black individuals compared with the other groups.⁸⁸

Teenagers and young adults

UK clinical expert advice indicated that teenagers and young adults are at risk of more severe Stage 3 T1D likely due to poor blood sugar level control and a lack of interest in using technology for disease management among individuals aged 19 to 25 years.¹⁷

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 the teplizumab TN-10 trial:

- TN-10 (Herold 2019 publication) - An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. Available at:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776880/pdf/nihms-1052607.pdf>

- TN-10 (ClinicalTrials.gov website) – Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk" Available at: <https://clinicaltrials.gov/study/NCT01030861>
- TN-10 extended follow-up (Sims 2021 publication) - Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8610022/pdf/nihms-1752540.pdf>

Further information on T1D:

- Breakthrough T1D. Available at: <https://breakthrought1d.org.uk/knowledge-support/about-type-1-diabetes/>
- Diabetes UK. Available at: <https://www.diabetes.org.uk/>
- NHS UK. Available at: <https://www.nhs.uk/conditions/diabetes/>
- International consensus guidelines. Available at: [Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes](#)

Further information on NICE and the role of patients:

- Public Involvement at NICE. Available at: [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs. Available at: [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](#)
- EFPIA – Working together with patient groups. Available at: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- The International Network of Agencies for Health Technology Assessment. Health technology assessment - What is Health Technology Assessment (HTA)? Available at: [The International Network of Agencies for Health Technology Assessment \(inahta.org\)](#)

4b) Glossary of terms

AEs/adverse events: an unexpected medical problem that arises during treatment with a drug or other therapy, also known as side effects. Adverse events may be mild, moderate, or severe.

Beta-cells: cells in the pancreas of the body that produce insulin.

Blood glucose: blood sugar.

C-peptide: a molecule that is released at the same time as insulin that generally stays in the blood longer than insulin. Therefore, this is a useful marker of T1D.

Cytokine release syndrome/CRS: serious side effect with signs and symptoms that include fever, nausea, feeling tired, headache, muscle and joint pain, or increased liver enzymes in your blood.

Diabetes-related autoantibodies: antibodies produced by the immune system that attack insulin-producing beta-cells in the body.

Diabetic ketoacidosis/DKA: when there is severe lack of insulin in the body which means the body cannot use sugar for energy and starts to use fat instead. When this happens, chemicals called ketones are released and if left unchecked, ketones can build up and make your blood become acidic (i.e., acidosis).

Dysglycaemia: blood sugar levels that are outside the normal range; these can either be too high (hyperglycaemia) or too low (hypoglycaemia).

Exogenous: coming from outside your body (e.g., insulin that is prescribed as a medicine and administered is exogenous).

Grade 2 adverse event: moderate side effect.

Grade 3 adverse event: severe or medically significant side effect, but not immediately life-threatening.

Hyperglycaemia: high blood sugar levels (relative to normal range).

Hypoglycaemia: low blood sugar levels (relative to normal range).

Insulin: hormone produced by beta-cells in the pancreas which helps to take up sugar from the blood.

Leukopenia: a low white blood cell count that can weaken your immune system and increase the risk of infections.

Lymphocytes: a type of white blood cell which helps to regulate the immune system.

Lymphopenia: an abnormally low level of lymphocytes in the blood which can increase the risk of infections.

Normoglycaemia: blood sugar levels that are in the normal range.

Quality of life: well-being or the overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living.

Randomised controlled trial: a clinical trial where factors are controlled to compare the effects of a drug or other therapy.

Stage 2 T1D: the presence of two or more diabetes-related autoantibodies in the blood and abnormal blood sugar levels, however, there are no noticeable symptoms. Insulin injections are not required yet.

Stage 3 T1D: the presence of two or more diabetes-related autoantibodies and appearance of noticeable symptoms of T1D as the body can no longer make enough insulin; therefore, blood sugar levels are too high.

T cells: cells produced by the immune system that specifically attack and damage healthy insulin-producing beta-cells.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Diabetes UK. Type 1 Diabetes Symptoms. Accessed June, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1/symptoms>
2. Libman I, Haynes A, Lyons S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1160-1174. doi:10.1111/pedi.13454
3. Sanofi. Tzield® (teplizumab-mzwv). Accessed 11 September, 2024. <https://www.tzield.com/type-1-diabetes-resources>
4. Sanofi. TZIELD Works Differently. Accessed 2024, 11 September. <https://www.tzield.com/about-tzield/how-tzield-works>
5. Besser REJ, Bell KJ, Couper JJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1175-1187. doi:10.1111/pedi.13410
6. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care*. Jan 1 2023;46(Suppl 1):S19-s40. doi:10.2337/dc23-S002
7. Juvenile Diabetes Research Foundation (JDRF). Type 1 diabetes and complications. Accessed 4 December 2023. <https://jdrf.org.uk/knowledge-support/guide-to-type-1-complications/>
8. Diabetes UK. Complications of diabetes. Accessed December 2023, <https://www.diabetes.org.uk/guide-to-diabetes/complications>
9. NHS. Type 1 diabetes - Avoiding complications. Updated 9 August 2021. <https://www.nhs.uk/conditions/type-1-diabetes/living-with-type-1-diabetes/avoiding-complications/>
10. Sanofi. What is Type 1 Diabetes. Accessed 11 September, 2024. <https://www.tzield.com/about-type-1-diabetes>
11. Insel RA, Dunne JL, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974. doi:10.2337/dc15-1419
12. van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev*. Jan 2011;91(1):79-118. doi:10.1152/physrev.00003.2010
13. Jacobsen LM, Haller MJ, Schatz DA. Understanding Pre-Type 1 Diabetes: The Key to Prevention. *Front Endocrinol (Lausanne)*. 2018;9:70. doi:10.3389/fendo.2018.00070
14. American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2022;45(S1):S17-S38.
15. McCall AL, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinol*. Jun 2013;38(2):145-63.
16. Diabetes UK. Type 1 Diabetes Screening. Accessed June, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1/type-1-diabetes-screening>
17. Sanofi (Data on File). *UK Advisory Board for teplizumab in Stage 2 aT1D Final report (MAT-XU-2401585)*. 2024. 3 July, 2024.
18. NHS Digital. *National Diabetes Audit 2021-22, Report 1: Care Processes and Treatment Targets, Detailed Analysis Report*. 2023. 12 October. <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2021-22-full-report>
19. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. *JAMA*. Jan 28 2020;323(4):339-351. doi:10.1001/jama.2019.21565
20. Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish

- population-based study using EQ-5D. *BMC Public Health*. Apr 22 2013;13:377. doi:10.1186/1471-2458-13-377
21. Rechenberg K, Koerner Ms R. General Anxiety, Diabetes-Specific Anxiety, and Quality of Life in Adolescents With Type 1 Diabetes. *Sci Diabetes Self Manag Care*. Dec 2022;48(6):469-475. doi:10.1177/26350106221125689
 22. Diabetes UK. Diabetes And Your Emotions. Accessed September, 2024. <https://www.diabetes.org.uk/guide-to-diabetes/emotions>
 23. López-Bastida J, López-Siguero JP, Oliva-Moreno J, et al. Health-related quality of life in type 1 diabetes mellitus pediatric patients and their caregivers in Spain: an observational cross-sectional study. *Curr Med Res Opin*. Sep 2019;35(9):1589-1595. doi:10.1080/03007995.2019.1605158
 24. Lafontaine S, Mok E, Frei J, et al. Associations of Diabetes-related and Health-related Quality of Life With Glycemic Levels in Adolescents With Type 1 Diabetes Preparing to Transition to Adult Care. *Can J Diabetes*. Aug 2023;47(6):525-531. doi:10.1016/j.jcjd.2023.05.002
 25. Liu S, Ludvigsson JF, Lichtenstein P, et al. Educational Outcomes in Children and Adolescents With Type 1 Diabetes and Psychiatric Disorders. *JAMA Netw Open*. Apr 3 2023;6(4):e238135. doi:10.1001/jamanetworkopen.2023.8135
 26. Willmot EG, Close KL, Jurišić-Eržen D, et al. Patient-reported outcomes in adults with type 1 diabetes in global real-world clinical practice: The SAGE study. *Diabetes Obes Metab*. Aug 2021;23(8):1892-1901. doi:10.1111/dom.14416
 27. Molvaer AK, Iversen MM, Igland J, et al. Metabolic predictors of pain, fatigue, depression and quality of life in people with long-term type 1 diabetes-the Dialong study. *Diabet Med*. Mar 2023;40(3):e15009. doi:10.1111/dme.15009
 28. Fischer KI, Fischer FH, Barthel D, et al. Trajectories of Health-Related Quality of Life and HbA1c Values of Children and Adolescents With Diabetes Mellitus Type 1 Over 6 Months: A Longitudinal Observational Study. *Front Pediatr*. 2019;7:566. doi:10.3389/fped.2019.00566
 29. Jacobson AM, Braffett BH, Cleary PA, Gubitosi-Klug RA, Larkin ME. The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications cohort. *Diabetes Care*. Oct 2013;36(10):3131-8. doi:10.2337/dc12-2109
 30. Glocker V, Bachmann S, Hess M, Szinnai G, Burckhardt MA. Fear of hypoglycemia and quality of life in young people with type 1 diabetes and their parents in the era of sensor glucose monitoring. *Front Endocrinol (Lausanne)*. 2022;13:958671. doi:10.3389/fendo.2022.958671
 31. Rossi MC, Nicolucci A, Ozzello A, et al. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. *Nutr Metab Cardiovasc Dis*. Jul 2019;29(7):736-743. doi:10.1016/j.numecd.2019.04.009
 32. Coolen M, Aalders J, Broadley M, et al. Hypoglycaemia and diabetes-specific quality of life in adolescents with type 1 diabetes. *Diabet Med*. Aug 2021;38(8):e14565. doi:10.1111/dme.14565
 33. Beverly EA, Rennie RG, Guseman EH, Rodgers A, Healy AM. High Prevalence of Diabetes Distress in a University Population. *J Am Osteopath Assoc*. Sep 1 2019;119(9):556-568. doi:10.7556/jaoa.2019.099
 34. Svedbo Engström M, Leksell J, Johansson UB, Gudbjörnsdóttir S. What is important for you? A qualitative interview study of living with diabetes and experiences of diabetes care to establish a basis for a tailored Patient-Reported Outcome Measure for the Swedish National Diabetes Register. *BMJ Open*. Mar 24 2016;6(3):e010249. doi:10.1136/bmjopen-2015-010249
 35. Carlsund Å, Söderberg S. Living with type 1 diabetes as experienced by young adults. *Nurs Open*. Apr 2019;6(2):418-425. doi:10.1002/nop2.222
 36. Whitemore R, Jaser S, Chao A, Jang M, Grey M. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ*. Jul-Aug 2012;38(4):562-79. doi:10.1177/0145721712445216
 37. NHS Digital. National Diabetes Audit Complications and Mortality Dashboard (Core Report 2 - Outcomes Dashboard). Accessed 22 May, 2024. <https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit/dashboards>
 38. Lawrence JM, Reynolds K, Saydah SH, et al. Demographic Correlates of Short-Term Mortality Among Youth and Young Adults With Youth-Onset Diabetes Diagnosed From 2002 to 2015: The SEARCH for Diabetes in Youth Study. *Diabetes Care*. Dec 2021;44(12):2691-2698. doi:10.2337/dc21-0728
 39. Samuelsson J, Samuelsson U, Hanberger L, Bladh M, Åkesson K. Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age-A population-based cohort study. *Pediatr Diabetes*. May 2020;21(3):479-485. doi:10.1111/pedi.12980
 40. Diabetes UK. What is DKA (Diabetic Ketoacidosis)? Accessed September, 2024. https://www.diabetes.org.uk/guide-to-diabetes/complications/diabetic_ketoacidosis
 41. Rawshani A, Rawshani A, Franzén S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *N Engl J Med*. Apr 13 2017;376(15):1407-1418. doi:10.1056/NEJMoa1608664
 42. Tran-Duy A, Knight J, Clarke PM, Svensson AM, Eliasson B, Palmer AJ. Development of a life expectancy table for individuals with type 1 diabetes. *Diabetologia*. Oct 2021;64(10):2228-2236. doi:10.1007/s00125-021-05503-6
 43. Eliasson B, Lyngfelt L, Strömblad SO, Franzén S, Eeg-Olofsson K. The significance of chronic kidney disease, heart failure and cardiovascular disease for mortality in type 1 diabetes: nationwide observational study. *Sci Rep*. Oct 26 2022;12(1):17950. doi:10.1038/s41598-022-22932-4

44. Bjerg L, Gudbjörnsdóttir S, Franzén S, et al. Duration of diabetes-related complications and mortality in type 1 diabetes: a national cohort study. *Int J Epidemiol*. Aug 30 2021;50(4):1250-1259. doi:10.1093/ije/dyaa290
45. NHS Digital. *National Diabetes Audit, 2017-18 Report 2a: Complications and Mortality (complications of diabetes), England and Wales*. 2019.
46. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. Aug 11 2018;392(10146):477-486. doi:10.1016/s0140-6736(18)31506-x
47. Samuelsson J, Bertilsson R, Bülow E, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. *Diabetologia*. Apr 2024;67(4):679-689. doi:10.1007/s00125-024-06086-8
48. Diabetes UK. Getting Tested for Diabetes. Accessed September, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/test-for-diabetes>
49. Besser REJ, Ng SM, Gregory JW, Dayan CM, Randell T, Barrett T. General population screening for childhood type 1 diabetes: is it time for a UK strategy? *Arch Dis Child*. Sep 2022;107(9):790-795. doi:10.1136/archdischild-2021-321864
50. INNODIA.org. INNODIA. Accessed August, 2024. <https://www.innodia.eu/>
51. Phillip M, Achenbach P, Addala A, et al. Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes. *Diabetes Care*. Jun 24 2024;doi:10.2337/dci24-0042
52. Sanofi (Data on File). *Sanofi Pre-symptomatic Type 1 Diabetes Care Pathway July 2024 Advisory Board Meeting Report v1.0 (MAT-XU-2402985)*. 2024. 19 July.
53. National Institute for Health and Care Excellence (NICE). Type 1 diabetes. Updated 2023. Accessed November 6, 2023. <https://bnfc.nice.org.uk/treatment-summaries/type-1-diabetes/>
54. Holt RIG, DeVries JH, Hess-Fischl A, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Nov 2021;44(11):2589-2625. doi:10.2337/dci21-0043
55. de Bock M, Codner E, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. *Pediatr Diabetes*. Dec 2022;23(8):1270-1276. doi:10.1111/pedi.13455
56. Diabetes UK. Type 1 Diabetes Treatments. Accessed September, 2024. <https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1/treatments>
57. NHS England. *Hybrid closed loop technologies: 5-year implementation strategy*. 2024. [https://www.england.nhs.uk/long-read/hybrid-closed-loop-technologies-5-year-implementation-strategy/#:~:text=Ng%2C%20et%20a%20\(2022\),over%20a%205%2Dyear%20period](https://www.england.nhs.uk/long-read/hybrid-closed-loop-technologies-5-year-implementation-strategy/#:~:text=Ng%2C%20et%20a%20(2022),over%20a%205%2Dyear%20period)
58. Nagy G, Szekely TE, Somogyi A, Herold M, Herold Z. New therapeutic approaches for type 1 diabetes: Disease-modifying therapies. *World J Diabetes*. Oct 15 2022;13(10):835-850. doi:10.4239/wjd.v13.i10.835
59. NHS Digital. *National Diabetes Inpatient Audit (NaDIA) 2016*. 2017. 8 March. <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-inpatient-audit/national-diabetes-inpatient-audit-nadia-2016>
60. Hou M, Amed S, Goldman RD. Insulin pump complications among children with diabetes. *Can Fam Physician*. Dec 2022;68(12):893-895. doi:10.46747/cfp.6812893
61. Lawton J, Blackburn M, Allen J, et al. Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocr Disord*. Feb 20 2018;18(1):12. doi:10.1186/s12902-018-0239-1
62. Commissariat PV, Boyle CT, Miller KM, et al. Insulin Pump Use in Young Children with Type 1 Diabetes: Sociodemographic Factors and Parent-Reported Barriers. *Diabetes Technol Ther*. Jun 2017;19(6):363-369. doi:10.1089/dia.2016.0375
63. Juvenile Diabetes Research Foundation (JDRF). *Barriers and drivers to technology*. 2019. November 2019.
64. US Food & Drug Administration (FDA). FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes. Updated November 17. Accessed November 3, 2023. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-can-delay-onset-type-1-diabetes>
65. Sanofi (Data on File). *TZIELD 2024 אישור עקרוני*.
66. Sanofi (Data on File). *Sanofi (Data on File) 2024 TZIELD-TeudatRishum-37817_07.24*. 2024.
67. Sanofi (Data on File). *Draft Summary of Product Characteristics (Tzield)*. 2024.
68. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. Aug 15 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
69. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med*. Mar 3 2021;13(583):doi:10.1126/scitranslmed.abc8980
70. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β -Cell Function in Newly Diagnosed Type 1 Diabetes. *N Engl J Med*. Oct 18 2023;doi:10.1056/NEJMoa2308743
71. Lloyd A, Swinburn P, Boye KS, et al. A valuation of infusion therapy to preserve islet function in type 1 diabetes. *Value Health*. Aug 2010;13(5):636-42. doi:10.1111/j.1524-4733.2010.00705.x
72. DiSantostefano RL, Sutphin J, Hedrick JA, Klein K, Mansfield C. Parent Preferences for Delaying Insulin Dependence in Children at Risk of Stage III Type 1 Diabetes. *Diabetes Technol Ther*. Aug 2020;22(8):584-593. doi:10.1089/dia.2019.0444

73. Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β -Cell Function. *Diabetes Care*. 2023;46(10):1848-1856. doi:10.2337/dc23-0675
74. Provention Bio Inc. (Data on File). *TN-10 Clinical Study Report Addendum: Anti-CD3 MAP (Teplizumab) for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus. Final Version 1.0*. 2020. September 3.
75. Sanofi. Tzield is Changing the way Autoimmune Type 1 Diabetes is Treated. Accessed 11 September, 2024. <https://www.tzield.com/about-tzield/why-tzield>
76. Sanofi. *TZIELD® US Prescribing Information*. 2023. December.
77. Rickels MR, Evans-Molina C, Bahnson HT, et al. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. *J Clin Invest*. Apr 1 2020;130(4):1850-1862. doi:10.1172/jci134057
78. Harsunen M, Haukka J, Harjutsalo V, et al. Residual insulin secretion in individuals with type 1 diabetes in Finland: longitudinal and cross-sectional analyses. *Lancet Diabetes Endocrinol*. Jul 2023;11(7):465-473. doi:10.1016/s2213-8587(23)00123-7
79. Kurpiewska E, Cieżki S, Jamiolkowska-Sztabkowska M, et al. Excessive BMI is associated with higher C-peptide level at recognition but also with its greater loss in two years clinical observation in children with new onset type 1 diabetes. *Front Immunol*. 2023;14:1176403. doi:10.3389/fimmu.2023.1176403
80. Gubitosi-Klug RA, Braffett BH, Hitt S, et al. Residual β cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. *J Clin Invest*. Feb 1 2021;131(3)doi:10.1172/jci143011
81. Fuhri Snethlage CM, McDonald TJ, Oram RD, et al. Residual β -Cell Function Is Associated With Longer Time in Range in Individuals With Type 1 Diabetes. *Diabetes Care*. Aug 3 2023;doi:10.2337/dc23-0776
82. Jeyam A, Colhoun H, McGurnaghan S, et al. Clinical Impact of Residual C-Peptide Secretion in Type 1 Diabetes on Glycemia and Microvascular Complications. *Diabetes Care*. Feb 2021;44(2):390-398. doi:10.2337/dc20-0567
83. Scott A, Chambers D, Goyder E, O'Cathain A. Socioeconomic inequalities in mortality, morbidity and diabetes management for adults with type 1 diabetes: A systematic review. *PLoS One*. 2017;12(5):e0177210. doi:10.1371/journal.pone.0177210
84. Apperley LJ, Ng SM. Socioeconomic Deprivation, Household Education, and Employment are Associated With Increased Hospital Admissions and Poor Glycemic Control in Children With Type 1 Diabetes Mellitus. *Rev Diabet Stud*. Summer-Fall 2017;14(2-3):295-300. doi:10.1900/rds.2017.14.295
85. Fallon C, Jones E, Oliver N, Reddy M, Avari P. The impact of socio-economic deprivation on access to diabetes technology in adults with type 1 diabetes. *Diabet Med*. Oct 2022;39(10):e14906. doi:10.1111/dme.14906
86. Scott A, O'Cathain A, Goyder E. Socioeconomic disparities in access to intensive insulin regimens for adults with type 1 diabetes: a qualitative study of patient and healthcare professional perspectives. *Int J Equity Health*. Oct 11 2019;18(1):150. doi:10.1186/s12939-019-1061-8
87. Royal College of Paediatrics and Child Health (RCPCH). *National Paediatric Diabetes Audit (NPDA) Report on Care and Outcomes 2022/23*. 2024. April 2024.
88. Majidi S, Ebekozi O, Noor N, et al. Inequities in Health Outcomes in Children and Adults With Type 1 Diabetes: Data From the T1D Exchange Quality Improvement Collaborative. *Clin Diabetes*. Jul 2021;39(3):278-283. doi:10.2337/cd21-0028

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Clarification questions response

January 2025

File name	Version	Contains confidential information	Date
ID6259 teplizumab EAG clarification response_17Jan2025 [noCON]	1.0	No	17 January 2025

Section A: Clarification on effectiveness data

Literature searches

A 1. For all searches in all sections (appendices D, G, H & I)

- a) Please can you confirm the date range for the Embase search in all sections.
- b) please confirm whether the MEDLINE/MEDLINE In-Process search also covered the Daily Updates and Epub ahead of print segments of MEDLINE?
- c) In Appendices D and G, both the Embase and MEDLINE searches contain a limit which includes the terms:
“(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.”
(for example, see line #80 in the Embase search in Appendix D, Table 1).
Please explain the rationale behind this limit, particularly the decision to remove the terms male and female and what affect this may have had on the recall of results.
- d) the numbers presented in the top box for each of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts (App D, Fig 1/ App G, Fig 3/ App H, Fig 4), do not appear to match the numbers provided in the search strategy tables. Please clarify and provide amended PRISMA flow charts
- e) Appendices D, G and H all report additional grey literature searches, including the handsearching of conference proceedings, HTA & regulatory websites and clinical trials registries (for example see App D, Table 5). Please provide full details of these searches for all sections, including keywords used and hits per resource.

[Thank you; please see responses below for each sub-question.](#)

- [a\) The clinical searches had no date limit for full-text articles, while the search extended back to 2013 for the economic and humanistic workstreams. However, given the](#)

volume of literature and the desire to keep the information relevant, the inclusion criteria were refined to limit the economic and humanistic literature to the last five years (2019 to 2024). Searches were run for all three sets on May 2, 2023 and updated on June 27, 2024.

- b) Yes, these have been included.
- c) These limits were included to remove papers where the singular use of these words only appeared in the title, with the goal of reducing the number of case studies brought in. We would expect that articles that met other criteria for capture would not have been eliminated.
- d) Thank you; we have confirmed that the PRISMA totals are accurate and included the appropriate information. We have updated the search yields; the searches were originally run on February 13, 2023 and again on May 2, 2023 with an update on June 27, 2024. The May 2023 results (with the June 2024 update) were those that informed the research, and are properly reflected in the totals in the PRISMA diagrams. Those associated yields are now provided in amended tables in Appendix 1, shared as a separate document along with this response.
- e) Grey literature searches were conducted together. Please see Table 1 for the results of each search.

Table 1. Grey literature searches and results

Resource	Search Terms	Results*
Website		
Canadian Agency for Drugs and Technologies in Health (CADTH) (https://www.cadth.ca/)	"Diabetes" "Type 1 Diabetes" and "Diabetes Mellitus" and "Type 1 diabetes mellitus"	274
US Food and Drug Administration (FDA) (https://www.fda.gov/)		357
National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/)		13
Scottish Medicines Consortium (SMC) (https://www.scottishmedicines.org.uk/)		126
Institute for Quality and Efficiency in Health Care (IQWiG) (https://www.iqwig.de/en/)		26
Clinical trial registry		
Clinicaltrials.gov (https://clinicaltrials.gov/)	"Diabetes" "Type 1 Diabetes" and "Diabetes Mellitus" and "Type 1 diabetes mellitus"	307
WHO International Clinical Trials Registry Platform (ICTR) (https://www.who.int/clinical-trials-registry-platform)		277
Conference Proceedings (not indexed in Embase)**		
Diabetes Canada/Canadian Society of Endocrinology and Metabolism 2022	"Type 1 Diabetes," "Risk"	54
European Foundation for the Study of Diabetes 2021 and 2022	"Type 1 Diabetes," "Risk," "Risk of type"	2930

Resource	Search Terms	Results*
American Diabetes Association 2024 Meeting	"Type 1 diabetes," "risk of type," "stage 1," "stage 2"	444
Advanced Technologies and Treatments for Diabetes Conference 2024	"Type 1 diabetes," "stage 1," "stage 2"	767

*Represents the total across search terms and updates and may include a small overlap leading to duplicate citations in yields

**Searches were adapted between conferences as necessary to adjust for the respective platforms and searchability functions of the conference proceedings

Clinical effectiveness searches

A 2. With regard to the Cochrane Central Register of Controlled Trials (CENTRAL) search (table 3), the lines limiting the conference searches to those published since 2021 appear to contain an error which results in the date limit being applied to the journal instead. Whilst this is rectified by a later line (#?) the conference proceedings appear to have been missed. Please can you confirm if this is the case and rerun the search to check that no relevant papers were missed.

Thank you; conference proceedings were captured for the conferences that were of pre-determined interest via their listing in Embase, or via hand-searching. As such, conference proceedings were not required from CENTRAL.

Adverse events searches

A 3. Please confirm whether any additional searches, other than those reported in Appendix D section D.1.2 were conducted to retrieve information regarding adverse events (AEs) for teplizumab and, if so, provide full details including date, resource names and search strategies used.

No additional AE-specific searches were conducted to support the systematic literature reviews (SLRs) beyond the larger searches reported.

Health-Related Quality of Life searches

A 4. The searches reported in Appendix G appear to contain a utilities facet. Please can you confirm if the results from this search were used to inform the sections on health-related quality of life (HRQoL), as well as the humanistic burden strategy reported in Appendix H. Both Document B and Appendix H section H.1 state that the original searches to identify papers on the humanistic burden of

type 1 diabetes (T1D) were undertaken on 2nd May 2023 and updated on 27th June 2024. However, the searches reported in Section H3, Tables 19 & 20 state that the original searches were conducted on 13 Feb 2023. Please clarify.

Any literature that was identified was considered when it was relevant for any of the other SLR workstreams. Therefore, any articles on utilities that were identified through the economic search strategies would have fed into the humanistic SLR as being brought in via an outside source.

With respect to the dates, we had originally run the searches on 13 February 2023 and then run them again in May 2023, updating the overall set of searches in June 2024. The searches used to support this work were those from May 2023 and the update in June 2024, and we have confirmed that they are now represented properly throughout the revised tables.

Costs searches

A 5. The External Assessment Group (EAG) noticed that the Costs/Resource use facet in the searches in appendix G (see lines 46-60, Table 9 Embase search) contain use of a frequency limit. Given the low number of relevant papers found, please rerun this search without this limit to check that no potential includes have been missed (given the likely high number of results a shorter date limit would be acceptable).

The frequency operators are to remove those articles that include words that are economic in nature but that are not used to indicate the focus of the research that was discussed (the assumption being that an article that actually reported or considered economic outcomes would use related words more than once). When the search is rerun without the frequency operators, the volume is 5,156 results from Embase alone; these results are provided as a RIS file following the SLR tables in Appendix 1, shared as a separate document along with this response.

Decision problem

A 6. Priority question: The decision problem specifies the population as ‘People aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia)’. The clinical pathway, illustrated in Figure 2 in the company submission (CS), starts with people already

diagnosed with Stage 2 T1D. However, as indicated in the submission from National Health Service (NHS) England: 'There are no NICE guidelines for identification and management of Stage 1 or Stage 2 T1D' and 'No commissioned targeted or general population screening and monitoring programme to identify individuals with Stage 1, Stage 2, and pre-symptomatic Stage 3 diabetes. Screening programs are only available via research trials.' Given the above, please describe how you anticipate people eligible for treatment would be identified; in particular, please specify:

- a) What criteria would be used to select people to receive screening or have diagnostic tests for Stage 2 T1D?
- b) What test or tests would be used and how would these be operationalised (e.g. please specify tests to be used, decision thresholds and parallel or sequential testing for pancreatic islet autoantibodies and dysglycaemia)?
- c) How would testing or screening for Stage 2 T1D be delivered in the NHS in England (e.g. setting, healthcare professionals, counselling and education)?
- d) How many people do you anticipate would be eligible to receive testing or screening for Stage 2 T1D annually?
- e) What proportion of those in c) would be eligible to receive treatment with teplizumab?
- f) What proportion of the population with Stage 2 T1D (i.e. those eligible for treatment with teplizumab) would be identified by the proposed testing?
- g) Please ensure that the full cost of testing/screening can be included in the cost effectiveness analysis.

Thank you for raising this point, however Sanofi believe the issue of screening for pre-symptomatic T1D, although hugely important, is entirely outside the scope of this appraisal for the following reasons:

- In line with the final scope, the patient population teplizumab is being evaluated in is “People aged 8 and over with stage 2 type 1 diabetes (2 or more pancreatic islet autoantibodies and dysglycaemia)”. These individuals are already confirmed as having Stage 2 disease.
- The NICE Manual clearly states the purpose of the final scope is to “define the issues for consideration (for example, population, comparators, care pathway, and outcome measures) and set the boundaries for the work to be done by the external assessment group, and any evidence submissions for the evaluation”.
- Any consideration of screening would be outside of the boundaries defined by the final scope (individuals who are not confirmed as having Stage 2 T1D based on “2 or more pancreatic islet autoantibodies and dysglycaemia”) and thus out of line with the NICE process.
- It is also not appropriate for Sanofi to pre-empt how a national screening programme would be operationalised and delivered in the NHS. The assessment and recommendation of population screening programmes is a responsibility of the National Screening Committee (NSC) and we believe it falls outside of NICE’s remit.¹
- Despite the absence of a national screening programme, evidence shows that people in England and Wales are being diagnosed with and managed for pre-symptomatic T1D (Stage 1 and Stage 2) both in routine care, as well as in research settings.

Further details are provided below in the context of teplizumab and T1D.

As the EAG note, there are no NICE guidelines for the identification or management of Stage 1 and/or Stage 2 T1D; despite this people with Stage 2 T1D are identified and managed in UK clinical practice. While Sanofi have not seen the full comment from NHS England nor the context in which it was made, we note their comment that ‘screening programmes are only available via research trials’. We would like to be clear that individuals are being identified outside of those screening programme settings in the UK; for example, recent research by the British Society for Paediatric Endocrinology and Diabetes (BSPED) indicates that more children and young people with early-stage T1D are identified in the NHS compared with research platforms (53% [including 47% via secondary care and 6% via primary care] vs. 47%, respectively).² Prof. Colin Dayan MA FRCP PhD, an external clinical

expert^a, highlighted this research when asked about identifying and managing patients in the NHS. Prof. Dayan further stated detection in adults within the NHS is also occurring due to widespread HbA1c testing for pre-type 2 diabetes (T2D) by which further laboratory investigation of dysglycaemic individuals can result in a diagnosis of pre-symptomatic T1D. Furthermore, there are at least two specialised pre-symptomatic T1D clinics in the NHS run out of Oxford³ and Birmingham hospitals.

There is growing interest and management within the clinical community on pre-symptomatic T1D. The clinical community now recognises that individuals with Stage 1 and 2 T1D do already have the disease itself, thus moving away from the view that these individuals are 'at risk of T1D;' indeed in recent International Society for Pediatric and Adolescent Diabetes (ISPAD) guidance 'people with two or more islet autoantibodies have early-stage T1D and should no longer be referred to as being "at risk for T1D"'. As such, there is rising interest, including in the UK, in improving support and management of these individuals when they are identified.^{4,5}

There is increasing clinical understanding that early identification can help prepare people for the management of Stage 3 T1D, avoid diagnosis at an 'acute' crisis by reducing the likelihood of diabetic ketoacidosis (DKA), a life-threatening condition, reduce glycaemic exposure prior to Stage 3 T1D and facilitate glucose control in the years that follow.^{4,5} This is not a movement predicated on the availability of teplizumab or any other treatment in development, but rather on an appreciation and improved understanding of the disease course of T1D. This is what is primarily driving the research on screening and international and national movement to proactive identification and management of pre-symptomatic T1D.

As described in the submission and aligned with the final scope, people over 8 years old are eligible for teplizumab if they have been diagnosed with Stage 2 T1D. This is identified by positive tests for ≥ 2 pancreatic islet autoantibodies and dysglycaemia (i.e., abnormal blood glucose levels, without overt hyperglycaemia).

Questions A6a-g infer the design and inclusion of a screening programme in the assessment. As communicated to Sanofi at multiple stakeholder advisory meetings, a population screening programme for pre-symptomatic T1D would be the premise of the NSC or national policy and guidance. The "NICE-wide topic prioritisation: the manual",⁶ confirms

^a Professor of Clinical Diabetes and Metabolism, Director of the Joint Research Office and Cardiff & Vale Health Board and Cardiff University and Senior Clinical Researcher (Wellcome Centre for Human Genetics, University of Oxford)

the view that the evaluation of screening falls outside of the Technology Appraisal Programme and NICE's remit more broadly.

Sanofi considers that it is inappropriate to include screening in the assessment of teplizumab. The patient population is defined in the final scope as 'Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes'.

This aligns with the patient population Sanofi anticipate will be eligible for treatment with teplizumab within licence, once granted, as set out in Section 4.1 of the draft teplizumab Summary of Product Characteristics (SmPC): '4.1 Therapeutic indications: Tzielid is indicated to delay the onset of Stage 3 type 1 diabetes in adult and paediatric patients 8 years of age and older with Stage 2 type 1 diabetes (T1D)'.

The patient population in the final scope has also been defined in a way that reflects how eligible individuals are currently identified, through UK clinical practice and clinical research programmes. This is consistent with the patient selection criteria in Section 4.2 of the draft SmPC: '4.2 Posology and method of administration, Patient Selection - Select adult and paediatric patients 8 years of age and older for Tzielid treatment who have a diagnosis of Stage 2 type 1 diabetes'.

In line with this, the NICE Diagnostics Assessment Programme (DAP) manual highlights that "assessing population screening programmes and making recommendations on their introduction, modification or withdrawal is undertaken by the UK NSC and is beyond the scope of our Programme. The NICE DAP evaluates screening tests that are applied to patients who are already suspected of having a disease."¹

For this reason, the economic analysis accounts for the cost of confirmatory tests in line with the SmPC prior to administration of teplizumab⁷, the costs of screening have not been included in the assessment of cost-effectiveness

In summary, it would be inappropriate for Sanofi to respond to how early detection of T1D is delivered in the NHS in England, and we respectfully decline to answer these questions at this time.

A 7. Priority question. The NICE scope specifies "Established clinical management (ECM)" with various options listed as examples as comparators and Table 1 in the CS states "As per final scope". Figure 2 in the CS includes such management following diagnosis of Stage 2 T1D.

However, as stated in question A6, there is currently no means to identify eligible patients in the NHS, and therefore it would seem that there is in fact no ECM. Therefore, please confirm the following:

- a) That this means the comparator is no screening and no management. Please also confirm that this means that the cost of Stage 2 T1D in the comparator arm of the economic model (see Table 45, CS) would also be zero for the comparator.**
- b) Whether this further means the intervention is in fact teplizumab plus screening (and what this entails for delivery in the NHS as specified in question A6).**

Sanofi recognise the importance of accurately representing the relevant comparator in our submission. However, as discussed in the response to question A6, screening for T1D does not fall within the scope of this appraisal. As such, a comparison to no screening and no treatment is out of scope both based on the population and comparator defined in the final scope. Thus, the framing of question A7 is fundamentally not applicable here. Inclusion of screening as part of the intervention and comparator would indeed be relevant in the context of an assessment of screening itself, and it may be valuable for the NSC. However, the fundamental premise of the single technology appraisal, and the anticipated product labelling, is that individuals with the disease are eligible for treatment. Building a cost-effectiveness model that includes costs and benefits of identifying those with the disease will also inevitably include costs (and benefits) of those without the disease, and is therefore not appropriate or relevant to evaluation of a product in treating a particular disease.

Question A7 also states that there are “no means to identify eligible patients,” which is not correct. Autoantibody tests are already widely used in the NHS, with established referral labs in place.^{2,8} In diabetes, autoantibody tests are used to identify people with T1D and to differentiate T2D from T1D.⁹ Recent data published by BSPED indicates that more than half of children and young people with early-stage T1D are being identified in the NHS setting.² Prof. Dayan, an external clinical expert, agreed that people are actively being identified and managed in the NHS setting, and referred to the BSPED study above.¹⁰

As defined in the CS, ECM for Stage 2 T1D consists of routine monitoring of blood glucose, psychosocial support and education on the management of T1D.^{9,11} This is aligned with the final scope, as well as current UK clinical management, international guidelines and UK expert opinion.^{9,11,12} While most individuals with T1D are managed by their diabetologist,

there are at least two NHS clinics for the management of pre-symptomatic T1D in England (Birmingham and Oxford) from which insights were gained to support the CS. The use of the term “established” in the CS is to ensure alignment with the final scope; however, we are aware that given the infancy of treatment for Stage 2 T1D, there may be variations between centres, with established practice continuing to evolve. Even in those diseases where there are official management guidelines, there is still variation across centres as to how these are implemented.

A 8. The final scope, issued by NICE, includes time to starting insulin treatment in the list of outcome measures to be considered. Section B.2.12.3 of the CS states that: *‘Individuals treated with teplizumab had a statistically significantly longer median time to onset of Stage 3 T1D of 5.0 years compared to 2.3 years in the placebo arm (2.7-year difference) with an acceptable safety profile, while also preserving the C-peptide response and postponing the need for insulin replacement.’* However, neither of the two publications cited reported time to initiation of insulin replacement. Please confirm that TrialNet [TN]-10 did not measure time to initiation of insulin replacement.

TN-10 did not measure time to initiation of insulin replacement specifically; however, the trial assessed time to onset of Stage 3 T1D as its primary endpoint.¹³ Insulin replacement therapy is not initiated until the onset of Stage 3 T1D.^{14,15} Therefore, by delaying the onset of Stage 3 T1D, as was demonstrated in the TN-10 trial^{16,17}, teplizumab can also be assumed to delay the initiation of insulin replacement.

Systematic review

A 9. Please provide a justification for the decision to exclude conference abstracts presented before 2021.

Sanofi use conference abstracts to supplement our searches and allow for the capture of the most recent research. Our expectation is that relevant meaningful research then goes on to be published in a full text article. A cutoff of conference abstracts from before 2021 therefore allows time for those research results to be published, peer reviewed, and be submitted to the stringent assessments typically conducted by journals. This approach is standard practice for SLRs.

A 10. Please provide a justification to restrict inclusion of studies to those that were published in English.

Inclusion of articles was restricted to English as the focus of the evidence was to support work in a UK population.

A 11. Please describe how many reviewers were involved in quality appraisals of included studies and whether such appraisals were conducted independently and in duplicate. Please also explain how any disagreements between reviewers (if relevant) were resolved?

Quality assessments were conducted by the initial team member during the extraction phase and then validated by a second team member as part of the validation step. Disagreements were resolved by a third reviewer.

Clinical effectiveness evidence

A 12. Priority question: Section B.2.3.1 of the CS states that: ‘Participants in TN-10 were identified through the ongoing TrialNet Natural History/Pathway to Prevention study (TN-01; NCT00097292) that included relatives of people with Stage 3 T1D who were diagnosed with Stage 2 T1D.’ With respect to the recruitment of participants to TN-10, please provide:

- a) A detailed description of how participants in TN-10 were selected from the eligible TN-01 population (participants in TN-01 who were autoantibody positive and who had dysglycaemia on oral glucose tolerance test [OGTT]).**

Participants in TN-10 were identified through the ongoing TrialNet Natural History/Pathway to Prevention study (TN-01; NCT00097292), in which relatives of people with Stage 3 T1D were screened for biochemical autoantibodies and islet cell antibodies.¹⁸ Those individuals who test positive are then further staged with the performance of an OGTT.¹³ The results of this OGTT performed in the TN-01 study were used to determine eligibility for TN-10 (Table 7 in Section B.2.3.3 of the CS).¹³ The TrialNet Natural History/Pathway to Prevention study screens participants at over 200 clinical sites.¹³

- b) The number of participants in TN-01 met the eligibility criteria specified for TN-10 (Table 6 of the CS)?**

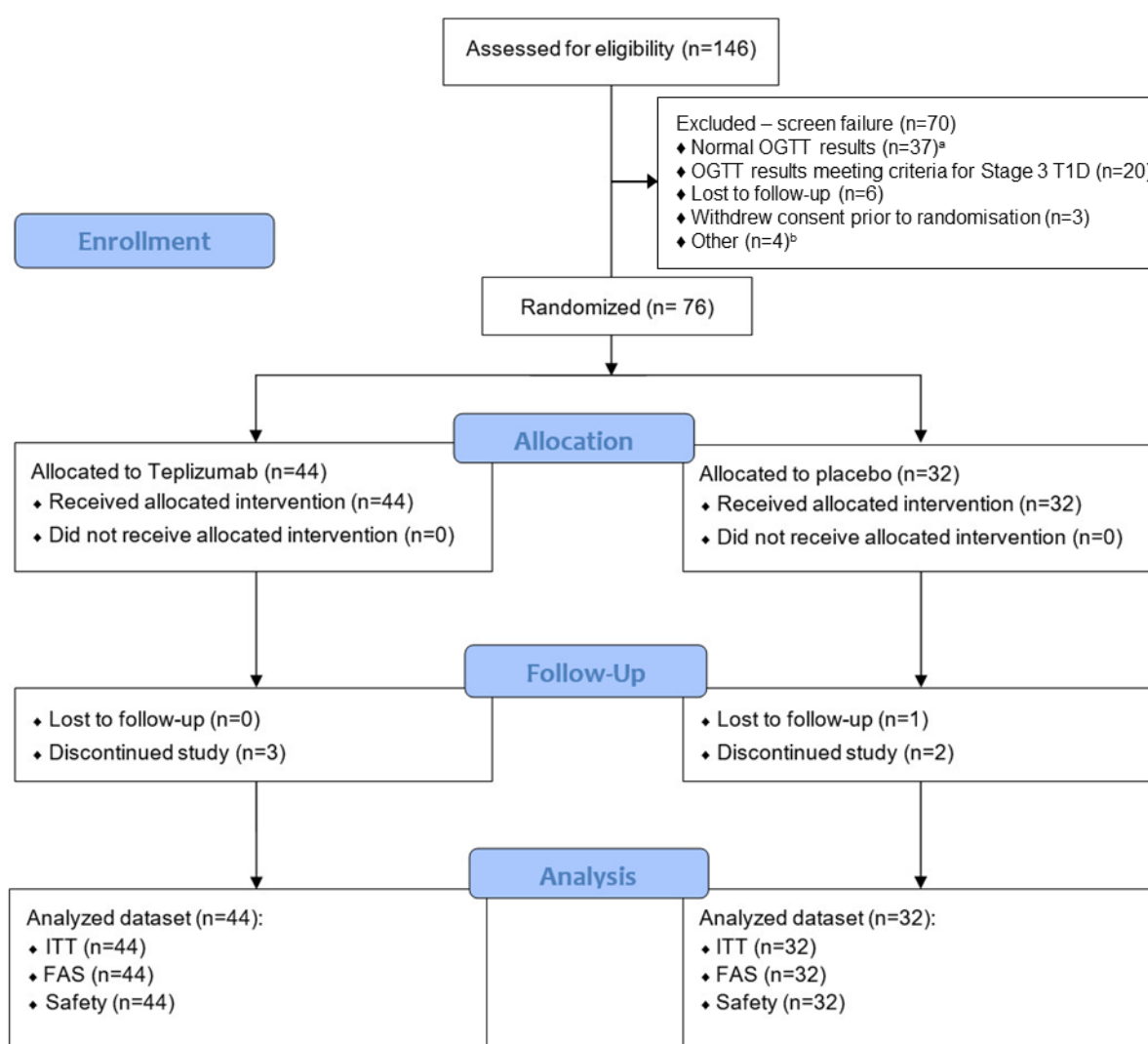
A total of 146 individuals who were identified through the TrialNet Natural History/Pathway to Prevention study and gave informed consent for this study were assessed for eligibility in

TN-10.¹⁶ Seventy participants were screen failures (Figure 1).¹⁶ Thus, 76 subjects met the eligibility criteria for TN-10 and were randomised to receive teplizumab or placebo in this study.¹⁶

c) A CONSORT diagram for TN-10. This diagram should include the steps for selecting participants from the eligible TN-01 population.

A CONSORT diagram for TN-10 is shown in Figure 1, including the 146 individuals who were identified through the TrialNet Natural History/Pathway to Prevention study and assessed for eligibility in TN-10.¹⁶

Figure 1. CONSORT diagram of participant disposition in TN-10



FAS = full analysis set; ITT = intent-to-treat

^a Did not meet criteria for dysglycaemia on OGTT

^b Failed screening secondary to chronic steroid use (n=2), T1D autoantibody count not meeting criteria (n=1) and lymphopenia (n=1)

Sources: Data on File – Provention Bio Inc. 2020 (CSR Addendum);¹⁶ Wood Heickman 2022 (FDA CDER Clinical Review)¹⁹

A 13. The intervention is a single treatment (14-day IV infusion) of teplizumab. The primary clinical efficacy outcome presented is time from randomisation to onset of Stage 3 T1D. Evidence is presented in support of the hypothesis that a single treatment with teplizumab can delay but not prevent the onset of Stage 3 T1D. Please clarify:

a) Is there potential for patients to benefit from further courses of teplizumab?

It is reasonable to assume that some individuals might benefit from further courses of teplizumab to further delay Stage 3 T1D. However, the question of how to determine in which individuals or at what time a re-dosing course is most beneficial to delay the onset of Stage 3 T1D cannot yet be answered definitively. Second courses have been examined in other studies (notably in the Stage 3 T1D population), and these have been applied to all participants at a specific time, 6 months or 12 months after the first course.

Today, Sanofi is considering if there are ways to identify Stage 2 T1D individuals who will specifically benefit from subsequent treatment (re-dosing), but at this time we are not able to propose a biomarker or other criteria for that selection.

b) Are there any ongoing or planned studies of multiple courses of teplizumab?

Whilst there are no studies currently underway, Sanofi is considering several options for studies to assess re-dosing of teplizumab in people with Stage 2 T1D, including in-silico simulations.

c) Are there other reasons why multiple courses of teplizumab have not been considered (e.g. long-term risk profile associated with T-cell suppression)?

As per the answers above, multiple courses have been examined in other studies (e.g., in the Stage 3 T1D population) and Sanofi is currently exploring ways to conduct research on re-dosing within the context of a Stage 2 T1D population. Long-term risk is always of crucial importance, but it is not the reason Sanofi have not yet settled on a design to examine re-dosing in Stage 2 T1D. Considerations such as criteria to select individuals who will benefit from treatment, along with the timing of re-dosing, are under review. In addition, practical design aspects of a study that will provide an answer to this question, without having to wait upwards of 10 years to discover the impact of re-dosing, is a pressing consideration.

A 14. With respect to the primary clinical effectiveness outcome (time from randomisation to onset of Stage 3 T1D), summarised in Table 13 of the CS, please provide 95% confidence intervals (CIs) for all median and median

difference values and for all hazard ratios (HRs) (including the extended follow-up analysis).

Table 2 has been updated to include 95% CIs for the medians and median difference values.

Table 2. Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Primary analysis		
Median (95% CI)	49.5 months (32.2, NE)	24.9 months (9.5, 48.6)
Median difference (95% CI)	24.6 months (NE, NE)	
HR (95% CI); p value	0.41 (0.22, 0.78); p=0.0066	
Extended follow-up analysis		
Median (95% CI)	59.6 months ██████████	27.1 months ██████████
Median difference (95% CI)	32.5 months ████████	
HR (95% CI); p value	0.457 (NR); p=0.01	

CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; T1D = type 1 diabetes
 Sources: Data on File – Provention Bio Inc. 2020 (CSR Addendum);¹⁶ Data on File – Provention Bio Inc. 2020 (CSR Tables – Table 2.1.1);²⁰ Sims 2021.¹⁷

A 15. Please provide a copy of the full clinical study report (CSR) for TN-10; tables and figures designated end of text (EOT) have been omitted from the version provided.

These are provided in the reference pack. Please see file names:

- Provention Bio (Data on File) 2020 TN-10 study-report Addendum_CONFIDENTIAL
- Provention Bio (Data on File) 2020 (14-1-figs_SEP2020)_CONFIDENTIAL
- Provention Bio (Data on File) 2020 (14-2-tables_SEP2020)_CONFIDENTIAL

A 16. With respect to the secondary outcome C-peptide response (area under the concentration–time curve [AUC] in 2-hour OGTT), summarised in Table 15 of the CS, please provide:

- a) Confirmation that, as indicated in Table 15, all study participants had a 6-month OGTT that contributed to this analysis

All participants in the teplizumab arm (n=44/44) and all except four participants in the placebo arm (n=28/32) were analysed for C-peptide response at 6 months, as indicated in Figure 4 in Sims et al. 2021.¹⁷ Please note that there is an inconsistency in the publication, as supplementary materials Figure S2, reports OGTT data at 6 months for all participants in the placebo arm (n=32/32).

- b) Confirmation that data from only one OGTT per participant were included in this analysis or details of how results from multiple OGTTs per participant were handled

Since TN-10 was designed as a time-to-event protocol, the variable time in the study for each participant made it a challenge to analyse the metabolic responses from the multiple OGTTs available per participant.¹⁷ Therefore, average on-study C-peptide, glucose and glycosylated haemoglobin (HbA1c) AUCs were used, which included all the available data for each participant.¹⁷

- c) The number of participants, in the teplizumab group and in the placebo group, for whom 24-month C-peptide AUC data were available (all participants, 24-month comparison)

24-month C-peptide AUC data were available for 30/44 participants in the teplizumab arm and 15/32 participants in the placebo arm, as per Figure 11 in the CSR.¹⁶

- d) The number of participants, in the teplizumab group and in the placebo group, for whom 24-month C-peptide AUC data were available and who progressed to Stage 3 T1D during the study (participants who progressed to Stage 3 T1D, 24-month comparison)

24-month C-peptide AUC data were available for 9/44 participants in the teplizumab arm and 8/32 participants in the placebo arm who progressed to Stage 3 T1D during the study, as per Figure 12 in the CSR.¹⁶

- e) Full numerical results, not just *p* values, for all comparisons of slope presented in Table 15

The results of the analysis of covariance (ANCOVA) analysis of C-peptide AUC slope over the first 6 months in TN-10 are presented in Table 3.

Table 3. ANCOVA analysis of C-peptide AUC slope over first 6 months in TN-10

Covariate	Coefficient	Standard Error	t-test	p-value
Intercept	-0.0234	0.00715	-3.27	0.00166
Pre-slope	-0.078	0.0438	-1.78	0.0795
Age	0.000469	0.000284	1.65	0.103
Teplizumab treatment	0.0219	0.00662	3.31	0.00149

ANCOVA = analysis of covariance; AUC = area-under-the-curve

Source: Sims 2021¹⁷

A 17. Please provide the duration of follow-up (median and range) for participants in the teplizumab group and for participants in the placebo group, in the TN-10 trial and in the extended follow-up analysis.

In the primary analysis of the TN-10 trial, the median follow-up time was [REDACTED] days (approximately [REDACTED] months; range: [REDACTED] days) for the teplizumab group and [REDACTED] days (approximately [REDACTED] months; range: [REDACTED] days) for the placebo group, with the follow-up period ending at the time of Stage 3 T1D onset.^{16,20}

In the extended follow-up analysis, the reported median follow-up time for all participants was 923 days (approximately 30.3 months; range: 74 to 3,119).¹⁷ The median follow-up times for each treatment arm are not available for the extended follow-up analysis, and thus Sanofi are unable to provide these data.

A 18. Section B.2.3.2 of the CS states that 'Participants were followed up in the TN-10 trial until at least 40 participants were confirmed to have Stage 3 T1D' and that 'Following this, participants who had not progressed to Stage 3 T1D by the end of the TN-10 trial continued to received follow-up OGTT monitoring.' Please clarify:

- a) Were any participants in TN-10 followed up after they had developed Stage 3 T1D?

No participants in TN-10 were followed up once they had been confirmed as progressed to Stage 3 T1D from Stage 2 T1D.

- b) If these data are available, please provide comparisons (teplizumab group versus placebo group) of C-peptide, insulin secretion and glucose in 2-hour OGTT, and HbA_{1c} levels, after determination of Stage 3 T1D.

No data are available after determination of Stage 3 T1D, since participants left the trial upon onset of Stage 3 T1D.¹⁶

A 19. In its interpretation of the clinical effectiveness evidence (section B.2.12.1.1), the company states that: 'Through its effects on preserving C-peptide levels, teplizumab may prolong the benefits associated with endogenous C-peptide production in reducing the burden of Stage 3 T1D, including the potential for better glycaemic control and lower rates of longer-term complications.' The results of 'an 'integrated efficacy analysis of C-peptide AUC data pooled from

five clinical studies in individuals with Stage 3 T1D' in support of the preservation of C-peptide response in teplizumab-treated individuals with Stage 3 T1D. With respect to the question of reduced burden of disease in Stage 3 T1D, please provide:

- a) Copies of the publications or data sets for each of the five studies included in the integrated analysis (Herold et al, 2023)

Study 1, AbATE, Protégé, Encore and Delay were included in the integrated efficacy analyses. AbATE, Protégé, Encore, Delay and TN-10 were integrated in the pooled safety analysis. All of the publications listed below are provided in the reference pack.

- **Study 1:**
 - Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 2002;346:1692–1698
 - Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes*. Jun 2005;54(6):1763-9
 - **AbATE:** Herold KC, Gitelman SE, Ehlers MR, et al.; AbATE Study Team. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes* 2013;62:3766–3774
 - **Protégé:** Sherry N, Hagopian W, Ludvigsson J, et al.; Protégé Trial Investigators. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet* 2011;378:487–497
 - **Encore:** no publication; some results reported on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00920582) (NCT00920582)
 - **Delay:** Herold KC, Gitelman SE, Willi SM, Gottlieb PA, Waldron-Lynch F, Devine L, Sherr J, Rosenthal SM, Adi S, Jalaludin MY, Michels AW, Dziura J, Bluestone JA. Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. *Diabetologia*. 2013 Feb;56(2):391-400
- b) All outcomes data, from each of these five studies, which are relevant to burden of disease in Stage 3 T1D (e.g. exogenous insulin use, HbA_{1c} levels).

Study 1, AbATE, Protégé, Encore and DELAY were included in the integrated efficacy analyses.²¹ All studies were in new-onset Stage 3 T1D.²¹ In the integrated efficacy analysis, there was significant preservation of C-peptide AUC levels in teplizumab-treated individuals at both 1 and 2 years of follow-up compared with controls ($p < 0.0001$).²¹ In addition, there was significantly lower insulin use in teplizumab-treated individuals at both 1 and 2 years of follow-up compared with controls ($p < 0.0001$ and $p = 0.0001$, respectively).²¹ HbA1c levels were not assessed in the integrated analysis.

Individually, four of the five studies (Study 1, AbATE, Protégé and DELAY)^b included in the integrated efficacy analysis demonstrated preservation of the C-peptide response with teplizumab compared with control, and three of these studies (Study 1, AbATE and DELAY) also demonstrated effects of teplizumab on outcomes relevant to the burden of Stage 3 T1D (HbA1c levels and/or insulin use).²²⁻²⁵

Study 1 was a randomised controlled trial (RCT) that evaluated the efficacy and safety of teplizumab vs. no treatment in 42 individuals with new-onset Stage 3 T1D aged 7.5 to 30 years.²² Over a 2-year period, stimulated C-peptide levels were significantly higher with teplizumab vs. no treatment ($p = 0.002$), with significantly higher mean C-peptide AUC for teplizumab at 12, 18 and 24 months ($p < 0.02$ for all timepoints).²² Teplizumab also led to significant improvement in HbA1c levels ($p = 0.004$) and insulin use ($p = 0.001$) compared with no treatment over the 2-year period.²² HbA1c levels in the teplizumab group remained below 7% from months 6 to 18, and were significantly lower compared with the no treatment group at months 6 and 18 ($p < 0.01$).²² Insulin doses were significantly lower for teplizumab vs. no treatment from months 6 to 24 ($p < 0.05$ for all timepoints).²²

AbATE was a randomised, open-label study that evaluated the efficacy and safety of teplizumab vs. no treatment in individuals with new-onset Stage 3 T1D aged 8 to 30 years.²³ In the intention-to-treat (ITT) population ($n = 77$), over a 2-year period, stimulated C-peptide levels declined significantly slower with teplizumab vs. no treatment ($p = 0.002$), with a 75% higher mean C-peptide AUC for teplizumab vs. no treatment at year 2.²³ The mean percentage change from baseline in stimulated C-peptide levels was significantly lower for teplizumab compared with no treatment ($p < 0.001$ [adjusted for baseline C-peptide AUC]).²³ Although HbA1c levels were not significantly different between teplizumab and no treatment, insulin use was significantly less in the teplizumab group vs. no treatment ($p = 0.036$ over the

^b Encore was terminated prematurely and as such there was a large amount of missing data.

2-year period; $p < 0.001$ for the overall trend at month 12; $p < 0.022$ at month 18 using ANCOVA).²³

DELAY was an RCT that investigated the effects of teplizumab on C-peptide response compared with placebo in 63 individuals with new-onset Stage 3 T1D aged 8 to 30 years.²⁴ At 12 months, the percentage change from baseline in C-peptide levels was significantly lower for teplizumab vs. placebo ($p = 0.04$; adjusted for baseline HbA1c and C-peptide levels), with an 18% higher C-peptide AUC for teplizumab vs. placebo ($p = 0.09$).²⁴ Although HbA1c levels were not significantly different between teplizumab and placebo, insulin use was significantly less in the teplizumab group vs. placebo over the 1-year period ($p = 0.014$).²⁴

Protégé was a randomised study that evaluated the safety and efficacy of teplizumab vs. placebo in 513 individuals with new-onset Stage 3 T1D aged 8 to 35 years.²⁵ Over a 1-year period, median change from baseline in C-peptide AUC declined significantly slower with teplizumab ($n = 207$ who received the 14-day full dose) vs. placebo ($n = 98$; $p < 0.05$), with a preservation or increase from baseline in C-peptide AUC in 40% vs. 28% of participants, respectively.²⁵ Although there was no statistically significant difference between the 14-day full dose teplizumab group and placebo in terms of HbA1c levels or insulin use over the 1-year study period, more participants treated with teplizumab than with placebo discontinued insulin or used very low doses of insulin.²⁵

Encore was a randomised, double-blind study that evaluated teplizumab vs. placebo in 254 individuals with Stage 3 T1D aged 8 to 35 years old.^{21,26} Results for Encore have not been published individually in a peer-reviewed journal; although results are available on the ClinicalTrials.gov website, statistical comparisons among treatment groups are not reported.²⁶ Based on individual study results reported alongside the integrated efficacy analysis in Herold et al. (2023), there was no statistically significant least-squares mean (LSM) difference in change from baseline in C-peptide AUC between teplizumab and placebo in Encore (note that Encore was terminated prematurely and as such there was a large amount of missing data).²¹ Although the LSM difference in change from baseline in insulin use favoured teplizumab over placebo (-0.05 [95% CI: $-0.12, 0.01$] for both observed and imputed data), the difference was not significant as the 95% CI crossed zero on the forest plot.²¹

A 20. Given that no involved participants were from England or Wales; and with question A6 in mind, please justify how these data can be generalised to a relevant clinical population in England and Wales?

As discussed in Section B.2.5.2 of the CS, the effectiveness of teplizumab demonstrated in TN-10 is likely to be generalisable to English and Welsh populations with Stage 2 T1D as these populations are expected to have a similar prognosis in terms of progressing from Stage 2 to Stage 3 T1D as the participants in TN-10. Although the TN-10 trial was restricted to individuals who had a relative with Stage 3 T1D, evidence from observational studies and UK clinical expert opinion suggests that their progression through the T1D continuum would be comparable to European populations that include both relatives and non-relatives of individuals with Stage 3 T1D. Findings from a Germany study of a public health early detection programme (Fr1da) demonstrated that the risk of progression in children with presymptomatic T1D is not significantly associated with having a first-degree relative.²⁷ Additionally, the risk of progression was found to be similar between Fr1da participants and participants treated with placebo in TN-10;²⁸ furthermore, at an advisory board convened by Sanofi in May 2024,²⁹ UK clinicians indicated that they did not expect the mechanism of T1D to be dissimilar for those who do and do not have a relative with Stage 3 T1D. Further supporting this expectation, the recently published 2025 guidance from the American Diabetes Association (ADA) also highlights that findings from a study of cohorts from Germany, Finland, and the US suggest ‘that the same sequence of events led to clinical disease in both “sporadic” and familial cases of T1D.’³⁰ Therefore, people would be expected to have the same outcome with teplizumab, in terms of time to progression, across the two groups.²⁹ In addition, there were no geographical differences in the response to teplizumab among people with new-onset Stage 3 T1D in the PROTECT study in North America and Europe (including UK sites).³¹

A 21. On page 34 of the CS it states ‘TN-10 trial was designed prior to staging nomenclature being widely accepted in clinical practice;³² therefore, these sources use the terms “nondiabetic, high-risk” to describe Stage 2 T1D and “clinical T1D” to describe Stage 3 T1D. This submission uses the Stage 2 and Stage 3 T1D terminology, as it increases clarity of the relevant patient population in relation to this submission, and is aligned with the final NICE scope.’ Please confirm that while the nomenclature is not consistent across

The AESIs were [REDACTED] events of [REDACTED] [REDACTED] for each event); [REDACTED]. [REDACTED], was considered [REDACTED] to the study drug. The other [REDACTED] were considered [REDACTED]. [REDACTED] resolved by the end of the study.¹⁶

In the subject who had [REDACTED], the subject was taken to the emergency department on [REDACTED] and the event was considered [REDACTED] days later ([REDACTED]).¹⁶

In the subject who had [REDACTED], the subject was taken to the [REDACTED], was admitted to [REDACTED], and the event was considered [REDACTED] days later ([REDACTED]).¹⁶

In the subject who had [REDACTED], the subject had presented to an [REDACTED], after which they were transported to [REDACTED].¹⁶ The event was considered [REDACTED].¹⁶

In the subject who had [REDACTED], the subject presented to the [REDACTED].¹⁶ The event was considered [REDACTED] days after the subject presented to the [REDACTED].¹⁶

A 23. For the TN-10 safety population, please provide a breakdown of all treatment-emergent SAEs by preferred term (PT), for the teplizumab group and for the placebo group.

Treatment-emergent SAEs in TN-10 by PT/System Organ Class (SOC) for the teplizumab and placebo groups are listed in Table 4.

Table 4. Treatment-emergent SAEs in TN-10 by PT/SOC

PT/SOC	Severity	Causality	Action	Reason for SAE	Outcome
Teplizumab					
Pneumonia/Infections and Infestations	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dizziness/Nervous system disorders	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Ankle fracture/Injury, poisoning and	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

PT/SOC	Severity	Causality	Action	Reason for SAE	Outcome
procedural complications					
Serum sickness/ Immune disorders	■	■	■	■	■
Musculoskeletal chest pain/ Musculoskeletal and connective tissue disorders	■	■	■	■	■
Cellulitis/ Infections and infestations	■	■	■	■	■
Wound infection/ Infections and infestations	■	■	■	■	■
Gastroenteritis/ Infections and infestations	■	■	■	■	■
Placebo					
Pelvi-ureteric obstruction/ Renal and urinary disorders	■	■	■	■	■

PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class
Source: Data on File – Provention Bio Inc. 2020 (CSR Addendum).¹⁶

A 24. For the TN-10 safety population, please provide a breakdown of all treatment-emergent adverse events (TEAEs) Grade ≥3 by PT, for the teplizumab group and for the placebo group.

Grade 3 TEAEs in TN-10 occurred in ■ participants ■ and 3 participants ■ in the teplizumab and placebo groups, respectively.¹⁶ Grade 4 and 5 TEAEs ■.¹⁶

Grade 3 TEAEs in TN-10 by PT/SOC for the teplizumab and placebo groups are listed in Table 5. ■ participants experienced Grade 3 infections, all of whom were in the teplizumab group; these events included (■), ■ (■), ■ (■) and (■).¹⁶ All of the

■.¹⁶

Table 5. Grade 3 TEAEs in the teplizumab and placebo groups of TN-10 by PT/SOC

Grade 3 TEAEs, n (%)	Teplizumab (n=44)	Placebo (n=32)
≥1 Grade 3 TEAE ^{a,b}		
Blood and lymphatic system disorders		
Lymphopenia		
Leukopenia		
Infections and infestations ^a		
Pneumonia		
Cellulitis		
Gastroenteritis		
Wound infection		
Nervous system disorders		
Peripheral motor neuropathy		
Peripheral sensory neuropathy		
Syncope		
Gastrointestinal disorders		
Oesophageal food impaction		
Injury, poisoning and procedural complications		
Ankle fracture		
Post-traumatic pain		
Tendon rupture		
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain		
Immune system disorders		
Serum sickness		
Renal and urinary disorders		
Nephrolithiasis		
Pelvi-ureteric obstruction		

^aData was missing for one participant in the placebo group.

^b

PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Source: Data on File – Provention Bio Inc. 2020 (CSR Addendum);¹⁶ Data on File – Provention Bio Inc. 2020 (CSR Tables – Table 3.1.8.1);²⁰

A 25. For the integrated safety analysis reported in section B.2.10.1.4 of the CS, please provide:

- a) A breakdown of all TEAEs occurring in >5% of participants, by preferred term, for the teplizumab group and for the placebo group. If possible, please limit inclusion in the teplizumab group to study participants who received the teplizumab regimen used in TN-10 (9034 mcg/m² over 14 days).

The Herold et al. (2023) study reported in section B.2.10.1.4 of the CS included a total of five clinical trials of teplizumab in the integrated safety analysis (AbATE, Protégé, Encore, DELAY and TN-10), the designs of which are summarised in Table 6.²¹

All five trials included in the integrated safety analysis used the same body surface area (BSA)–based dosing schedule of 9,034 mcg/m² over 14 days; however, Protégé and Encore also included subgroups of participants receiving other BSA-based dosing schedules (Table 6).²¹ As the subgroups who received other BSA-based dosing schedules in Protégé and Encore cannot be removed from the integrated analysis, it is not possible to provide safety data from this analysis only for the 435 participants (56%) who received the teplizumab regimen used in TN-10 (9,034 mcg/m² over 14 days).

Table 6. Study design of trials included in the integrated safety analysis conducted by Herold et al. (2023)

	AbATE	Protégé	Encore	DELAY	TN-10
Population	Individuals aged 8 to 30 years with Stage 3 T1D	Individuals aged 8 to 35 years with Stage 3 T1D	Individuals aged 8 to 35 years with Stage 3 T1D	Individuals aged 8 to 30 years with Stage 3 T1D	Individuals aged 8 to 45 years with Stage 2 T1D
Treatment groups	• Teplizumab: 52 • Standard of care: 25	• Teplizumab: 453 • Placebo: 98	• Teplizumab: 192 • Placebo: 62	• Teplizumab: 31 • Placebo: 27	• Teplizumab: 44 • Placebo: 32
Teplizumab dose and dosing schedule, n	9,034 mcg/m ² over 14 days	• 9,034 mcg/m² (full) over 14 days (n=245) • 2,985 mcg/m² (1/3) over 14 days (n=102) • 2,426 mcg/m² (6-day) over 6 days (n=106)	• 9,034 mcg/m² over 14 days (n=63) • 2,985 mcg/m² (1/3) over 14 days (n=66) • 2,426 mcg/m² over 6 days (n=63)	9,034 mcg/m ² over 14 days	9,034 mcg/m ² over 14 days
Teplizumab regimen	2 courses: • Baseline • 12 months	2 courses: • Baseline • 6 months	2 courses: • Baseline • 6 months	1 course: • Baseline	1 course: • Baseline
Follow-up timepoints	• Baseline • Month 6 • Month 12 • Month 18 • Month 24	• Baseline • Day 140 • Month 12 • Month 18 • Month 24	• Baseline • Day 140 • Month 12 • Month 18 • Month 24	• Baseline • Month 6 • Month 12	• Baseline • Month 3 • Month 6 • Every 6 months thereafter

mcg = microgram; T1D = type 1 diabetes

Source: Herold et al. 2023.²¹

In the integrated safety analysis, TEAEs occurring in ≥5% of participants occurred in [REDACTED] individuals ([REDACTED]) and [REDACTED] individuals ([REDACTED]) in the teplizumab and control groups, respectively.

TEAEs in the integrated safety analysis occurring in ≥5% of participants by SOC and PTs are listed in Table 7.

Table 7. TEAEs: Events ≥5% by SOC and PTs (safety population)

SOC ^c PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a			
Blood and lymphatic system disorders (total)			
Lymphopenia			
Leukopenia			
Neutropenia			
Thrombocytopenia			
Anaemia			
Eosinophilia			
Investigations			
Blood bicarbonate decreased			
Haemoglobin decreased			
Aspartate aminotransferase increased			
Alanine aminotransferase increased			
Blood sodium decreased			
Blood alkaline phosphatase increased			
Blood calcium decreased			
Blood potassium increased			
Blood albumin decreased			
Blood bilirubin increased			
Gamma-glutamyltransferase increased			
Blood creatinine increased			
Blood potassium decreased			
Infections and infestations			
Upper respiratory tract infection			
Nasopharyngitis			
Pharyngitis			
Skin and subcutaneous tissue disorders			
Rash			
Pruritus			
Metabolism and nutrition disorders			
Hyponatraemia			
Hypocalcaemia			
Hyperkalaemia			
Hypoalbuminemia			
Hypoglycaemia			
Hypokalaemia			
Hypercalcaemia			
General disorders and administration site conditions			
Pyrexia			
Fatigue			
Chills			
Gastrointestinal disorders			
Nausea			

SOC ^c PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Vomiting			
Diarrhoea			
Abdominal pain			
Abdominal pain upper			
Nervous system disorders			
Headache			
Respiratory, thoracic, and mediastinal disorders			
Oropharyngeal pain			
Cough			
Renal and urinary disorders			
Proteinuria			
Immune system disorders			
Cytokine release syndrome			
Hepatobiliary disorders			
Hyperbilirubinemia			

^a Subjects who had more than one AE or SAE for a treatment were counted once.

^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count.

^c Only SOC with subject count meeting threshold are included.

SOCs and PTs are based on MedDRA version 23.0

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = Systems Organ Class; TEAE = treatment-emergent adverse event.

Source: Data on File

- b) A breakdown of all treatment-emergent SAEs by PT, for the teplizumab group and for the placebo group. If possible, please limit inclusion in the teplizumab group to study participants who received the teplizumab regimen used in TN-10 (9034 mcg/m² over 14 days).

At least one type of treatment-emergent serious adverse event (TESAE) occurred in ■ individuals (■) and ■ individuals (■) in the teplizumab and control groups, respectively.

TESAEs in the integrated safety analysis by SOC and PTs are listed in Table 8.

Table 8. TESAEs: Events by SOC and PTs (safety population)

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a			
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
Hyperglycaemia			
Hypoglycaemia			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Diabetes mellitus inadequate control			
Dehydration			
Diabetic ketosis			
Ketoacidosis			
Ketosis			
Infections and infestations			
Gastroenteritis			
Cellulitis			
Gastroenteritis viral			
Infection			
Pneumonia			
Anal abscess			
Appendicitis			
Arthritis infective			
Bronchitis			
Dengue fever			
Epididymitis			
Gastritis viral			
Hepatic amoebiasis			
Hepatitis A			
Infectious mononucleosis			
Paronychia			
Pharyngotonsillitis			
Pilonidal cyst			
Pulmonary tuberculosis			
Pyelonephritis			
Renal abscess			
Sepsis			
Staphylococcal sepsis			
Tuberculosis			
Urinary tract infection			
Wound infection			
Nervous system disorders			
Hypoglycaemic seizure			
Hypoglycaemia unconsciousness			
Hypoglycaemic coma			
Central nervous system haemorrhage			
Dizziness			
Gastrointestinal disorders			
Gastritis			
Abdominal pain			
Abdominal pain upper			
Diarrhoea			
Intestinal obstruction			
Nausea			
Vomiting			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Immune system disorders			
Cytokine release syndrome			
Drug hypersensitivity			
Hypersensitivity			
Serum sickness			
Injury, poisoning and procedural complications			
Splenic rupture			
Ankle fracture			
Concussion			
Facial bones fracture			
Fall			
Fibula fracture			
Foot fracture			
Skull fracture			
Upper limb fracture			
Blood and lymphatic system disorders			
Neutropenia			
Lymphopenia			
General disorders and administration site conditions			
Non-cardiac chest pain			
Pyrexia			
Pain			
Psychiatric disorders			
Suicide attempt			
Hallucination			
Mental disorder			
Renal and urinary disorders			
Intercapillary glomerulosclerosis			
Ketonuria			
Microalbuminuria			
Pelvi-ureteric obstruction			
Hepatobiliary disorders			
Biliary dyskinesia			
Biloma			
Cholecystitis acute			
Hepatosplenomegaly			
Investigations			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Magnetic resonance imaging brain abnormal			
Eye disorders			
Cataract subcapsular			
Corneal erosion			
Skin and subcutaneous tissue disorders			
Rash			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Cardiac disorders			
Acute myocardial infarction			
Cardio-respiratory arrest			
Ventricular tachycardia			
Ear and labyrinth disorders			
Deadness neurosensory			
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Metastatic malignant melanoma			
Pregnancy, puerperium and perinatal conditions			
Complication of pregnancy			
Vascular disorder			
Subclavian vein thrombosis			

^a Subjects who had more than one AE or SAE for a treatment were counted once.

^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count.

SOCs and PTs are based on MedDRA version 23.0

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = Systems Organ Class;

TESAE = treatment-emergent serious adverse event.

Source: Data on File

- c) A breakdown of all TEAEs Grade ≥ 3 by PT, for the teplizumab group and for the placebo group. If possible, please limit inclusion in the teplizumab group to study participants who received the teplizumab regimen used in TN-10 (9034 mcg/m² over 14 days).

A breakdown of all Grade ≥ 3 TEAEs is not available. However, information on the following AESIs assessed in the integrated safety analysis population is available:

- **Grade ≥ 3 infections:** Reported in [REDACTED] of the teplizumab group and [REDACTED] of the control group
- **Acute mononucleosis-like illness:** [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- **Lymphomas or other malignancies:** [REDACTED]
[REDACTED]
[REDACTED]
- **Major hypoglycaemia:** [REDACTED]
[REDACTED]

- **Grade ≥3 liver function abnormalities:** [REDACTED]
- **Grade ≥3 thrombocytopenia:** [REDACTED]
- **Grade ≥3 neutropenia:** [REDACTED]
- **Grade ≥4 allergic/hypersensitivity reaction:** [REDACTED]
- **Grade ≥3 rash:** [REDACTED]
- **Grade ≥4 CRS:** [REDACTED]
- **Severe lymphopenia (lymphocyte count <500 mm³ for ≥7 days):** [REDACTED]

Table 9 presents treatment-emergent AEs in the integrated safety analysis by SOC and PTs. Treatment-emergent AEs of Grade ≥3 infections are listed in Table 9 by grade.

Table 9. Treatment-emergent AEs: Events by SOC and PTs (safety population)

SOC^c PT	Teplizumab N=791^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a	[REDACTED]	[REDACTED]	[REDACTED]
Blood and lymphatic system disorders	[REDACTED]	[REDACTED]	[REDACTED]
Neutropenia	[REDACTED]	[REDACTED]	[REDACTED]
Lymphadenopathy	[REDACTED]	[REDACTED]	[REDACTED]
Lymphopenia	[REDACTED]	[REDACTED]	[REDACTED]
Thrombocytopenia	[REDACTED]	[REDACTED]	[REDACTED]
Infections and infestations	[REDACTED]	[REDACTED]	[REDACTED]
Epstein-Barr viremia	[REDACTED]	[REDACTED]	[REDACTED]
Cellulitis	[REDACTED]	[REDACTED]	[REDACTED]
Infectious mononucleosis	[REDACTED]	[REDACTED]	[REDACTED]
Gastroenteritis viral	[REDACTED]	[REDACTED]	[REDACTED]
Herpes zoster	[REDACTED]	[REDACTED]	[REDACTED]
Gastroenteritis	[REDACTED]	[REDACTED]	[REDACTED]
Infection	[REDACTED]	[REDACTED]	[REDACTED]
Pneumonia	[REDACTED]	[REDACTED]	[REDACTED]
Anal abscess	[REDACTED]	[REDACTED]	[REDACTED]
Appendicitis	[REDACTED]	[REDACTED]	[REDACTED]
Arthritis infective	[REDACTED]	[REDACTED]	[REDACTED]
Conjunctivitis	[REDACTED]	[REDACTED]	[REDACTED]
Dengue fever	[REDACTED]	[REDACTED]	[REDACTED]
Epstein-Barr virus infection	[REDACTED]	[REDACTED]	[REDACTED]
Hepatic amoebiasis	[REDACTED]	[REDACTED]	[REDACTED]
Liver abscess	[REDACTED]	[REDACTED]	[REDACTED]

SOC^c PT	Teplizumab N=791^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Malaria			
Mononucleosis syndrome			
Pilonidal cyst			
Staphylococcal sepsis			
Tuberculosis			
Wound infection			
Wound infection staphylococcal			
Investigations			
Epstein-Barr virus antibody positive			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Cytomegalovirus test positive			
Gamma-glutamyltransferase increased			
Epstein-Barr virus test positive			
Blood bilirubin increased			
Nervous system disorders			
Hypoglycaemic seizure			
Hypoglycaemia unconsciousness			
Hypoglycaemic coma			
Skin and subcutaneous tissue disorders			
Pruritus			
Rash			

^a Subjects who had more than one AE or SAE for a treatment were counted once.

^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count.

^c Only SOC with subject count meeting threshold are included.

SOCs and PTs are based on MedDRA version 23.0

AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = Systems Organ Class; TESA = treatment-emergent serious adverse event.

Source: Data on File

A 26. Priority question. Please provide any data for AESI (as specified in Table 17 of the CS) collected for teplizumab, in its anticipated licensed dosing regimen or the equivalent dose (e.g. as used in TN-10), as described in section B.2.3.4.1 of the CS. This should include data from any study over the entire development of the product, regardless of anticipated indication during this period.

Please refer to the response to question A22 for AESI data from the TN-10 trial, which used an equivalent dose of teplizumab to the anticipated licensed dosing regimen of teplizumab (as confirmed by the US Center for Drug Evaluation and Research [CDER] Office of Clinical Pharmacology [BLA761183]³⁴).

In the Herold et al. (2023) integrated safety analysis of five studies of teplizumab (AbATE, Protégé, Encore, DELAY and TN-10), rates of selected AEs were discussed (including CRS, infection and hypersensitivity reactions), although these were not explicitly defined as AESI in this analysis.²¹ As described in the response to question A25, it is not possible to provide safety data from this analysis only for participants who received the teplizumab regimen used in TN-10 (9,034 mcg/m² over 14 days) due to the use of other dosing regimens in subgroups of some of the included studies. Data for AESI in the integrated safety analysis are provided in the response to question A25c above.

Ongoing studies

A 27. Priority question. Please provide any available results, including interim analyses, for the TN-10 extension study NCT04270942.

An analysis of efficacy and safety in six participants who received teplizumab and were followed after having progressed to Stage 3 T1D in the TN-10 extension study will be presented at the 2025 ADA conference.³⁵ The abstract is provided in the reference pack, shared in confidence for the purposes of this submission.

Section B: Clarification on cost-effectiveness data

Please note that some requested revisions to the cost-effectiveness model have been made in response to certain clarification questions. The revised model results are presented in Appendix 2, shared as a separate document along with this response.

Published studies

B 1. Please provide details of the screening of the search results and discuss the possibility of having missed potentially relevant studies such as Nguyen et al. 2022 (<https://doi.org/10.1089/dia.2021.0329>).

Searches were run to identify literature on clinical efficacy and safety in individuals with Stage 2 T1D, and literature on economic and humanistic outcomes in individuals with either Stage 2 or Stage 3 T1D. References were screened according to pre-developed criteria for inclusion. For the purposes of this submission, studies most aligned with the population and location of interest (i.e., those with Stage 2 T1D or those taking place in the UK) were prioritised for discussion in the reporting. This reference by Nguyen et al. was therefore identified but was not selected for further discussion as it takes place in the United States and evaluates the treatments of interest in individuals with new-onset Stage 3 T1D.

Population

B 2. In the CS (section B.3.2.1) it is mentioned that baseline patient characteristics of the target population for the economic evaluation were derived from the TN-10 study, which was conducted in individuals aged 8 years and older. Please clarify to what extent the trial population is representative for the UK patient population.

The age range of the TN-10 trial population (≥ 8 years) is representative of individuals with T1D in the UK, as the peak age of T1D diagnosis in England and Wales is 12 years (based on National Diabetes Audit [NDA] data from 2019-2020).^{13,36}

Furthermore, as discussed in the response to question A20, the results of the TN-10 trial are expected to be relevant and generalisable to UK clinical practice given that the risk of progression from presymptomatic to symptomatic Stage 3 T1D is expected to be similar between those who have and who do not have a first-degree relative with Stage 3 T1D²⁷ and that the response to teplizumab is not expected to be dependent on geographic location based on evidence from individuals from North America and Europe (including the UK) with new-onset Stage 3 T1D.³¹

For more information on generalisability, please see Section B.2.5.2 of the CS.

Comparator

B 3. Priority question. The economic model includes ECM without teplizumab as comparator. ECM is defined in the CS and in the NICE final scope to include, but not being limited to, monitoring blood glucose, psychosocial support and education. However, as stated in question A7, currently there is no established treatment for patients with Stage 2 T1D as there is no screening to identify these patients. Also, the comparator in the TN-10 trial (the main source of clinical effectiveness evidence) was placebo.

- a) Please therefore express the comparator ECM in the economic model as that which would be found in actual current clinical practice i.e. in the absence of any screening to detect Stage 2 T1D patients, including appropriate costing.**

In line with question A7b, please define the intervention for those testing positive for Stage 2 T1D.

Please refer to the response to question A7, which explains that the definition of ECM for Stage 2 T1D used in the CS (routine monitoring of blood glucose, psychosocial support and education on the management of T1D) was based on the final scope, UK clinical management, international guidelines and UK expert opinion.^{9,11,12} In line with this definition of ECM for Stage 2 T1D, the model already includes the current clinical practice as the comparator. The appropriate intervention for individuals with Stage 2 T1D is therefore teplizumab with ECM as currently included in the model.

Clinical effectiveness

B 4. Priority question. Based on Figure 6 in the CS (observed KM curves (ITT population), the placebo arm of the RCT seems to have a very high rate of progression to Stage 3 T1D shortly after randomisation. Please explain the possible reasons for this initial large impact and whether it could impact on the validity of findings. In addition, comparing Figure 4 to Figure 6 in the CS, the timings of progression to Stage 3 T1D appear to be different, with the initial events occurring between 3 and 6 months in Figure 4, and at around 3 months in Figure 6. Please explain why the KM Survival Curves differ and which was used for the model. Finally, please discuss the impact of using KM data from Figure 4 on the appropriateness of the proportional hazards assumption, should the data from Figure 4 be included in the economic model.

The high rate of progression to Stage 3 T1D in the placebo arm shortly after randomisation is consistent with medical literature demonstrating that the rate of progression within the first year is higher than in subsequent years, with more than 40% of relatives of individuals with Stage 3 T1D progressing to onset of Stage 3 T1D after 1 year and ~60% progressing after 2 years.³⁷ This was reviewed with an external clinical expert, Prof. Colin Dayan, who agreed the rate of progression in the placebo arm is as expected.¹⁰ Prof. Dayan explained that as individuals were recruited from TN-01 into TN-10, a proportion of these participants would have been in Stage 2 T1D for a longer period of time; it is likely that these participants were the first to progress to Stage 3 T1D following randomisation.¹⁰

The baseline characteristics of participants in the primary analysis of TN-10 were well-balanced across the two arms.¹³ This included mean glucose levels at baseline¹⁶, indicating

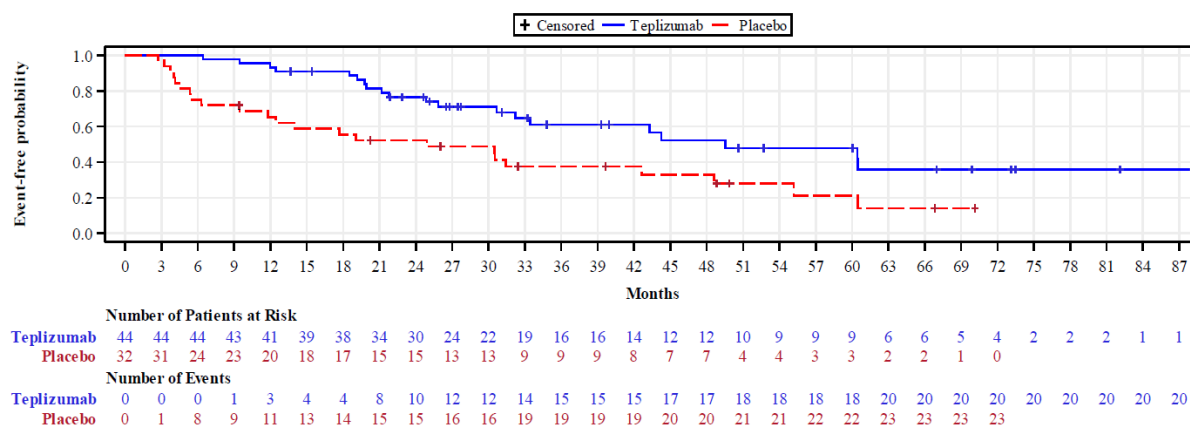
that participants in both arms had a similar degree of glycaemia at baseline and would therefore be expected to have a similar risk of progression to onset of Stage 3 T1D. When baseline T1D-related characteristics were shared with Prof. Dayan, he stated that “the glucose and c-peptide seem reasonably well matched, suggesting there is no evidence that the control population are at a more advance stage”.¹⁰

Furthermore, when asked if there would be any impact if in real-world practice people were administered teplizumab earlier in Stage 2 T1D than in the TN-10 trial, Prof. Dayan indicated that teplizumab would be efficacious independent of time from Stage 2 T1D diagnosis.¹⁰

Both Figure 4 and 6 in the CS are based on individual patient data from the TN-10 study, albeit derived from different data cuts. The data depicted in Figure 6 was used to inform the economic model due to the longer follow-up; from the Kaplan-Meier (KM) curves, the maximum follow-up for placebo in Figure 4 (Figure 2 below) is approximately 70 months, whereas the maximum follow-up for placebo in Figure 6 (Figure 3 below) is approximately 84 months.

Thus, the data from Figure 4 has not been included in the model; regardless, if the data were to be included, the conclusions about the proportional hazards assumption would not change.

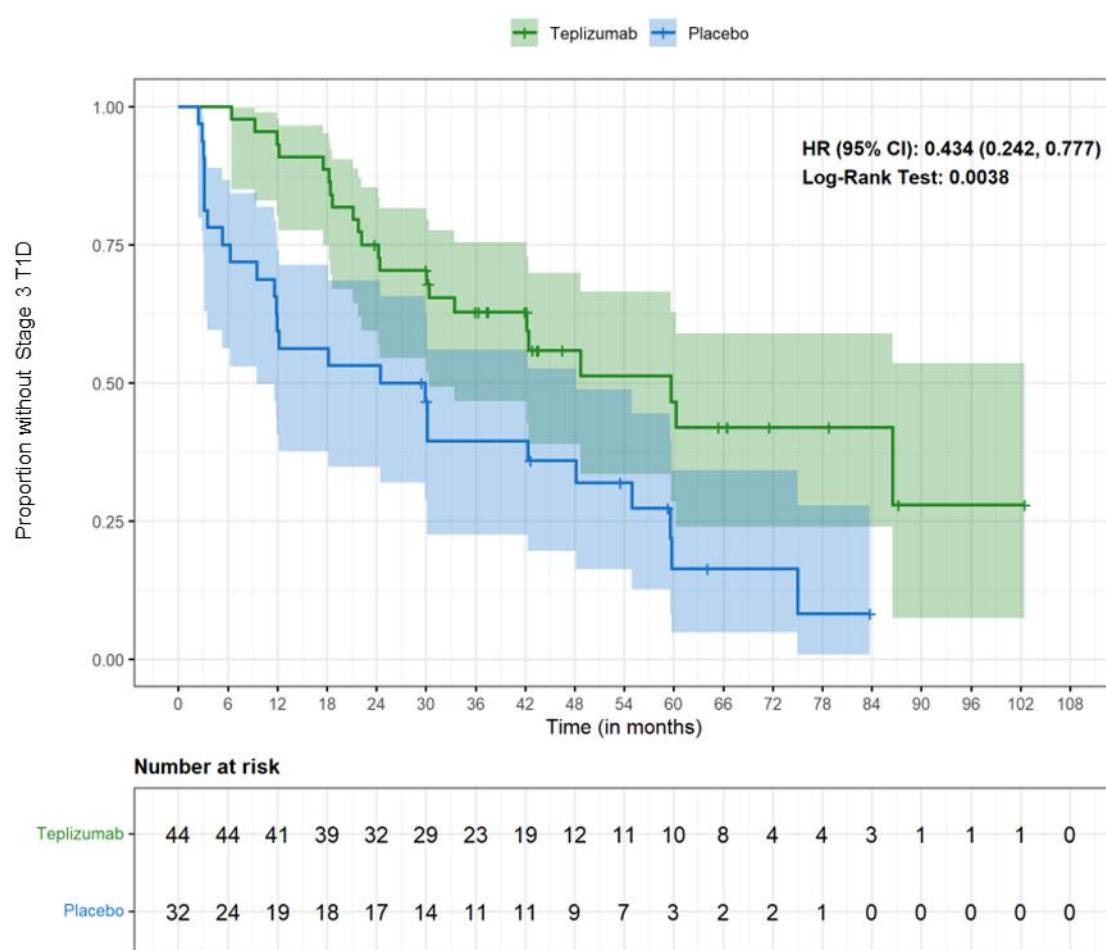
Figure 2. KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis) – Figure 4 from the CS



CS = company submission; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

Source: Data on File – Provention Bio Inc. 2020 (CSR Addendum).¹⁶

Figure 3. Observed KM curves (ITT population) – Figure 6 from the CS



CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

B 5. Priority question. Please provide for both teplizumab and ECM a plot of the observed hazard functions over time. Please justify selecting different types of independent parametric distributions for teplizumab and ECM (log-normal and exponential, respectively) when for example NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 recommends that “if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type”. Please consider revising the selection of parametric distributions for the base-case based on the evidence already

presented in the CS, NICE DSU TSD 14 recommendations, and the hazard functions over time.

Figure 4 shows a plot of the observed hazard functions over time as requested. The average hazards or rates (events per person-time) are calculated based on the quintiles (i.e., 20th, 40th, 60th, 80th percentiles) of times where events were observed across both groups.

Figure 4. Observed hazard functions over time

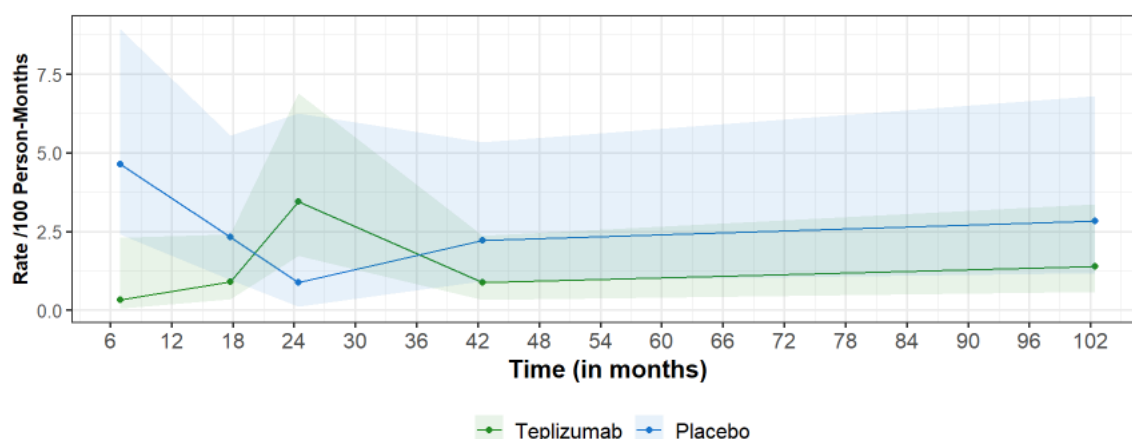
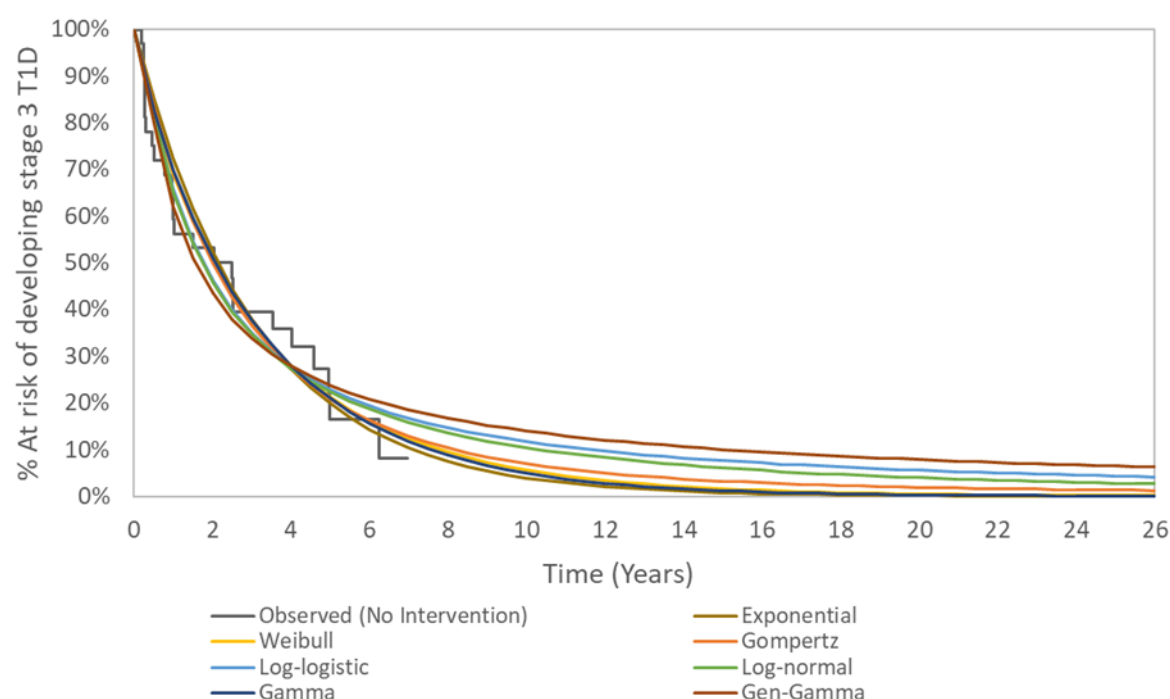


Figure 5 shows the parametric fitting for the placebo arm. For the selection of base case fits, the Akaike information criterion (AIC)/Bayesian information criterion (BIC) for the log-normal fit for teplizumab were the lowest among all distributions. For placebo, the best parametric fits differ depending on whether using AIC or BIC, resulting in log-normal or exponential selections, respectively.

Figure 5. Parametric fitting for the placebo arm



T1D = type 1 diabetes

The exponential and log-normal curves were reviewed by an external clinical expert, Prof. Colin Dayan.¹⁰ Prof. Dayan agreed with the proposed approach of selecting the exponential fit.¹⁰ The curve aligns with the curve of individuals progressing from Stage 2 to Stage 3 T1D from the Diabetes Prevention Trial–Type 1 (DPT-1) study which is highlighted in the scientific statement from the Breakthrough T1D (formerly the JDRF), Endocrine Society, and ADA (Insel et al. [2015]).^{10,32} Prof. Dayan cited evidence from the Slow or Non-progressive Autoimmunity to the Islets of Langerhans (SNAIL), which has found that there are very few participants across multiple cohorts of autoantibody-positive populations who do not progress to Stage 3 T1D within 10 years.^{10,38,39}

B 6. Priority question: On page 74 of the CS, it is mentioned that for “individuals receiving ECM, the log-normal distribution produced clinically unrealistic estimates of the proportion of individuals who will not have progressed to Stage 3 T1D in the long term (Table 26)”. Please justify this statement. In addition, please present an extended version of Table 26 of the CS including all parametric distributions for both teplizumab and ECM. Please explain also why “the generalised gamma model clearly overpredicted the KM curve from year 5 onward”, when the number of patients at risk at year 5 (Figure 6) is small in both arms, but especially for ECM.

The proportion of individuals in Stage 2 T1D by each parametric distribution is shown in Table 10 for the ECM arm and in Table 11 for the teplizumab arm.

Table 10. Proportion of individuals in Stage 2 T1D by parametric distribution (ECM)

Time (years)	Exponential	Log-normal	Gamma	Weibull	Gompertz	Log-logistic	Gen-gamma
0							
5							
10							
15							

ECM = established clinical management; T1D = type 1 diabetes
The grey coloured column indicates the base-case in the CS.

Table 11. Proportion of individuals in Stage 2 T1D by parametric distribution (teplizumab)

Time (years)	Log-normal	Exponential	Gamma	Weibull	Gompertz	Log-logistic	Gen-gamma
0							
5							
10							
15							

T1D = type 1 diabetes
The grey coloured column indicates the base-case in the CS.

As discussed in the response to question B5, parametric fitting of the placebo arm indicated that an exponential approach would be preferred. The exponential approach was also confirmed by clinical expert opinion (Prof. Dayan) based on alignment with the curve of individuals progressing to Stage 3 T1D from the DPT-1 study as reported in the Insel et al. (2015) scientific statement, and evidence from the SNAIL study that few individuals with autoantibodies do not progress to Stage 3 T1D within 10 years.^{10,38,39}

Sanofi discussed the validity of the generalised-gamma distribution with Prof. Dayan who agreed this could be discounted in line with the answer to question B5, given this distribution predicts 10% of people remain in Stage 2 T1D at 15 years.¹⁰

B 7. Please justify why the study by Besser et al. 2022 was selected to estimate the DKA risk at onset of Stage 3 T1D. Please provide a comparison with other studies such as NICE TA943 or Roze et al. 2021.

NICE TA943 and Roze et al. 2021 used the CORE diabetes model. There is limited information about the precise data behind the use of the model in both the EAG assessment report for NICE TA943 and the publication by Roze et al. A publication reporting on the validation of the CORE model⁴⁰ refers to the use of Diabetes Control and Complications Trial (DCCT; US data) to inform the risk of DKA (1.8%-2% of individuals experiencing DKA events, an estimate that is close to the value from the Besser et al. publication). The

publication by Besser et al. reports DKA risk for newly diagnosed individuals in the UK, as well as reduction in this risk if individuals are monitored.

B 8. Please justify why the Swedish studies by Samuelsson et al. 2024 and Rawshani et al. 2018 were selected to estimate the excess mortality due to Stage 3 T1D. Please provide a comparison of approaches with other studies such as NICE TA943 or Roze et al. 2021.

Samuelsson et al. (2024) and Rawshani et al. (2018) were selected because of their robust designs. Samuelsson et al. (2024) is an analysis of the Swedish National Diabetes Register that included data for 15,188 individuals with Stage 3 T1D and 74,210 controls (2000 to 2019); since the study included data through 2019, the study may reflect an improved survival profile for individuals living with T1D, based on better clinical management available during this relatively recent studied period.⁴¹ Rawshani et al. (2018) is also an analysis of the Swedish National Diabetes Registry that included 27,195 persons with Stage 3 T1D in and 135,178 matched control subjects from the general population (1998 to 2012).⁴²

As noted above, both Roze 2021 and the EAG model for NICE TA943 are based on the CORE diabetes model. Therefore, risk of death is based on the specific diabetes-related events that are experienced by individuals in the model (e.g. stroke, hypoglycaemia) and their associated risk of death, which can be modelled as a case fatality (dying from the event itself) or as an increased risk of death that persists over time following the clinical event. For this reason, the methods are not directly comparable to the current model structure in the CS. Also of note, the EAG assessment report for NICE TA943 or the publication by Roze et al. provided limited information on the precise mortality data used as inputs in these models.

Health-related Quality of Life

B 9. Priority question: On page 23 of the CS, it is mentioned that “Parent QoL in terms of family impact was worse in parents of young children (<13 years of age) than in parents of adolescents (≥13 years of age)”. In the model, however, this is applied to <18 years of age. Please adjust the model so that the age at which the parent disutility is applied can be changed by the user. Furthermore, the study by López-Bastida et al. 2019, includes children aged 2-17. In the CS it is mentioned, and in the study the same is observed, that the score for carers is lower when children are younger. The carer EQ-5D-5L score of 0.92 was based on the whole

sample (Table 3 in López-Bastida et al. 2019), therefore this is likely an underestimation of the utility score that should be used in the model (the disutility should be less). Please adjust the model to include the carer disutility corresponding to children aged 8+ years.

The publication by López-Bastida et al. did not provide the carer's utility stratified by the age of the individuals with T1D that these carers were supporting. Therefore, Sanofi do not think the publication provided appropriate data to update the model to meet the requested adjustment.

Regarding the age at which the parent disutility is applied, in the model the age threshold (e.g., <18 years of age) is a user defined value (cell D50 in <Utilities>).

B 10. Priority question: In the probabilistic sensitivity analysis (PSA), the model generates very low (close to 0) utilities on occasion. For example, for the age group 50-60 year 10% of iterations yield a utility below 0.6, where the point estimate is 0.859. This level of variation does not appear plausible. In the model, the random draws for the utilities are based on the point estimate and a standard error that is defined as a percentage of the point estimate, with the percentage increasing by age group from 7% to 29%. Please explain how these percentages were determined and please estimate the appropriate standard errors for the utility per age group using the coefficients and their standard errors of the model estimated by Hernández-Alava et al.

The publication by Hernández-Alava et al. provides a regression model with several terms and coefficients that are used to derive UK-utilities for a given combination of age and sex. The variability provided by Hernández-Alava et al. regression model is around the coefficients of the regression and not the utility values generated.

A different publication (Janssen et al. 2021⁴³) was used to inform the variability of the general population utilities stratified by age. Janssen et al. 2021 developed a set of pooled normative EQ-5D-3L values for the five largest European economies (France, Germany, Italy, Spain, and the UK). EQ-5D index values were reported by age groups and for each group its standard deviation (SD) was also included (Table 3 from Janssen et al. 2021). We calculated the ratio SD/mean (coefficient of variation) noting an increase in the variability of the mean EQ-5D as age increases (Table 12). A regression model was fitted to the SD/mean values (Figure 6). This regression model was used to estimate a standard error

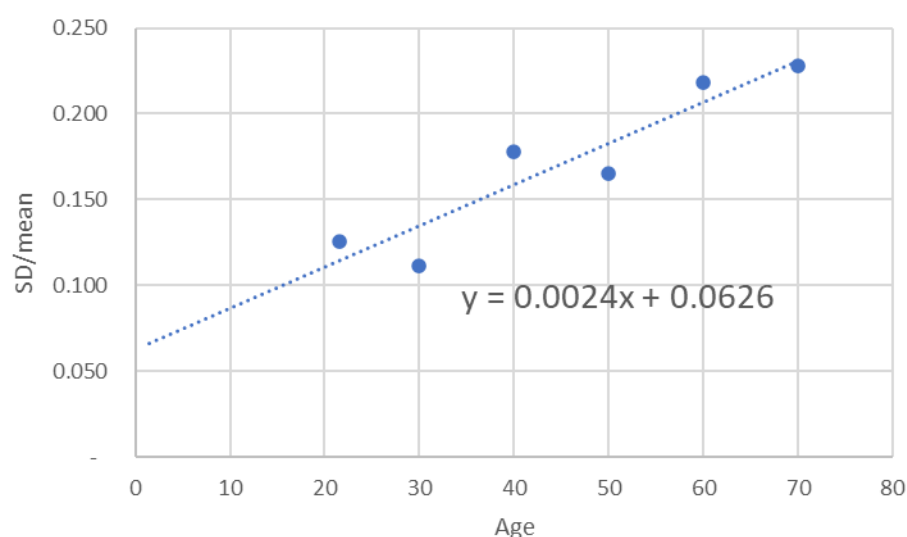
defined as a percentage of the point estimate for the mean utilities derived from Hernández-Alava et al. Also of note, when sampling utilities during a PSA run, a single random number is used across the different age categories capturing general population utility norms per age category.

Table 12. Calculated SD/mean of general population EQ-5D values from Janssen et al. (2021)

Age (years)	18-24	25-34	35-44	45-54	55-64	65-74	75+
Mean EQ-5D	0.963	0.959	0.939	0.927	0.885	0.865	0.785
SD	0.121	0.107	0.167	0.153	0.193	0.197	0.274
SD/mean	0.126	0.112	0.178	0.165	0.218	0.228	0.349

SD = standard deviation
Source: Janssen 2021.⁴³

Figure 6. Regression model fitted to SD/mean of general population EQ-5D values from Janssen et al. (2021)



SD = standard deviation

B 11. Please justify why Sparring 2013 and Sullivan 2011 were selected to estimate disutilities for Stage 3 T1D. Please provide a comparison of approaches with other studies such as NICE TA943 or Roze et al. 2021.

In Sanofi's model, utilities, estimated in an aggregate manner, depended on the time since onset of Stage 3 T1D and were assigned over time depending on the individual's health state. The study conducted in Sweden by Sparring et al. 2013 was considered the most appropriate available input source for onset of Stage 3 T1D because HRQoL for Swedish individuals with Stage 3 T1D was reported since onset and over the duration of the disease, which aligned with the needs for the model. No UK sources were identified by the SLR that reported appropriate data for the model. An appropriate UK source was identified for Stage 3 T1D vs. the general population utilities, Sullivan et al. 2011, which reports nationally

representative preference-based HRQoL scores for having diabetes without complications in the UK, based on the EQ-5D (NICE's preferred measure).

As noted above in the response to questions B7 and B8, both Roze et al. 2021 and the EAG model for NICE TA943 are based on the CORE diabetes model. Hence, like the handling of mortality, the approach to determining individuals' utility is based on the specific diabetes-related events that are experienced (e.g., stroke, hypoglycaemia) and their associated impact on quality of life. For this reason, the methods are not directly comparable to the current model structure in the CS, which is based on aggregated utilities for individuals with Stage 3 T1D.

B 12. Please adjust the model to include a multiplicative approach to utilities as recommended by NICE. The user should be able to choose between the current additive or a multiplicative approach.

The model has now been updated so that either the current additive or a multiplicative approach can be used.

Sparring et al. 2013 reported a multiple regression model on EQ-5D index, including the disutilities for a disease duration (Stage 3 T1D) of 8, 15 and 24 years (which were used in the base case based on an additive approach). As shown in the third column of Table 13, these disutilities are now expressed as a percentage (i.e., using the multiplicative approach) of a reference utility (the intercept of the regression model reported by Sparring et al. 2013, 0.93, was used). The long-term disutility is modelled based on a linear regression of the relative (%) disutility, resulting in the equation: "relative disutility" = $-0.337\% \times \text{'disease duration (years)'}$. The relative disutilities are applied on top of reference utilities based on general population norms for the UK (the same as when using the additive approach).

Table 13. Absolute and relative disutility values for people with Stage 3 T1D based on time since onset of Stage 3

Time from onset of Stage 3 T1D	Disutility (absolute) ⁴⁴	Disutility (relative)
8 years	-0.023	-0.023/0.93 = -2.473%
15 years	-0.055	-0.055/0.93 = -5.914%
24 years	-0.074	-0.074/0.93 = -7.957%

T1D = type 1 diabetes

Resource use and costs

B 13. Priority question. Please explain how teplizumab acquisition cost per 14-vial treatment course are calculated in the model. In the CS, there is a

detailed description of the treatment course using a BSA-based dosing, but it seems this has not been used in the model.

In TN-10, dosing was determined based on BSA. Consequently, some participants with a higher BSA required elevated doses of the intervention (placebo n=1 [3.1%], teplizumab n=1 [2.3%]). When transitioning to routine clinical practice in the UK and at the anticipated licensed dosing regimen, it is anticipated that most individuals will require treatment with 14 vials only.

The final dosing distribution will ultimately depend on the guidance provided by NICE and the specific population covered by the recommendation. For the purposes of the current cost-effectiveness model, it is assumed that all individuals in the UK will receive the lower dose, and this assumption has been incorporated into the economic analysis. The treatment acquisition cost per 14-vial treatment course applied in the model is based on an assumed flat per-person rate. Therefore, all individuals in the teplizumab arm receive the same one-off cost of teplizumab at the model baseline.

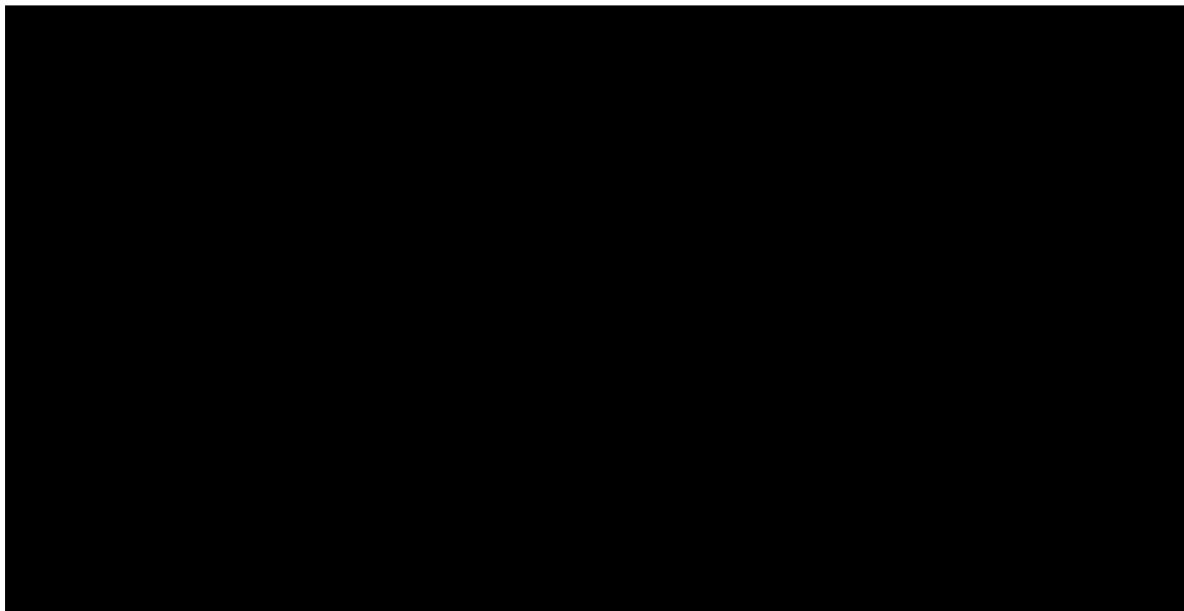
B 14. Priority question. Costs for Stage 3 T1D were estimated based on four regression models (informed by data from Ou et al. 2014). In the PSA, each parameter in each model was drawn separately from a Normal distribution without taking into account the correlation between parameters. This results in highly variable cost estimates and sometimes impossible (i.e., negative) values. This appears to explain (at least partially) the (unusual) distribution of PSA outcomes in the cost-effectiveness scatter plot and results of the cost-effectiveness acceptability curve (CEAC). Please adjust the model to take into account the correlation between parameters in the cost regression models in the PSA, otherwise, the PSA results would be deemed as incorrect.

The approach to costing disease management during Stage 3 T1D depends on a starting cost (informed by a UK publication by Hex et al. 2024⁴⁵) combined with trends indicating how the initial cost increases over time (derived from a different publication by Ou et al. 2016⁴⁶). The publication by Ou et al. 2016, from which the long-term trends were derived, reported disease management costs results in dollars; hence, those trends were scaled based on the starting cost from the UK publication, so that the projected cost represented UK costs.

We have updated the PSA methods in the model to address the EAG's concerns, when compared with the version that was originally submitted by Sanofi. In the latest updated

model, the variability related to Stage 3 T1D is captured by imposing the variability on only the starting cost (i.e. the coefficients of the regression models are kept constant). However, since that starting cost is then used to scale the long-term trends (scaling done in < Stored Value> within the Excel economic model), this results in a variation of Stage 3 T1D costs that better represents the uncertainty in estimating them. Figure 7 shows the base case and 30 random samples for Stage 3 T1D costs generated using this approach, with no impossible (i.e., negative) values occurring. In the updated approach to capture the variability of Stage T1D 3 costs, the long-term trends determined by the parameters of the regression models change only as a result of the sampling of values around the starting cost, i.e., the regression parameters are not sampled individually.

Figure 7. Potential Stage 3 T1D disease management costs sampling trajectories during a PSA run



PSA = probabilistic sensitivity analysis; T1D = type 1 diabetes
Note: Each line in the figure represents a different random sample

B 15. Priority question. To calculate costs for Stage 3 T1D, data from two sources were combined. An initial monthly cost at the onset of Stage 3 T1D was estimated based on data from Hex et al. 2024 (Table 1). This initial cost was then increased over time based on cost trajectories observed in Ou et al. 2016 (Figure 2). The initial cost at onset of Stage 3 is estimated by the total annual cost of diagnosing and treating people with type 1 diabetes in the UK divided by the current prevalence of T1D. This cost reflects the full cost of type 1 diabetes management including individuals who have had Stage 3 T1D for many years and not just after

onset of Stage 3 T1D. Please explain why this approach was used to estimate costs at progression to Stage 3 T1D.

The Hex et al. (2024) study was selected as the best available source to inform the initial monthly costs incurred at the onset of Stage 3 T1D in the cost-effectiveness model.⁴⁵ This study is a high-quality, up-to-date assessment of current and projected cost estimates for diabetes, representing the best UK data currently available, given that no alternative UK-specific sources were identified. The methodology used in Hex et al. (2024) was well-aligned with the structure of the cost-effectiveness model, which required an estimate of the aggregate cost associated with the Stage 3 T1D population. The study developed a cost-of-illness model from an NHS, personal social services (PSS), and societal perspective, and included costs for diagnosis, treatment, complications, and indirect costs in the estimation of total costs.⁴⁵ Within the economic model, the value for the total annual direct healthcare costs of T1D is used to inform the initial monthly costs incurred at the onset of Stage 3 T1D.

B 16. Priority question. Data on the increase in costs over time was estimated based on observed cost trajectories in Ou et al. 2016. It seems that data on total healthcare costs rather than diabetes specific costs (which were also presented) were selected. Please explain why data on total healthcare costs were chosen and not diabetic specific. If this was incorrect, please amend the model to include the correct costs.

Total healthcare costs associated with Stage 3 T1D were used to inform the model in order to capture all costs related to T1D. The clinical burden of Stage 3 T1D includes acute metabolic complications as well as several long-term complications.⁴⁷⁻⁴⁹ As individuals with Stage 3 T1D age through adulthood, the clinical burden of the disease persists, with diabetes-related complications being compounded with the onset of age-related conditions.⁵⁰ Given that these complications are a consequence of Stage 3 T1D, they are related to diabetes and therefore can be considered diabetes-specific costs. Furthermore, the total healthcare costs from Ou et al. (2016) are aligned with the structure of the cost-effectiveness model, which required an estimate of the aggregate cost associated with the Stage 3 T1D population, and as per NICE guidance (section 5.5.7).⁵¹

B 17. Priority question. Related to question A6b, please provide estimates of the costs associated with this test/ these tests. In addition, please provide an estimate of the number of patients that would be screened to find one patient eligible for treatment with teplizumab.

Diagnostic tests for Stage 2 T1D include positive tests for ≥ 2 pancreatic islet autoantibodies and evidence of dysglycaemia, often using an OGTT.^{11,52,53} Autoantibody testing involves testing for three autoantibodies (anti-GAD, anti-ZnT8 and anti-IA2).⁸ Confirmation of dysglycaemia using an OGTT involves testing blood glucose at five timepoints (fasting and at 30, 60, 90 and 120 minutes).⁵⁴ As stated in the CS, the cost of the autoantibody tests (anti-GAD, anti-ZnT8 and anti-IA2) is £29.04 (based on an NHS laboratory that is utilised as a referral lab for this assay [Exeter Clinical Laboratory International]).⁸ The cost of the OGTT includes the cost of glucose solution (£3.98; based on the NICE British National Formulary [BNF]) and the cost of the blood glucose tests (£7.85 x 5 timepoints = £39.25 based on the National Schedule of NHS costs).^{54,55}

As discussed in the response to question A6, screening for and early detection of T1D do not fall within the remit of this single technology appraisal. For this reason, Sanofi have not provided an estimate of the number of individuals that would be screened to find one individual eligible for treatment with teplizumab.

B 18. Please justify the choice of sources to estimate resource use and costs. For Stage 3, please provide a comparison of approaches with other studies such as NICE TA943 or Roze et al. 2021.

Given there are no formal guidelines for the management of Stage 2 T1D, expert UK clinical advice was sought to understand the current clinical management of individuals with Stage 2 T1D. This was obtained through an advisory board convened by Sanofi with 11 leading clinical experts from across the UK (for more information on the advisory board, please see Appendix M of the CS).¹² The patient pathway derived from the advisory board, which is in line with international guidelines, was used to estimate resource use and cost both for ECM and the administration of teplizumab.^{9,12}

Regarding NICE TA943 and Roze et al. 2021, these studies evaluate individuals during Stage 3 T1D. Their approach to estimating resource use is based on the occurrence of complication events. When an individual with Stage 3 experiences a complication event, then specific costs are applied accounting for the management of said event. Sanofi's model in the CS uses an aggregated approach to costing the disease management during Stage 3, hence the approach from NICE TA943 or Roze et al. 2021 are not comparable.

B 19. Costs of DKA events upon progression to Stage 3 T1D are included separately. Please explain whether DKA costs are included or excluded from the broader Stage 3 T1D costs and if there is a risk of double counting.

The aggregated costs reported for DKA in the publication informing the model (Hex at al. 2024) appear to refer to the overall DKA burden. Therefore, to avoid double counting, no DKA-specific costs were applied when individuals resided in the Stage 3 T1D stage. However, as described in Section B.3.3.2.2 of the CS, there is a high risk of costly and life threatening DKA events in Stage 3 T1D that can be reduced with appropriate monitoring during Stage 2. Therefore, to account for these risks with and without monitoring, a one-off rate of these events, and the costs of treating them, were included at the onset of Stage 3 T1D.

B 20. Stage 3 T1D costs in the ‘Costs’ tab of the model are monthly costs (E54:G256) and cycle length is 6 months. It is unclear whether these monthly costs are multiplied by the cycle length or not. Please provide clarification.

Yes, the monthly costs are multiplied by the cycle length (in the table aggregating results within either model engine; BE28:BF29).

Cost-effectiveness results

Model validation

B 21. Priority question: Please provide a comparison of the model results vs. Table 3 and Table 13 in the CS.

The projected risk of progression to Stage 3 T1D among individuals on ECM is reported in Table 14. Likewise, the median time to progression derived from the base case parametric models selected for teplizumab and ECM (log-normal and exponential) are reported in Table 15.

Table 14 Risk of progression to onset of Stage 3 T1D among individuals diagnosed with Stage 2 T1D

Study	Population	Risk of progression to onset of Stage 3 T1D at		
		2 years	4 years	5 years
TrialNet Natural History Study ³⁷	First- and second-degree relatives ^a aged 1 to 45 years	~60%	74%	NR
DPT-1 ⁵⁶	First- and second-degree relatives ^a aged 3 to 45 years ⁵⁷	NR	65%	~75%
Fr1da ⁵⁸	Children aged 1.75 to 10 years from the general population, including 3.9% with a first-degree relative	58.6%	NR	NR
Sanofi's Model	As per TN-10			

DPT-1 = Diabetes Prevention Trial–Type 1; NR = not reported; T1D = type 1 diabetes

^a Of people with Stage 3 T1D

Sources: Krischer 2013³⁷; Sosenko 2009⁵⁶; Weiss 2022⁵⁸

Table 15. Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Primary analysis		
Median	49.5 months (32.2, NE)	24.9 months (9.5, 48.6)
Median difference	24.6 months (NE, NE)	
HR (95% CI); p value	0.41 (0.22, 0.78); p=0.0066	
Extended follow-up analysis		
Median	59.6 months ██████████	27.1 months ██████████
Median difference	32.5 months ██████████	
HR (95% CI); p value	0.457 (NR); p=0.01	
Sanofi's model (base case)		
Median	██████████	██████████
Median difference	██████████	

CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; T1D = type 1 diabetes
Sources: Data on File – Provention Bio Inc. 2020 (CSR Addendum);¹⁶ Data on File – Provention Bio Inc. 2020 (CSR Tables – Table 2.1.1);²⁰ Sims 2021.¹⁷

B 22. Priority question. In Section B.3.14 of the CS, the company conducted three validation exercises comparing the model results with other published studies. Please answer the following questions:

Comparison with NICE TA943: please justify the conclusion that “Quality-adjusted life year (QALYs) and life-years (LYs) were relatively consistent across the two models”. This seems arbitrary since the difference especially in LYs cannot be deemed as minor. We understand that the company’s model includes patients with Stage 2 T1D, whereas the NICE TA943 includes only Stage 3 T1D. Therefore, “to allow for direct comparison” please consider changing not only the baseline age but also “switching off” the Stage 2 health state, with all patients starting in Stage 3 T1D. The rationale for this scenario is that once patients are in Stage 3, results should be comparable to those in NICE TA943.

- a) Comparison with Roze et al. 2021: as mentioned in the previous question, please consider “switching off” the Stage 2 health state to allow for a direct comparison.**
- b) Comparison with Mital et al. 2020: please justify the conclusion that QALYs for both no treatment and teplizumab were larger in the company’s model, but the differences do not appear substantial. This**

might be true for the incremental QALYs but not for the total QALYs estimated for each treatment arm.

c) Please discuss the validation of the cost results compared to these two studies as well.

There are differences between the outputs from Sanofi's model when compared with other relevant published models, but these may be explained by the different modelling approaches. The published models were based on individual patient simulation where outcomes (e.g., life years and costs) are determined by the occurrence of Stage 3 T1D-related complications over time. In contrast, Sanofi's model uses an aggregated approach based on mean outcomes associated with both Stage 2 and Stage 3 T1D.

In the CORE model, the risk of death depends on the occurrence of T1D-related complications and associated changes to survival because of the complications; in turn, the risk of complications depends on changes over time in surrogate outcomes like HbA1c. However, as pointed in the CS (Section B.3.2.2.2), evidence gathered by Daly et al. (2022)⁵⁹ suggests that the accuracy of HbA1c as a predictor of mortality is strongly disputed. In other words, the projection of surrogate outcome measures over the longer term introduces uncertainty and this can limit the external validity of models (e.g., the CORE model), especially over a lifetime horizon.

Furthermore, the models use different data sources for key inputs such as risk of death, which in turn drives the resulting life-years. Sanofi's base case model used a source for increased/excess risk of death based on data from 2000 to 2019 (Samuelsson et al. 2024⁴¹). This recent data may reflect an improved survival profile for individuals living with T1D, based on better clinical management available during this relatively recent studied period. This improved survival may be driving the higher life-years reported by Sanofi's model (e.g., when compared with NICE TA943). Other outcomes such as total costs could also be impacted.

Lastly, the use of either approach to mortality (i.e., CORE vs. Sanofi's model) impacts both comparators in the same way within each model, and hence the relative/incremental merits of each treatment should be identifiable using either model.

Taken together, the submitted model remains the best approach to address the decision problem.

Model implementation

B 23. Table 46 shows some units in \$. Please clarify if this is correct or not.

This is correct given that the costs in the original publication were reported in dollars (2012).⁴⁶

B 24. Column “Outcomes” in Table 21 seems to be incorrect when compared to the values reported in Mital et al. 2020 Table 3, since the correct comparison should be against no treatment. Please confirm this.

Thank you for raising this. Sanofi can confirm that the outcomes reported in Table 21 of the CS should be as follows for comparing against no treatment:

- Incremental QALY of teplizumab vs. no treatment: 0.54
- Incremental cost of teplizumab vs. no treatment: US\$57,942
- Incremental cost-effectiveness ratio (ICER; per QALY gained): US\$107,300

B 25. The Excel model possibly contains an error regarding the implementation of the half cycle correction. When the time horizon is set to 1 year, the Result sheet (as well as the Model Engine_XXX sheets) show that for example the No Treatment group accumulated 0.037 LY in Stage 3 and the rest, 0.963 LY, in Stage 2. When checking this in the Model Engine_NoTx sheet, we see that this value is found by adding AB11 and AB12 together, and then multiplying by 6/12 (cycleLength/Time.MonthsInYear). AB11 is the average of T10 and T11, and AB12 the average of T11 and T12. Now T10 is actually the header of column T containing text, and T11 is 0, hence excel returns an average of 0 for AB11, and AB12 is the average of 0% and 14.97% = 7.48%. Adding 0% and 7.48% and multiplying by 6/12 yields the 0.037 LYs as reported in the results. However, we can see in the not HCC values that at t=0 0% of patients is in Stage 3, at t=6 months 14.97% and at t=12 months 27.69%. Thus, during the first cycle, on average 7.48% of patients were in Stage 3, and in the 2nd cycle 21.33% of patients. Multiplying each by 6/12 and then adding (or adding first and then multiplying) yields 0.144 LYs in Stage 3. The most straightforward way to solve this problem might be to adjust columns G, I and J by shifting everything down one row, such that row 12 concerns the first cycle (from t=0 to t=6), row 13 the

second cycle etc. Please check if this indeed currently incorrect, and please provide a revised version of the model with, if applicable, a new set of results.

[Model updates were made according to the feedback.](#)

Section C : References

1. National Institute for Health and Care Excellence (NICE). *Diagnostics Assessment Programme manual* 2011. December. <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf>
2. Swaby R, Randell T, Martin R, et al. How many children are out there? A BSPED survey of children and young people with early-stage type 1 diabetes. presented at: 51st Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes; 08 Oct 2024 - 10 Oct 2024; Glasgow, UK.
3. Swaby R, Jones S, Damazer K, Besser R. Establishing clinical follow-up in early-stage pre-symptomatic type 1 diabetes: results from the oxford pre-T1D clinical service. presented at: Endocrine Abstracts; 2024;
4. Besser REJ, Ng SM, Gregory JW, Dayan CM, Randell T, Barrett T. General population screening for childhood type 1 diabetes: is it time for a UK strategy? *Arch Dis Child*. Sep 2022;107(9):790-795. doi:10.1136/archdischild-2021-321864
5. Narendran P, Newland-Jones P, Kanumilli N, Stewart R, Regan F, Randell T. Highlighting the new consensus guidelines for managing people at risk of, and with early-stage type 1 diabetes-Relevance to clinical care in the UK. *Diabet Med*. Dec 29 2024:e15508. doi:10.1111/dme.15508
6. National Institute for Health and Care Excellence (NICE). *NICE-wide topic prioritisation: the manual*. 2024. 29 May. <https://www.nice.org.uk/process/pmg46/resources/nicewide-topic-prioritisation-the-manual-pdf-72286839710917>
7. Sanofi (Data on File). *Draft Summary of Product Characteristics (Tziel)*. 2024.
8. Exeter Clinical Laboratory International. Glutamic Acid Decarboxylase (GAD) Antibodies. Accessed 31 October, 2024. <https://www.exeterlaboratory.com/test/gad-antibodies/>
9. Phillip M, Achenbach P, Addala A, et al. Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes. *Diabetes Care*. Jun 24 2024;doi:10.2337/dci24-0042
10. Sanofi (Data on File). *Clinical Opinion: Professor Colin Dayan*. 2025. 16 January 2025.
11. Besser REJ, Bell KJ, Couper JJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1175-1187. doi:10.1111/pedi.13410
12. Sanofi (Data on File). *Sanofi Pre-symptomatic Type 1 Diabetes Care Pathway July 2024 Advisory Board Meeting Report v1.0 (MAT-XU-2402985)*. 2024. 19 July.
13. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. Aug 15 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
14. National Institute for Health and Care Excellence (NICE). Type 1 diabetes. Updated 2023. Accessed November 6, 2023. <https://bnfc.nice.org.uk/treatment-summaries/type-1-diabetes/>
15. Holt RIG, DeVries JH, Hess-Fischl A, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Nov 2021;44(11):2589-2625. doi:10.2337/dci21-0043
16. Provention Bio Inc. (Data on File). *TN-10 Clinical Study Report Addendum: Anti-CD3 MAP (Teplizumab) for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus. Final Version 1.0*. 2020. September 3.
17. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med*. Mar 3 2021;13(583)doi:10.1126/scitranslmed.abc8980
18. ClinicalTrials.gov. TrialNet Pathway to Prevention of T1D. Accessed July 9, 2024. <https://clinicaltrials.gov/study/NCT00097292>

19. Wood Hickman LK. *FDA Center for Drug Evaluation and Research. Clinical Review. Application Number: 761183Orig1s000*. 2022. 17 February.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000MedR.pdf
20. Provention Bio Inc. (Data on File). *PRV-031 TN-10 Tables Final 07SEP2020*. 2020.
21. Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β -Cell Function. *Diabetes Care*. 2023;46(10):1848-1856. doi:10.2337/dc23-0675
22. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes*. Jun 2005;54(6):1763-9. doi:10.2337/diabetes.54.6.1763
23. Herold KC, Gitelman SE, Ehlers MR, et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes*. Nov 2013a;62(11):3766-74. doi:10.2337/db13-0345
24. Herold KC, Gitelman SE, Willi SM, et al. Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. *Diabetologia*. Feb 2013b;56(2):391-400. doi:10.1007/s00125-012-2753-4
25. Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. Aug 6 2011;378(9790):487-97. doi:10.1016/s0140-6736(11)60931-8
26. ClinicalTrials.gov. Protege Encore Study- Clinical Trial of Teplizumab (MGA031) in Children and Adults With Recent-Onset Type 1 Diabetes Mellitus. Updated 20 December 2023. Accessed 9 January, 2024. <https://www.clinicaltrials.gov/study/NCT00920582>
27. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. *JAMA*. Jan 28 2020;323(4):339-351. doi:10.1001/jama.2019.21565
28. Koeger M, Hummel S, Weiss A, et al. Abstract #413: Use of teplizumab to delay stage 3 type 1 diabetes: generalisability of the TN-10 trial to a European population. . 2024. IDS 2024. 4-8 November.
29. Sanofi (Data on File). *UK May 2024 Advisory Board for teplizumab in Stage 2 aT1D Final report (MAT-XU-2401585)*. 2024. *Summary Report*. Date of preparation: November 2024.
30. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. *Diabetes Care*. Jan 1 2025;48(Supplement_1):S27-s49. doi:10.2337/dc25-S002
31. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β -Cell Function in Newly Diagnosed Type 1 Diabetes. *N Engl J Med*. Oct 18 2023;doi:10.1056/NEJMoa2308743
32. Insel RA, Dunne JL, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974. doi:10.2337/dc15-1419
33. Haller MJ, Bell KJ, Besser REJ, et al. ISPAD Clinical Practice Consensus Guidelines 2024: Screening, Staging, and Strategies to Preserve Beta Cell Function in Children and Adolescents with Type 1 Diabetes. *Horm Res Paediatr*. Dec 11 2024;1-30. doi:10.1159/000543035
34. CDER Office of Clinical Pharmacology. *CLINICAL PHARMACOLOGY REVIEW(S) (761183Orig1s000)*. 2022.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000ClinPharmR.pdf
35. Herold KC, Sherry JL, Haller MJ, et al. [Data on File] Tn-10 Extension Study: Teplizumab Following Stage 3 Type 1 Diabetes Diagnosis in Participants From The Tn-10 Trial. presented at: American Diabetes Association (ADA) 85th Scientific Sessions; 2025; Chicago, IL, USA.
36. NHS Digital. *National Diabetes Audit, 2019-20 Type 1 Diabetes*. 2021. 12 August.
<https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F>

- [AC%2F6F045A%2FNDFA%25202019-20%2520Type%25201%2520Diabetes%2520Report.pptx&wdOrigin=BROWSELINK](#)
- 37.Krischer JP. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. *Diabetologia*. Sep 2013;56(9):1919-24. doi:10.1007/s00125-013-2960-7
 - 38.Long AE, Wilson IV, Becker DJ, et al. Characteristics of slow progression to diabetes in multiple islet autoantibody-positive individuals from five longitudinal cohorts: the SNAIL study. *Diabetologia*. Jun 2018;61(6):1484-1490. doi:10.1007/s00125-018-4591-5
 - 39.Hanna SJ, Powell WE, Long AE, et al. Slow progressors to type 1 diabetes lose islet autoantibodies over time, have few islet antigen-specific CD8(+) T cells and exhibit a distinct CD95(hi) B cell phenotype. *Diabetologia*. Jun 2020;63(6):1174-1185. doi:10.1007/s00125-020-05114-7
 - 40.Palmer AJ, Roze S, Valentine WJ, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin*. Aug 2004;20 Suppl 1:S27-40. doi:10.1185/030079904x2006
 - 41.Samuelsson J, Bertilsson R, Bülow E, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. *Diabetologia*. Apr 2024;67(4):679-689. doi:10.1007/s00125-024-06086-8
 - 42.Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. Aug 11 2018;392(10146):477-486. doi:10.1016/s0140-6736(18)31506-x
 - 43.Janssen MF, Pickard AS, Shaw JW. General population normative data for the EQ-5D-3L in the five largest European economies. *Eur J Health Econ*. Dec 2021;22(9):1467-1475. doi:10.1007/s10198-021-01326-9
 - 44.Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish population-based study using EQ-5D. *BMC Public Health*. Apr 22 2013;13:377. doi:10.1186/1471-2458-13-377
 - 45.Hex N, MacDonald R, Pocock J, et al. Estimation of the direct health and indirect societal costs of diabetes in the UK using a cost of illness model. *Diabet Med*. Sep 2024;41(9):e15326. doi:10.1111/dme.15326
 - 46.Ou HT, Yang CY, Wang JD, Hwang JS, Wu JS. Life Expectancy and Lifetime Health Care Expenditures for Type 1 Diabetes: A Nationwide Longitudinal Cohort of Incident Cases Followed for 14 Years. *Value Health*. Dec 2016;19(8):976-984. doi:10.1016/j.jval.2016.05.017
 - 47.Juvenile Diabetes Research Foundation (JDRF). Type 1 diabetes and complications. Accessed 4 December 2023, <https://jdrf.org.uk/knowledge-support/guide-to-type-1-complications/>
 - 48.Diabetes UK. Complications of diabetes. Accessed December 2023, <https://www.diabetes.org.uk/guide-to-diabetes/complications>
 - 49.NHS. Type 1 diabetes - Avoiding complications. Updated 9 August 2021. <https://www.nhs.uk/conditions/type-1-diabetes/living-with-type-1-diabetes/avoiding-complications/>
 - 50.Chiang JL, Kirkman MS, Laffel LM, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care*. Jul 2014;37(7):2034-54. doi:10.2337/dc14-1140
 - 51.National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013 [PMG9]*. 2013. <https://www.nice.org.uk/process/pmg9/chapter/foreword>
 - 52.ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care*. Jan 1 2023;46(Suppl 1):S19-s40. doi:10.2337/dc23-S002
 - 53.Libman I, Haynes A, Lyons S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. Dec 2022;23(8):1160-1174. doi:10.1111/pedi.13454

54. National Health Services (NHS). *National Schedule of NHS Costs 2021/22 (V3, updated 19 May 2023)*. 2023. <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>
55. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Glucose Medicinal forms. Accessed 1 November, 2024. <https://bnf.nice.org.uk/drugs/glucose/medicinal-forms/>
56. Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. *Diabetes Care*. Sep 2009;32(9):1603-7. doi:10.2337/dc08-2140
57. Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. May 30 2002;346(22):1685-91. doi:10.1056/NEJMoa012350
58. Weiss A, Zapardiel-Gonzalo J, Voss F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. *Diabetologia*. Dec 2022;65(12):2121-2131. doi:10.1007/s00125-022-05780-9
59. Daly MJ, Elvidge J, Chantler T, Dawoud D. A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for Treatments of T1DM & T2DM. *Front Pharmacol*. 2022;13:887298. doi:10.3389/fphar.2022.887298

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Clarification questions response – Appendix 1

January 2025

File name	Version	Contains confidential information	Date
ID6259 teplizumab EAG clarification response_Appendix 1_17Jan2025 [noCON]	1.0	No	17 January 2025

Appendix 1: Appended SLR Tables and RIS File

Appended SLR Tables (Question A1)

Table 1 Clinical SLR: Embase search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	insulin dependent diabetes mellitus/	140066	148755
2	exp diabetic ketoacidosis/	16943	19050
3	(diabet\$ adj3 (typ\$ 1 or typ\$ I or type1 or typei or typ\$ one)).ti,ab.	102554	108167
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or utosensit\$ or auto utose\$ or sudden onset)).ti,ab.	46036	49088
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	42931	43851
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	49987	53757
7	or/1-6	227458	240099
8	exp prevention/	1726906	1822125
9	(early detect\$ or early therap\$ or new onset or early onset).ti,ab.	234512	255180
10	(prevent or prevention or prevented or delay or delays or delayed or delaying).ti,ab.	2447492	2586716
11	(postpone\$ or prolong\$ or slow or slowdown or holdup or halt).ti,ab.	920628	967908
12	or/8-11	4655818	4925074
13	(stage 2 or stage two or stage II).ti,ab.	83401	88406
14	asymptomatic disease/	21552	23744
15	((asymptomatic or presymptomatic or "pre symptomatic" or nonsymptomatic or "non symptomatic" or inapparent or subclinical or "sub clinical" or symptomless or symptom less) adj3 (condition\$ or disease\$ or disorder\$ or state or states)).ti,ab.	23110	24178
16	high risk patient/ or high risk population/ or risk factor/	1572337	1693136
17	(high risk adj3 (group\$ or population\$ or patient\$ or subject\$)).ti,ab.	236164	252833
18	family history/	134927	145608
19	((family or familial) adj3 (history or histories or anamnesis)).ti,ab.	140397	149492
20	exp pancreas islet/ and exp autoantibody/	3610	3845
21	((islet or langerhan\$ island\$ or nesidioblast\$ or utosens\$) adj3 (utosensitiz\$ or auto antibod\$)).ti,ab.	2542	2728
22	autoimmunity/	78015	79672
23	(utosensitiz\$ or utosensiti\$ or auto utose\$ or utosensitizat\$ or utosensitization or autosensitization).ti,ab.	57119	59714
24	or/13-23	2027376	2175287
25	teplizumab/	359	454
26	(teplizumab or tzield or anti-CD3 or antcd3 or mga031 or "mga 031").ti,ab,m.	14968	15615
27	golimumab/	9820	10889
28	(golimumab or cnto 148 or cnto148 or mk 8259 or mk8259 or sch 900259 or sch900259 or shinponi or utosen).ti,ab,m.	9970	11060

29	abatacept/	12267	13383
30	(abatacept or bms 188667 or bms188667 or bms 224818 or bms224818 or belatacept or CTLA-4\$ or CTLA4\$ or cytotoxic t lymphocyte associated antigen 4 immunoglobulin\$ or lea29y or nulojix or utosen or 332348-12-6).ti,ab,mn,tn.	38238	41812
31	glutamate decarboxylase/	8950	9266
32	((glutamic or glutamate) adj3 (decarboxylase or carboxylase or carboxy lyase)).ti,ab.	10547	10905
33	(GAD alum or GADalum).ti,ab.	70	74
34	nicotinamide/	15274	16398
35	(niacinamide or nicotinamide or vitamin B3 or vitamin b 3).ti,ab,mn.	35360	37516
36	hydroxychloroquine/	44994	48593
37	(hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrochloroquine or hydroxychlorochin or oxychlorochin or oxychloroquine or plaquenil or quensyl or sn 8137 or sn8137 or tlc 19 or tlc19 or win 1258 or win1258 or 118-42-3 or 137433-23-9 or 137433-24-0 or 525-31-5).ti,ab,mn,tn.	46170	49942
38	exp insulin treatment/ or insulin pump/ or insulin infusion/ or artificial pancreas/	52788	56472
39	(insulin adj3 (therapy or therapies or therapeutics or treatment\$ or infus\$ or inject\$ or pump\$ or parenteral\$ or intravenous\$ or oral\$ or nasal\$ or intranasal\$ or deliver\$ or catheter\$)).ti,ab.	80976	84330
40	or/25-39	252437	268443
41	Randomized controlled trial/	781932	829066
42	Controlled clinical study/	469140	473450
43	random\$.ti,ab.	1959492	2084911
44	randomization/	99098	99469
45	intermethod comparison/	296743	307188
46	placebo.ti,ab.	364918	379122
47	(compare or compared or comparison).ti.	602149	8017507
48	(compare or compared or comparison).ti.	602149	2947909
49	(open adj label).ti,ab.	108471	116359
50	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	273585	283890
51	double blind procedure/	209818	220576
52	parallel group\$1.ti,ab.	32070	33769
53	(crossover or cross over).ti,ab.	124141	128948
54	((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.	413185	436140
55	(assigned or allocated).ti,ab.	486828	515459
56	(controlled adj7 (study or design or trial)).ti,ab.	448776	475361
57	(volunteer or volunteers).ti,ab.	281612	290417
58	human experiment/	647443	663161
59	trial.ti.	400946	427916
60	single arm.ti,ab.	27682	31824
61	(phase II trial\$ or phase 2 trial\$ or phase two trial\$ or phase II study or phase 2 study or phase two study or phase II studies or phase 2 studies or phase two studies).ti,ab.	75483	79693
62	(prospective trial\$ or prospective study or prospective studies).ti,ab.	342748	362178

63	or/41-62	4657381	10731467
64	(random\$ adj sampl\$ adj7 (cross section\$ or questionnaire\$1 or survey\$ or database\$1)).ti,ab. Not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. Or randomly assigned.ti,ab.)	9442	10025
65	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. Or control group\$1.ti,ab.)	345665	397200
66	((case adj control\$) and random\$) not randomi?ed controlled).ti,ab.	21501	22526
67	(Systematic review not (trial or study)).ti.	257843	289534
68	(nonrandom\$ not random\$).ti,ab.	18871	19574
69	Random field\$.ti,ab.	2943	3084
70	(random cluster adj3 sampl\$).ti,ab.	1530	1658
71	(review.ab. and review.pt.) not trial.ti.	1109855	1206412
72	'we searched'.ab. and (review.ti. or review.pt.)	49397	53435
73	'update review'.ab.	138	143
74	(databases adj4 searched).ab.	61751	69072
75	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti. and animal experiment/	1223619	1257313
76	Animal experiment/ not (human experiment/ or human/)	2570275	2644135
77	or/64-76	4313537	4562983
78	63 not 77	4152667	9396027
79	7 and (12 or 24) and 40 and 78	2012	4260
80	(case report or case study or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	1117377	1184678
81	case reports/ or case study/ or case report\$.jx. or case report\$.jw.	203877	393092
82	(News or "Newspaper Article" or Editorial or Comment or Overall or Short Survey or Tombstone or Books).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	4074953	4226925
83	or/80-82	5271707	5600685
84	79 not 83	1908	3987
85	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
86	84 not 85	1354	2681
87	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
88	limit 87 to yr="2021 -Current"	625407	1036823
89	84 and 88	71	286
90	86 or 89	1425	2967
91	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$.dc. or ("202305" or "202306" or "202307" or "202308" or "202309" or 20231\$ or 20232\$ or 20233\$ or 20234\$ or 20235\$ or 2024\$).em.	--	3605114
92	90 and 91	--	388

Trials filter based on: Technical Supplement to Chapter 4. Box 3.e Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2020 revision); Embase.com format;² Higgins 2022;¹ O'Rourke 2016.³
SLR = systematic literature review

Table 2 Clinical SLR: MEDLINE search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	exp Diabetes Mellitus, Type 1/	85824	88883
2	Diabetic Ketoacidosis/	7444	7767
3	(diabet\$ adj3 (typ\$ 1 or typ\$ I or type1 or typei or typ\$ one)).ti,ab.	63517	67851
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or utosensit\$ or auto utose\$ or sudden onset)).ti,ab.	31349	33352
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	34651	35224
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	27729	30258
7	or/1-6	149559	156548
8	Secondary Prevention/	22593	22954
9	(early detect\$ or early therap\$ or new onset or early onset).ti,ab.	151904	168038
10	(prevent or prevention or prevented or delay or delays or delayed or delaying).ti,ab.	1827818	1952744
11	(postpone\$ or prolong\$ or slow or slowdown or holdup or halt).ti,ab.	694081	733898
12	or/8-11	2569769	2742037
13	(stage 2 or stage two or stage II).ti,ab.	47694	50739
14	exp Asymptomatic Diseases/	9969	10213
15	((asymptomatic or presymptomatic or "pre symptomatic" or nonsymptomatic or "non symptomatic" or inapparent or subclinical or "sub clinical" or symptomless or symptom less) adj3 (condition\$ or disease\$ or disorder\$ or state or states)).ti,ab.	15455	16355
16	risk factors/	951206	987385
17	(high risk adj3 (group\$ or population\$ or patient\$ or subject\$)).ti,ab.	142087	154446
18	exp Genetic Predisposition to Disease/	156590	160851
19	((family or familial) adj3 (history or histories or anamnesis)).ti,ab.	77505	81951
20	Islets of Langerhans/ and exp Autoantibodies/	2122	2155
21	((islet or langerhan\$ island\$ or nesidioblast\$ or utosens\$) adj3 (utosensitiz\$ or auto antibod\$)).ti,ab.	1703	1813
22	Autoimmunity/	20299	20948
23	(utosensitiz\$ or utosensiti\$ or auto utose\$ or utosensitizat\$ or utosensitization or autosensitization).ti,ab.	40302	42399
24	or/13-23	1341333	1400853
25	(teplizumab or tziel or anti-CD3 or antcd3 or mga031 or "mga 031").ti,ab,rm.	9529	9753
26	(golimumab or cnto 148 or cnto148 or mk 8259 or mk8259 or sch 900259 or sch900259 or shinponi or utosen).ti,ab,rm.	1556	1668
27	Abatacept/	3313	3450
28	(abatacept or bms 188667 or bms188667 or bms 224818 or bms224818 or belatacept or CTLA-4\$ or CTLA4\$ or cytotoxic t lymphocyte associated antigen 4 immunoglobulin\$ or lea29y or nulojix or utosen or 332348-12-6).ti,ab,rm.	17306	18937
29	Glutamate Decarboxylase/	8709	8796
30	((glutamic or glutamate) adj3 (decarboxylase or carboxylyase or carboxy lyase)).ti,ab.	8800	9081
31	(GAD alum or GADalum).ti,ab.	45	46

32	Niacinamide/	13429	13716
33	(niacinamide or nicotinamide or vitamin B3 or vitamin b 3).ti,ab,rn.	34095	35879
34	Hydroxychloroquine/	5781	6070
35	(hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrochloroquine or hydroxychlorochin or oxychlorochin or oxychloroquine or plaquenil or quensyl or sn 8137 or sn8137 or tlc 19 or tlc19 or win 1258 or win1258 or 118-42-3 or 137433-23-9 or 137433-24-0 or 525-31-5).ti,ab,rn.	10179	10941
36	exp Insulins/ and exp Administration, Oral/	3597	3636
37	exp Insulins/ and Administration, Intranasal/	448	455
38	exp Insulins/ and exp Parenteral Nutrition/	675	678
39	Insulin Infusion Systems/	6365	6645
40	Pancreas, Artificial/	999	1042
41	(insulin adj3 (therapy or therapies or therapeutics or treatment\$ or infus\$ or inject\$ or pump\$ or parenteral\$ or intravenous\$ or oral\$ or nasal\$ or intranasal\$ or deliver\$ or catheter\$)).ti,ab.	52335	54433
42	or/25-41	140548	147464
43	randomized controlled trial.pt.	591853	615729
44	controlled clinical trial.pt.	95290	95561
45	randomized.ab.	601623	650301
46	placebo.ab.	237833	249386
47	clinical trials as topic.sh.	200961	202688
48	randomly.ab.	407340	436106
49	trial.ti.	284250	311974
50	single arm.ti,ab.	12644	15201
51	(phase II trial\$ or phase 2 trial\$ or phase two trial\$ or phase II study or phase 2 study or phase two study or phase II studies or phase 2 studies or phase two studies).ti,ab.	36964	39010
52	(prospective trial\$ or prospective study or prospective studies).ti,ab.	219458	232993
53	or/43-52	1733459	1835485
54	exp animals/ not humans.sh.	5117568	5234510
55	53 not 54	1609750	1706115
56	7 and (12 or 24) and 42 and 55	812	835
57	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	932976	995864
58	case reports/ or case study/ or case report\$.jw.	2365003	2446666
59	("Introductory Journal Article" or letter or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	4016786	4166528
60	or/57-59	6624308	6876044
61	56 not 60	783	803
62	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).ed,dt.	--	2396589
63	61 and 62	--	27

Trials filter based on: Technical Supplement to Chapter 4. Box 3.d Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format; Higgins 2022;¹ O'Rourke 2016.³
SLR = systematic literature review

Table 3 Clinical SLR: Cochrane Central Register of Controlled Trials search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	exp diabetes mellitus, type 1/	6694	7619
2	Diabetic Ketoacidosis/	210	209
3	(diabet\$ adj3 (typ\$ 1 or typ\$ I or type1 or typei or typ\$ one)).ti,ab.	9644	10568
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or utosensit\$ or auto utose\$ or sudden onset)).ti,ab.	3541	3871
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	4500	4647
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	4169	4707
7	or/1-6	18364	19865
8	secondary prevention/	3825	4055
9	(early detect\$ or early therap\$ or new onset or early onset).ti,ab.	8602	9533
10	(prevent or prevention or prevented or delay or delays or delayed or delaying).ti,ab.	177944	193943
11	(postpone\$ or prolong\$ or slow or slowdown or holdup or halt).ti,ab.	60788	66318
12	or/8-11	237554	258975
13	(stage 2 or stage two or stage II).ti,ab.	10459	11578
14	exp Asymptomatic Diseases/	301	371
15	((asymptomatic or presymptomatic or "pre symptomatic" or nonsymptomatic or "non symptomatic" or inapparent or subclinical or "sub clinical" or symptomless or symptom less) adj3 (condition\$ or disease\$ or disorder\$ or state or states)).ti,ab.	1043	1155
16	risk factors/	32655	37744
17	(high risk adj3 (group\$ or population\$ or patient\$ or subject\$)).ti,ab.	21159	23127
18	exp genetic predisposition to disease/	1592	1776
19	((family or familial) adj3 (history or histories or anamnesis)).ti,ab.	4219	4602
20	Islets of Langerhans/ and exp Autoantibodies/	61	65
21	((islet or langerhan\$ island\$ or nesidioblast\$ or utosens\$) adj3 (utosensitiz\$ or auto antibod\$)).ti,ab.	120	130
22	autoimmunity/	173	142
23	(utosensitiz\$ or utosensiti\$ or auto utose\$ or utosensitizat\$ or utosensitization or autosensitization).ti,ab.	632	683
24	or/13-23	67510	75811
25	(teplizumab or tziel or anti-CD3 or antcd3 or mga031 or "mga 031").ti,ab.	245	261
26	(golimumab or cnto 148 or cnto148 or mk 8259 or mk8259 or sch 900259 or sch900259 or shinponi or utosen).ti,ab.	747	778
27	Abatacept/	347	416
28	(abatacept or bms 188667 or bms188667 or bms 224818 or bms224818 or belatacept or CTLA-4\$ or CTLA4\$ or cytotoxic t lymphocyte associated antigen 4 immunoglobulin\$ or lea29y or nulojix or utosen or 332348-12-6).ti,ab.	1902	2070
29	Glutamate Decarboxylase/	94	106
30	((glutamic or glutamate) adj3 (decarboxylase or carboxylyase or carboxy lyase)).ti,ab.	169	183
31	(GAD alum or GADalum).ti,ab.	52	51

32	Niacinamide/	1049	1129
33	(niacinamide or nicotinamide or vitamin B3 or vitamin b 3).ti,ab.	835	968
34	Hydroxychloroquine/	711	792
35	(hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrochloroquine or hydroxychlorochin or oxychlorochin or oxychloroquine or plaquenil or quensyl or sn 8137 or sn8137 or tlc 19 or tlc19 or win 1258 or win1258 or 118-42-3 or 137433-23-9 or 137433-24-0 or 525-31-5).ti,ab.	1777	1915
36	exp Insulins/ and exp Administration, Oral/	533	596
37	exp Insulins/ and Administration, Intranasal/	103	124
38	exp Insulins/ and exp Parenteral Nutrition/	101	113
39	Insulin Infusion Systems/	824	977
40	Pancreas, Artificial/	94	110
41	(insulin adj3 (therapy or therapies or therapeutics or treatment\$ or infus\$ or inject\$ or pump\$ or parenteral\$ or intravenous\$ or oral\$ or nasal\$ or intranasal\$ or deliver\$ or catheter\$)).ti,ab.	12480	13379
42	or/25-41	19456	20940
43	7 and (12 or 24) and 42	968	1057
44	conference\$.pt.	218194	241463
45	43 not 44	801	862
46	limit 45 to yr="2021 -Current"	87	127
47	43 and 46	87	127
48	45 or 47	801	862
49	(EUCTR\$ or NCT\$ or ICTRP\$ or CTRI\$ or ISRCTN\$ or chict\$ or actrn\$ or IRCT\$ or NTR\$).tn.	503815	588697
50	(trial regist\$ or trial protocol).pt.	458095	515023
51	(clinicaltrials\$ or ictrp\$).so.	5680	5547
52	or/49-51	565660	656373
53	48 not 52	426	447
54	limit 53 to yr="2023 -Current"	--	18

SLR = systematic literature review

Table 4 Clinical SLR: CDSR search strategy (via OvidSP)

Search Number	Search Terms	Original Results: May 2, 2023	Update Search: June 27, 2024
1	(diabet\$ adj3 (typ\$ 1 or typ\$ I or type1 or typei or typ\$ one)).ti,ab,kw.	54	56
2	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or utosensit\$ or auto utose\$ or sudden onset)).ti,ab,kw.	15	18
3	((insulin\$ adj2 depend\$) or insulinindepend\$).ti,ab,kw.	50	53
4	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab,kw.	3	4
5	or/1-4	104	110
6	(early detect\$ or early therap\$ or new onset or early onset).ti,ab,kw.	106	109
7	(prevent or prevention or prevented or delay or delays or delayed or delaying).ti,ab,kw.	3604	3689
8	(postpone\$ or prolong\$ or slow or slowdown or holdup or halt).ti,ab,kw.	451	475

9	or/6-8	3916	4017
10	(stage 2 or stage two or stage II).ti,ab,kw.	43	43
11	((asymptomatic or presymptomatic or "pre symptomatic" or nonsymptomatic or "non symptomatic" or inapparent or subclinical or "sub clinical" or symptomless or symptom less) adj3 (condition\$ or disease\$ or disorder\$ or state or states)).ti,ab,kw.	22	21
12	(high risk adj3 (group\$ or population\$ or patient\$ or subject\$)).ti,ab,kw.	117	127
13	((family or familial) adj3 (history or histories or anamnesis)).ti,ab,kw.	23	22
14	((islet or langerhan\$ island\$ or nesidioblast\$ or utosens\$) adj3 (utosensitiz\$ or auto antibod\$)).ti,ab,kw.	0	0
15	(utosensitiz\$ or utosensiti\$ or auto utose\$ or utosensitizat\$ or utosensitization or autosensitization).ti,ab,kw.	5	5
16	or/10-15	204	213
17	5 and (9 or 16)	27	29
18	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).up.	--	3917
19	17 and 18	--	15

CDSR = Cochrane Database of Systematic Reviews; SLR = systematic literature review

Table 5 Economic SLR: Embase search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	insulin dependent diabetes mellitus/	140066	148755
2	exp diabetic ketoacidosis/	16943	19050
3	(diabet\$ adj3 (typ\$ 1 or typ\$ i or type1 or typei or typ\$ one)).ti,ab.	102554	108167
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or autoimmun\$ or auto immun\$ or sudden onset)).ti,ab.	46036	49088
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	42931	43851
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	49987	53757
7	(ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab.	20049	21974
8	or/1-7	232109	245141
9	teplizumab/	359	454
10	(teplizumab or tziel or anti-CD3 or anticd3 or mga031 or "mga 031").ti,ab,rn.	14968	15615
11	golimumab/	9820	10889
12	(golimumab or cnto 148 or cnto148 or mk 8259 or mk8259 or sch 900259 or sch900259 or shinponi or simponi).ti,ab,rn.	9970	11060
13	abatacept/	12267	13383
14	(abatacept or bms 188667 or bms188667 or bms 224818 or bms224818 or belatacept or CTLA-4\$ or CTLA4\$ or cytotoxic t lymphocyte associated antigen 4 immunoglobulin\$ or lea29y or nulojix or orencia or 332348-12-6).ti,ab,rn,tn.	38238	41812

15	glutamate decarboxylase/	8950	9266
16	((glutamic or glutamate) adj3 (decarboxylase or carboxylase or carboxy lyase)).ti,ab.	10547	10905
17	(GAD alum or GADalum).ti,ab.	70	74
18	nicotinamide/	15274	16398
19	(niacinamide or nicotinamide or vitamin B3 or vitamin b 3).ti,ab,rn.	35360	37516
20	hydroxychloroquine/	44994	48593
21	(hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrochloroquine or hydroxychlorochin or oxychlorochin or oxychloroquine or plaquenil or quensyl or sn 8137 or sn8137 or tlc 19 or tlc19 or win 1258 or win1258 or 118-42-3 or 137433-23-9 or 137433-24-0 or 525-31-5).ti,ab,rn,tn.	46170	49942
22	exp insulin treatment/ or insulin pump/ or insulin infusion/ or artificial pancreas/	52788	56472
23	(insulin adj3 (therapy or therapies or therapeutics or treatment\$ or infus\$ or inject\$ or pump\$ or parenteral\$ or intravenous\$ or oral\$ or nasal\$ or intranasal\$ or deliver\$ or catheter\$)).ti,ab.	80976	84330
24	or/9-23	252437	268443
25	economic evaluation/	19743	21519
26	cost utility analysis/	12191	13035
27	cost benefit analysis/	93792	97309
28	cost minimization analysis/	3976	4146
29	cost effectiveness analysis/	179702	192011
30	quality adjusted life year/	35064	37809
31	(cost\$ adj3 (utilit\$ or effective\$ or assess\$ or evaluat\$ or analys\$ or model\$ or benefit\$ or minimi\$ or threshold\$ or outcome or outcomes)).ti,ab.	338823	363809
32	(economic\$ adj3 (evaluat\$ or assess\$ or analys\$ or model\$ or benefit\$ or minimi\$ or threshold\$ or outcome or outcomes)).ti,ab.	69748	75152
33	(CEA or CUA or CBA).ti,ab.	56678	59378
34	exp Monte Carlo method/	51851	55785
35	Markov chain/	10094	11644
36	"decision tree"/	21212	24922
37	(markov adj3 (chain\$ or model\$ or economic\$)).ti,ab.	31895	33911
38	monte carlo.ti,ab.	61064	64533
39	(decision adj2 (tree\$ or analy\$ or model\$)).ti,ab.	47806	54506
40	statistical model/	173942	177813
41	statistical model\$.ti,ab.	24397	25784
42	((incremental adj2 cost\$) or icer).ti,ab.	30410	32552
43	(quality adjusted life\$ or QALY\$).ti,ab.	32830	35091
44	or/25-43	852749	906905
45	8 and 24 and 44	1199	1285
46	exp *health care cost/	75344	78541
47	*health care utilization/	25372	27637
48	**"cost"/	14221	14537

49	(econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti. or (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ab. /freq=3	385452	408488
50	((healthcare or health care or health resource or medical resource) adj3 ("use" or utili?ation)).ti. or ((healthcare or health care or health resource or medical resource) adj3 ("use" or utili?ation)).ab. /freq=2	25563	27801
51	(HCRU or MRU).ti. or (HCRU or MRU).ab. /freq=2	2111	2641
52	((economic or health\$ or resource) adj3 burden).ti. or ((economic or health\$ or resource) adj3 burden).ab. /freq=2	12587	13886
53	(expenditure\$ not energy).ti. or (expenditure\$ not energy).ab. /freq=2	18532	19620
54	(value adj2 money).ti. or (value adj2 money).ab. /freq=2	646	666
55	budget\$.ti. or budget\$.ab. /freq=2	16455	17368
56	or/46-55	472838	500754
57	((metabolic adj cost) or (energy adj cost) or (energy adj expenditure)).ti,ab.	42142	43965
58	56 not 57	469788	497566
59	8 and 58	2669	2862
60	limit 59 to (english language and yr="2013 -Current")	1722	1909
61	quality adjusted life year/	35064	37809
62	(quality adjusted or adjusted life year\$).ti,ab.	33803	36762
63	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab.	26681	28655
64	(illness state\$1 or health state\$1).ti,ab.	14503	15477
65	(hui or hui1 or hui2 or hui3).ti,ab.	3050	3348
66	(multiattribute\$ or multi attribute\$).ti,ab.	1490	1605
67	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab.	31068	33434
68	utilities.ti,ab.	14907	15865
69	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab.	30742	33763
70	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab.	8952	9672
71	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab.	45221	47290
72	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab.	3484	3708
73	or/61-72	151952	163144
74	8 and 73	1236	1358
75	limit 74 to (english language and yr="2013 -Current")	834	954
76	45 or 60 or 75	3086	3400
77	animal/ or animal experiment/	4640727	4819669
78	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.	7603288	7872744
79	77 or 78	7603288	7872744

80	exp human/ or human experiment/	25405238	26718992
81	79 not (79 and 80)	5708765	5866509
82	76 not 81	3032	3342
83	(case report or case study or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	1117377	1184678
84	case reports/ or case study/ or case report\$.jx. or case report\$.jw.	203877	393092
85	(news or "newspaper article" or editorial or comment or letter or overall or short survey or tombstone or books).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	5291375	5466298
86	or/83-85	6454829	6790415
87	82 not 86	2851	3137
88	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
89	87 not 88	1823	1991
90	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
91	limit 90 to yr="2021 -Current"	625407	1036823
92	87 and 91	161	273
93	89 or 92	1984	2264
94	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).dc. or ("202305" or "202306" or "202307" or "202309" or 20231\$ or 20232\$ or 20233\$ or 20234\$ or 20235\$ or 2024\$).em.	--	3603470
95	93 and 94	--	519

Utilities filter based on: Arber 2017.¹⁰

SLR = systematic literature review

Table 6 Economic SLR: MEDLINE search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	exp Diabetes Mellitus, Type 1/	85824	88883
2	Diabetic Ketoacidosis/	7444	7767
3	(diabet\$ adj3 (typ\$ 1 or typ\$ i or type1 or typei or typ\$ one)).ti,ab.	63517	67851
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or autoimmun\$ or auto immun\$ or sudden onset)).ti,ab.	31349	33352
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	34651	35224
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	27729	30258
7	(ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab.	13154	14283
8	or/1-7	153165	160427
9	(teplizumab or tziel or anti-CD3 or anticd3 or mga031 or "mga 031").ti,ab,rm.	9529	9753

10	(golimumab or cnto 148 or cnto148 or mk 8259 or mk8259 or sch 900259 or sch900259 or shinponi or simponi).ti,ab,rn.	1556	1668
11	Abatacept/	3313	3450
12	(abatacept or bms 188667 or bms188667 or bms 224818 or bms224818 or belatacept or CTLA-4\$ or CTLA4\$ or cytotoxic t lymphocyte associated antigen 4 immunoglobulin\$ or lea29y or nulojix or orencia or 332348-12-6).ti,ab,rn.	17306	18937
13	Glutamate Decarboxylase/	8709	8796
14	((glutamic or glutamate) adj3 (decarboxylase or carboxylase or carboxylase)).ti,ab.	8800	9081
15	(GAD alum or GADalum).ti,ab.	45	46
16	Niacinamide/	13429	13716
17	(niacinamide or nicotinamide or vitamin B3 or vitamin b 3).ti,ab,rn.	34095	35879
18	Hydroxychloroquine/	5781	6070
19	(hydroxychloroquine or chloroquinol or ercoquin or hydrochloroquine or hydrochloroquine or hydroxychlorochin or oxychlorochin or oxychloroquine or plaquenil or quensyl or sn 8137 or sn8137 or tlc 19 or tlc19 or win 1258 or win1258 or 118-42-3 or 137433-23-9 or 137433-24-0 or 525-31-5).ti,ab,rn.	10179	10941
20	exp Insulins/ and exp Administration, Oral/	3597	3636
21	exp Insulins/ and Administration, Intranasal/	448	455
22	exp Insulins/ and exp Parenteral Nutrition/	675	678
23	Insulin Infusion Systems/	6365	6645
24	Pancreas, Artificial/	999	1042
25	(insulin adj3 (therapy or therapies or therapeutics or treatment\$ or infus\$ or inject\$ or pump\$ or parenteral\$ or intravenous\$ or oral\$ or nasal\$ or intranasal\$ or deliver\$ or catheter\$)).ti,ab.	52335	54433
26	or/9-25	140548	147464
27	Cost-Benefit Analysis/	92238	95001
28	disability-adjusted life years/ or quality-adjusted life years/	15683	16733
29	(cost\$ adj3 (utilit\$ or effective\$ or assess\$ or evaluat\$ or analys\$ or model\$ or benefit\$ or minimi\$ or threshold\$ or outcome or outcomes)).ti,ab.	241830	265409
30	(economic\$ adj3 (evaluat\$ or assess\$ or analys\$ or model\$ or benefit\$ or minimi\$ or threshold\$ or outcome or outcomes)).ti,ab.	49344	54391
31	(CEA or CUA or CBA).ti,ab.	38797	40675
32	monte carlo method/	32103	32998
33	markov chains/	15939	16237
34	Decision Trees/	12071	12252
35	(markov adj3 (chain\$ or model\$ or economic\$)).ti,ab.	23054	24949
36	monte carlo.ti,ab.	57973	61792
37	(decision adj2 (tree\$ or analy\$ or model\$)).ti,ab.	34460	40879
38	exp models, statistical/	450227	458514
39	statistical model\$.ti,ab.	20142	21697
40	((incremental adj2 cost\$) or icer).ti,ab.	17490	19148
41	(quality adjusted life\$ or QALY\$).ti,ab.	19038	20838
42	or/27-41	887488	935168

43	8 and 26 and 42	635	666
44	exp *Health Care Costs/	32185	32578
45	**costs and cost analysis"/ or exp **cost control"/ or exp **cost of illness"/ or exp *health expenditures/	40097	41014
46	(econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti. or (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ab. /freq=3	284962	306751
47	((healthcare or health care or health resource or medical resource) adj3 ("use" or utili?ation)).ti. or ((healthcare or health care or health resource or medical resource) adj3 ("use" or utili?ation)).ab. /freq=2	16103	17995
48	(HCRU or MRU).ti. or (HCRU or MRU).ab. /freq=2	792	1009
49	((economic or health\$ or resource) adj3 burden).ti. or ((economic or health\$ or resource) adj3 burden).ab. /freq=2	7366	8397
50	(expenditure\$ not energy).ti. or (expenditure\$ not energy).ab. /freq=2	14118	15111
51	(value adj2 money).ti. or (value adj2 money).ab. /freq=2	518	549
52	budget\$.ti. or budget\$.ab. /freq=2	12135	12849
53	or/44-52	340548	365741
54	((metabolic adj cost) or (energy adj cost) or (energy adj expenditure)).ti,ab.	33507	35186
55	53 not 54	337725	362761
56	8 and 55	1470	1573
57	limit 56 to yr="2013 -Current"	815	918
58	quality-adjusted life years/	15585	16520
59	(quality adjusted or adjusted life year\$).ti,ab.	22626	25368
60	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab.	14097	15497
61	(illness state\$1 or health state\$1).ti,ab.	8196	8826
62	(hui or hui1 or hui2 or hui3).ti,ab.	1929	2095
63	(multiattribute\$ or multi attribute\$).ti,ab.	1239	1411
64	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab.	19408	21220
65	utilities.ti,ab.	9135	9915
66	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab.	16797	18992
67	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab.	5805	6489
68	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab.	26029	27623
69	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab.	2320	2479
70	or/58-69	91402	100100
71	8 and 70	603	668
72	limit 71 to yr="2013 -Current"	369	434
73	43 or 56 or 72	2111	2261
74	exp animals/ not humans/	5117568	5234510
75	73 not 74	2073	2222

76	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	932976	995864
77	case reports/ or case study/ or case report\$.jw.	2365003	2446666
78	("Introductory Journal Article" or letter or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	4016786	4166528
79	or/76-78	6624308	6876044
80	75 not 79	1956	2102
81	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).ed,dt.	--	2396589
82	80 and 81	--	185

Utilities filter based on: Arber 2017.¹⁰

SLR = systematic literature review

Table 7 Economic SLR: EconLit search strategy

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	(diabet\$ adj3 (typ\$ 1 or typ\$ i or type1 or typei or typ\$ one)).ti,ab.	31	35
2	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or autoimmun\$ or auto immun\$ or sudden onset)).ti,ab.	10	10
3	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	10	11
4	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	15	16
5	(ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab.	0	0
6	1 or 2 or 3 or 4 or 5	53	58
7	limit 6 to yr="2013-current"	37	42
8	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).up.	--	87366
9	7 and 8	--	5

SLR = systematic literature review

Table 8 HRQoL SLR: Embase search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	insulin dependent diabetes mellitus/	140066	148755
2	exp diabetic ketoacidosis/	16943	19050
3	(diabet\$ adj3 (typ\$ 1 or typ\$ i or type1 or typei or typ\$ one)).ti,ab.	102554	108167
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or autoimmun\$ or auto immun\$ or sudden onset)).ti,ab.	46036	49088

5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	42931	43851
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	49987	53757
7	(ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab.	20049	21974
8	or/1-7	232109	245141
9	*productivity/	9818	10440
10	*absenteeism/	5856	5929
11	*caregiver burden/	4320	4573
12	*caregiver/	30217	33014
13	*work disability/	2145	2182
14	**quality of life"/	138747	146721
15	*patient satisfaction/ or *satisfaction/ or *life satisfaction/ or *patient preference/ or *daily life activity/	69406	72368
16	*patient-reported outcome/	16992	19154
17	(quality of life or life quality or qol or hrqol or activities of daily living).ti. or (quality of life or life quality or qol or hrqol or activities of daily living).ab. /freq=2	291179	313342
18	(patient satisfaction or life satisfaction).ti. or (patient satisfaction or life satisfaction).ab. /freq=2	30886	33038
19	(patient reported outcome\$ or patient reported treatment or self reported outcome\$ or PROs or PROMs).ti. or (patient reported outcome\$ or patient reported treatment or self reported outcome\$ or PROs or PROMs).ab. /freq=2	34389	39062
20	((human\$ or social\$ or societ\$ or work\$ or employee\$ or business\$ or communit\$ or famil\$ or carer\$ or caregiver\$) adj3 (burden\$ or consequenc\$ or impact\$ or problem\$ or productivity or sickness or impairment\$)).ti. or ((human\$ or social\$ or societ\$ or work\$ or employee\$ or business\$ or communit\$ or famil\$ or carer\$ or caregiver\$) adj3 (burden\$ or consequenc\$ or impact\$ or problem\$ or productivity or sickness or impairment\$)).ab. /freq=2	51858	56081
21	((long standing or longstanding or long term or longterm or permanent or employee\$) adj2 (absence\$ or absent\$ or ill\$ or sick\$ or disab\$)).ti. or ((long standing or longstanding or long term or longterm or permanent or employee\$) adj2 (absence\$ or absent\$ or ill\$ or sick\$ or disab\$)).ab. /freq=2	3700	3833
22	((lshi or ((emergenc\$ or domestic\$ or famil\$ or carer\$ or caregiver\$) adj3 leave\$)).ti. or ((lshi or ((emergenc\$ or domestic\$ or famil\$ or carer\$ or caregiver\$) adj3 leave\$)).ab. /freq=2	421	455
23	(burden adj2 (illness\$ or disease\$ or sickness\$)).ti. or (burden adj2 (illness\$ or disease\$ or sickness\$)).ab. /freq=2	14371	16248
24	((allowance or status or long-term or pension\$ or benefit\$) adj2 (disab\$ or incapacit\$)).ti. or ((allowance or status or long-term or pension\$ or benefit\$) adj2 (disab\$ or incapacit\$)).ab. /freq=2	4995	5269
25	((unable or inability or incapacit\$ or incapab\$) adj3 work).ti. or ((unable or inability or incapacit\$ or incapab\$) adj3 work).ab. /freq=2	732	769
26	((resource\$ or fund\$) adj2 (use\$ or utili?ation)).ti. or ((resource\$ or fund\$) adj2 (use\$ or utili?ation)).ab. /freq=2	17935	19395
27	((health or healthcare) adj2 (resource\$ or fund\$)).ti. or ((health or healthcare) adj2 (resource\$ or fund\$)).ab. /freq=2	13899	15250
28	("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ti. or ("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ab. /freq=2	46813	50310
29	((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention\$ or trip or trips or visit\$ or stay\$ or admission\$ or admitted	105394	113102

	or transport\$)).ti. or ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention\$ or trip or trips or visit\$ or stay\$ or admission\$ or admitted or transport\$)).ab. /freq=2		
30	((GP or general practitioner\$ or doctor\$ or clinician\$ or specialist\$ or physician\$) adj2 (appointment\$ or attention\$ or trip or trips or visit\$)).ti. or ((GP or general practitioner\$ or doctor\$ or clinician\$ or specialist\$ or physician\$) adj2 (appointment\$ or attention\$ or trip or trips or visit\$)).ab. /freq=2	5233	5513
31	(in-patient stay\$ or inpatient stay\$).ti. or (in-patient stay\$ or inpatient stay\$).ab. /freq=2	1245	1337
32	or/9-31	685246	736449
33	8 and 32	5689	6175
34	Clinical study/	162896	167076
35	Case control study/	205319	219284
36	Family study/	25778	25837
37	Longitudinal study/	192760	215999
38	Retrospective study/	1457809	1640877
39	Prospective study/	871966	924325
40	Randomized controlled trials/	258768	276345
41	39 not 40	861109	913022
42	Cohort analysis/	1027447	1183307
43	(Cohort adj (study or studies)).mp.	474719	522658
44	(Case control adj (study or studies)).tw.	168437	176991
45	(follow up adj (study or studies)).tw.	73626	76476
46	(observational adj (study or studies)).tw.	252477	279336
47	(epidemiologic\$ adj (study or studies)).tw.	122358	126249
48	(cross sectional adj (study or studies)).tw.	335925	377345
49	or/34-38,41-48	3896280	4274298
50	33 and 49	1795	2009
51	animal/ or animal experiment/	4640727	4819669
52	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.	7603288	7872744
53	51 or 52	7603288	7872744
54	exp human/ or human experiment/	25405238	26718992
55	53 not (53 and 54)	5708765	5866509
56	50 not 55	1788	2002
57	(case report or case study or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	1117377	1184678
58	case reports/ or case study/ or case report\$.jx. or case report\$.jw.	203877	393092
59	(news or "newspaper article" or editorial or comment or letter or overall or short survey or tombstone or books).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	5291375	5466298
60	or/57-59	6454829	6790415
61	56 not 60	1738	1946
62	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
63	61 not 62	1102	1209

64	("conference abstract" or "conference review" or "conference paper").pt. or conference\$.so,st.	5562908	6020150
65	limit 64 to yr="2021 -Current"	625407	1036823
66	61 and 65	144	236
67	63 or 66	1246	1445
68	limit 67 to yr="2013 -Current"	1018	1218
69	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).dc. or ("202305" or "202306" or "202307" or "202309" or 20231\$ or 20232\$ or 20233\$ or 20234\$ or 20235\$ or 2024\$).em.	--	3603470
70	68 and 69	--	357

Observational studies filter: Scottish Intercollegiate Guidelines Network 2023.³⁰

HRQoL = health-related quality of life; SLR = systematic literature review

Table 9 HRQoL SLR: MEDLINE search strategy (via OvidSP)

Search Number	Search Terms	Original Search Results: May 2, 2023	Update Search: June 27, 2024
1	exp Diabetes Mellitus, Type 1/	85824	88883
2	Diabetic Ketoacidosis/	7444	7767
3	(diabet\$ adj3 (typ\$ 1 or typ\$ i or type1 or typei or typ\$ one)).ti,ab.	63517	67851
4	(diabet\$ adj3 (britt\$ or juvenil\$ or pediatric or paediatric or early or keto\$ or labil\$ or acidosis\$ or autoimmune\$ or auto immun\$ or sudden onset)).ti,ab.	31349	33352
5	((insulin\$ adj2 depend\$) or insulindepend\$).ti,ab.	34651	35224
6	(dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ti,ab.	27729	30258
7	(ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis).ti,ab.	13154	14283
8	or/1-7	153165	160427
9	*absenteeism/	4450	4515
10	*caregivers/	31833	33735
11	**"Quality of Life"/	111551	118442
12	*personal satisfaction/ or exp *Patient Satisfaction/ or **Activities of Daily Living"/	72144	73931
13	*patient reported outcome measures/	5577	6055
14	(quality of life or life quality or qol or hrqol or activities of daily living).ti. or (quality of life or life quality or qol or hrqol or activities of daily living).ab. /freq=2	180410	198982
15	(patient satisfaction or life satisfaction).ti. or (patient satisfaction or life satisfaction).ab. /freq=2	22318	24493
16	(patient reported outcome\$ or patient reported treatment or self reported outcome\$ or PROs or PROMs).ti. or (patient reported outcome\$ or patient reported treatment or self reported outcome\$ or PROs or PROMs).ab. /freq=2	20399	24322
17	((human\$ or social\$ or societ\$ or work\$ or employee\$ or business\$ or communit\$ or famil\$ or carer\$ or caregiver\$) adj3 (burden\$ or consequenc\$ or impact\$ or problem\$ or productivity or sickness or impairment\$)).ti. or ((human\$ or social\$ or societ\$ or work\$ or employee\$ or business\$ or communit\$ or famil\$ or carer\$ or caregiver\$) adj3	39926	43841

	(burden\$ or consequenc\$ or impact\$ or problem\$ or productivity or sickness or impairment\$)).ab. /freq=2		
18	((long standing or longstanding or long term or longterm or permanent or employee\$) adj2 (absence\$ or absent\$ or ill\$ or sick\$ or disab\$)).ti. or ((long standing or longstanding or long term or longterm or permanent or employee\$) adj2 (absence\$ or absent\$ or ill\$ or sick\$ or disab\$)).ab. /freq=2	2934	3064
19	(lksi or ((emergenc\$ or domestic\$ or famil\$ or carer\$ or caregiver\$) adj3 leave\$)).ti. or (lksi or ((emergenc\$ or domestic\$ or famil\$ or carer\$ or caregiver\$) adj3 leave\$)).ab. /freq=2	382	419
20	(burden adj2 (illness\$ or disease\$ or sickness\$)).ti. or (burden adj2 (illness\$ or disease\$ or sickness\$)).ab. /freq=2	9057	10653
21	((allowance or status or long-term or pension\$ or benefit\$) adj2 (disab\$ or incapacit\$)).ti. or ((allowance or status or long-term or pension\$ or benefit\$) adj2 (disab\$ or incapacit\$)).ab. /freq=2	3548	3818
22	((unable or inability or incapacit\$ or incapab\$) adj3 work).ti. or ((unable or inability or incapacit\$ or incapab\$) adj3 work).ab. /freq=2	584	607
23	((resource\$ or fund\$) adj2 (use\$ or utili?ation)).ti. or ((resource\$ or fund\$) adj2 (use\$ or utili?ation)).ab. /freq=2	10103	11114
24	((health or healthcare) adj2 (resource\$ or fund\$)).ti. or ((health or healthcare) adj2 (resource\$ or fund\$)).ab. /freq=2	8956	9885
25	("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ti. or ("length of stay" or "duration of stay" or "extended stay" or "prolonged stay").ab. /freq=2	24695	27043
26	((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention\$ or trip or trips or visit\$ or stay\$ or admission\$ or admitted or transport\$)).ti. or ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention\$ or trip or trips or visit\$ or stay\$ or admission\$ or admitted or transport\$)).ab. /freq=2	64376	70110
27	((GP or general practitioner\$ or doctor\$ or clinician\$ or specialist\$ or physician\$) adj2 (appointment\$ or attention\$ or trip or trips or visit\$)).ti. or ((GP or general practitioner\$ or doctor\$ or clinician\$ or specialist\$ or physician\$) adj2 (appointment\$ or attention\$ or trip or trips or visit\$)).ab. /freq=2	3447	3642
28	(in-patient stay\$ or inpatient stay\$).ti. or (in-patient stay\$ or inpatient stay\$).ab. /freq=2	625	677
29	or/9-28	481689	524904
30	Epidemiologic studies/	9310	9557
31	exp case control studies/	1411436	1515809
32	exp cohort studies/	2475312	2620700
33	Case control.tw.	152380	163095
34	(cohort adj (study or studies)).tw.	309679	355645
35	Cohort analy\$.tw.	11565	13197
36	(Follow up adj (study or studies)).tw.	55890	58385
37	(observational adj (study or studies)).tw.	157956	180207
38	Longitudinal.tw.	317812	348353
39	Retrospective.tw.	731756	820463
40	Cross sectional.tw.	503250	568346
41	Cross-sectional studies/	464714	506455
42	or/30-41	3752688	4027383
43	8 and 29 and 42	1264	1375
44	exp animals/ not humans/	5117568	5234510

45	43 not 44	1262	1373
46	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	932976	995864
47	case reports/ or case study/ or case report\$.jw.	2365003	2446666
48	("Introductory Journal Article" or letter or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	4016786	4166528
49	or/46-48	6624308	6876044
50	45 not 49	1228	1338
51	limit 50 to yr="2013 -Current"	804	914
52	(202302\$ or 202303\$ or 202304\$ or 202305\$ or 202306\$ or 202307\$ or 202308\$ or 202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$).ed,dt.	--	2396589
53	51 and 52	--	139

Observational studies filter: Scottish Intercollegiate Guidelines Network 2023.³⁰

HRQoL = health-related quality of life; SLR = systematic literature review

RIS file of Requested Update to Cost Searches (Question A5)



Embase Economic
Searches No Frequen

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Teplizumab for delaying the onset of stage 3
type 1 diabetes in people 8 years and over with
stage 2 type 1 diabetes [ID6259]**

Clarification questions response – Appendix 2

January 2025

File name	Version	Contains confidential information	Date
ID6259 teplizumab EAG clarification response_Appendix 2_17Jan2025 [noCON]	1.0	No	17 January 2025

Appendix 2 : Updated model results

Base case results

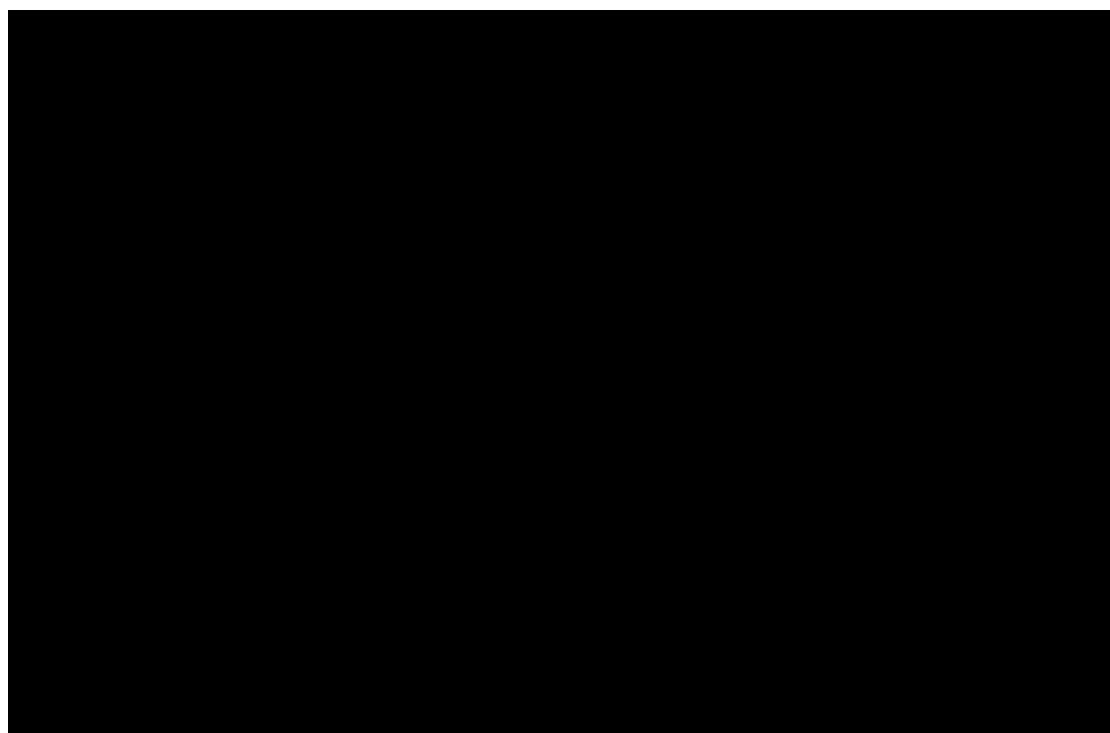
Table 1. Summary of base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
Established clinical management								
Teplizumab							–	£27,534
Probabilistic results								
Established clinical management								
Teplizumab							–	£29,488

ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Probabilistic sensitivity analysis

Figure 1. PSA convergence



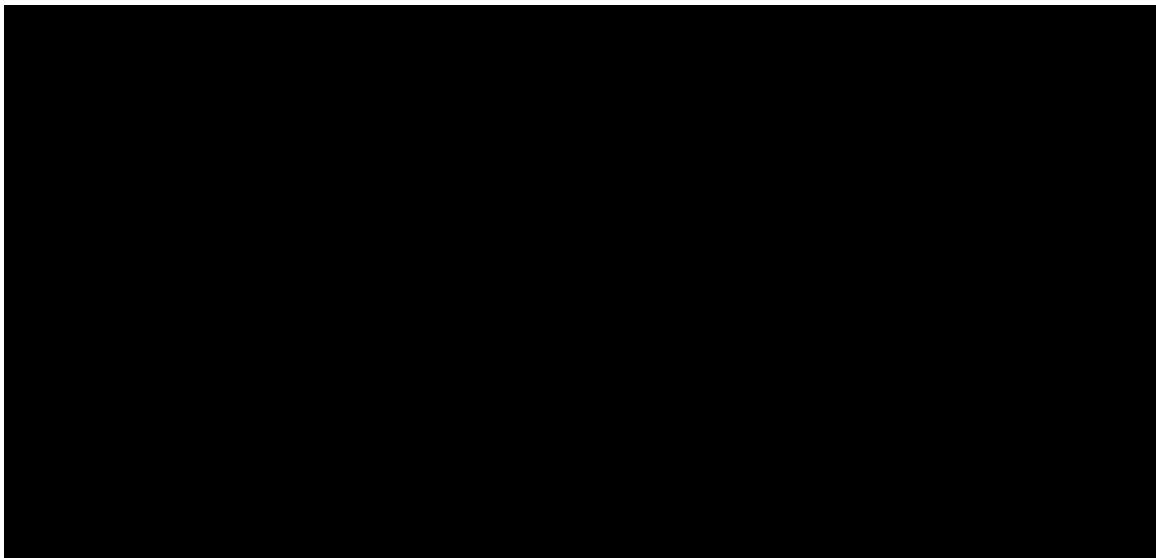
ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis

Figure 2. PSA Scatter plot (teplizumab cost-effective in 49% of replications)



PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

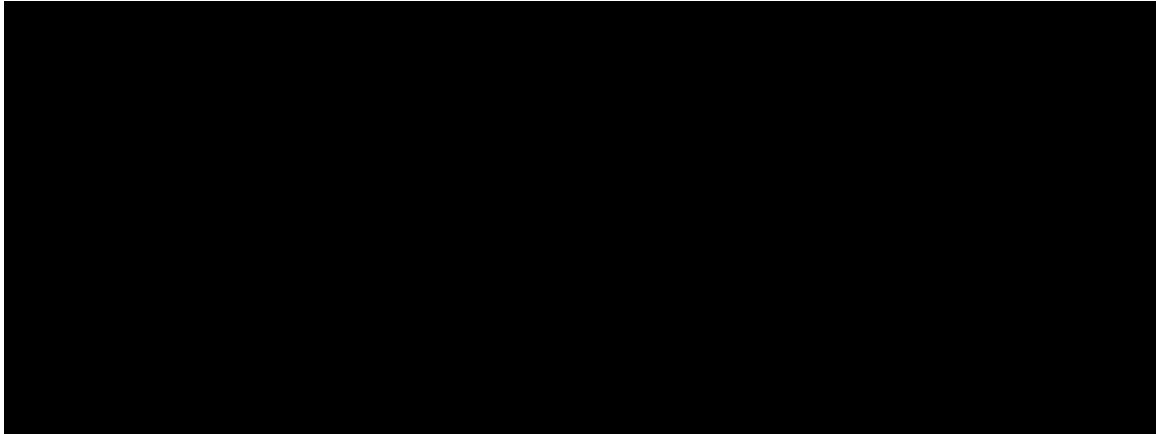
Figure 3. CEAC



QALY = quality-adjusted life year

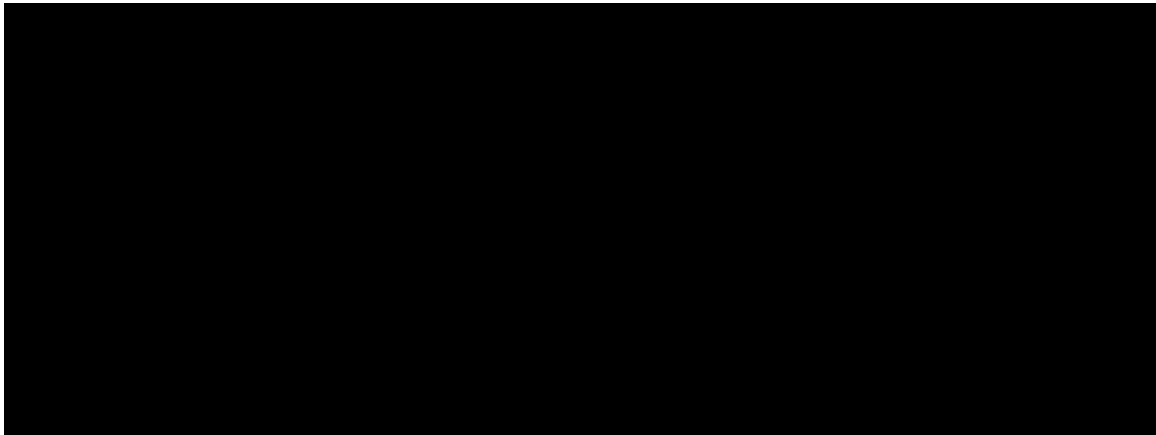
Deterministic sensitivity analysis

Figure 4. Incremental Costs



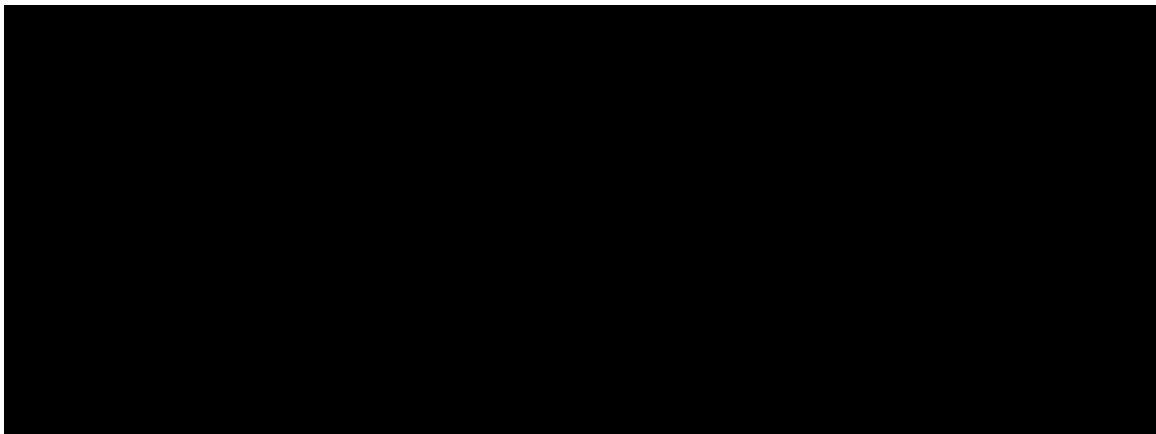
AE = adverse event; T1D = type 1 diabetes

Figure 5. Incremental QALYs



AE = adverse event; QALY = quality-adjusted life year; T1D = type 1 diabetes

Figure 6. ICER



ICER = incremental cost-effectiveness ratio; T1D = type 1 diabetes

Scenarios

Table 2. Summary of model results by scenarios

	Scenario description	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base case
0	Base case	██████	████	£29,488	NA
1	30% of individuals receive treatment at a hospital (increased from 10% in base case)	██████	████	£29,783	1.0%
2	No closer-to-home administration which assumes 100% of individuals receive all 14 days of treatment in hospital <i>In practice (and in the base case), a proportion of individuals were expected to use the closer-to-home option.</i>	██████	████	£30,813	4.5%
3	Stage 3 T1D excess risk of death informed by Rawshani et al. (2018), testing more granularity when defining the impact of age of onset of Stage 3 T1D on survival <i>The base case uses a more recent data source.</i>	██████	████	£30,405	3.1%
4	UK life tables from pre-COVID years (2017-2018). <i>The life tables used in the base case (2020-2022) include effects of COVID in overall survival, hence why the scenario tests an earlier data source.</i>	██████	████	£29,307	-0.6%
5	Maximum time to Stage 3 T1D onset for established clinical management set to 10 years <i>A maximum number of years was not set in the base case.</i>	██████	████	£25,422	-13.8%
6	Maximum time to Stage 3 T1D onset for established clinical management set to 15 years <i>A maximum number of years was not set in the base case.</i>	██████	████	£28,607	-3.0%

	Scenario description	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base case
7	Discount rates for both cost and health benefits set to 1.5% <i>The base case uses a discount rate of 3.5%, per NICE guidance</i>	■	■	£401	-98.6%
8	Disutilities associated with Stage 3 T1D based on a multiplicative approach <i>The base case uses an additive approach</i>	■	■	£30,023	1.8%

COVID-19 = Coronavirus disease 2019; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life year; T1D = type 1 diabetes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Clarification questions addendum

January 2025

File name	Version	Contains confidential information	Date
ID6259 teplizumab EAG clarification addendum to company 30012025 [CON]	1.0	Yes	30 January 2025

Clarification questions addendum

B3 follow-up question 1: Please include in the model the costing of the three elements of ECM (routine monitoring of blood glucose, psychosocial support and education on the management of T1D).

Please see Section B.3.5.2.1 of the company submission (CS). These costs are already included in the model in aggregate (annualised [Table 44] & converted to a monthly cost [Table 45]).

B3 follow-up question 2: The comparator in the TN-10 trial was placebo (saline) administered via IV infusion for 14-days in the outpatient setting. Please provide estimates of ECM treatment effect compared to placebo and include these in the economic model.

Subjects in TN-10 received either teplizumab + close monitoring for Stage 3 type 1 diabetes (T1D) development or placebo + close monitoring for Stage 3 T1D development; background care for both arms was the same (1). Close monitoring in TN-10 consisted of metabolic monitoring with a scheduled oral glucose tolerance test (OGTT) every 6 months and an additional random glucose measurement scheduled every 3 months with a reflex to OGTT should the glucose level be abnormal. Participants were educated about the symptoms associated with Stage 3 T1D at each visit and via routine contact in between visits.

ECM as described in the submission and included in the economic model can therefore be considered comparable to close monitoring per the clinical trial, TN-10.

B17 follow-up question 1: Please provide an estimate (citing the appropriate sources) of the number of individuals that would be screened/tested to find one individual eligible for treatment with teplizumab or ECM, using the methods reported for patients identified in the UK NHS (i.e. 'family screening' and 'autoimmune screening'), as reported in Swaby 2024 (cited in response to clarification as evidence that patients are currently identified in the UK NHS).

Please refer to the company response to the EAG clarification questions A6 and B17. For the reasons previously outlined, the inclusion of screening or a testing programme for pre-symptomatic T1D, although important, is outside of the scope of this appraisal. Therefore, Sanofi have not provided an estimate of the number of individuals that would be screened/tested to find one individual eligible for treatment with teplizumab or ECM.

In addition, although screening or testing is a common component of the care pathway, its inclusion would have a neutral effect on the cost-effectiveness assessment, as it would introduce equivalent costs to both arms of the cost effectiveness model.

B17 follow-up question 2: Please provide a cost estimate (citing the appropriate sources) of the screening/testing needed to find patients eligible for treatment with teplizumab or ECM.

Estimating the cost of identifying people with Stage 2 T1D via screening or testing is not appropriate in this context. Screening/testing applies earlier in the care pathway and to a broader population than considered in this technology appraisal. Sanofi re-emphasise that evaluating screening falls under the remit of the National Screening Committee (NSC). For any meaningful assessment, it would be essential to characterise key parameters including consideration of who should be screened/tested, the frequency of screening/testing, the accuracy of testing itself, and the appropriate healthcare setting.

Each of these factors would significantly influence the number of individuals screened/tested, the rate of positive tests, and the associated cost profiles. Furthermore, as noted in reply to B17 follow-up question 1, as any costs would apply equally to both arms of the cost-effectiveness assessment, their inclusion would have a neutral effect and would introduce unnecessary complexity in the assessment.

References

1. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. Aug 15 2019;381(7):603-613. doi:10.1056/NEJMoa1902226

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

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	Breakthrough T1D UK (formerly JDRF UK)
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breakthrough T1D is the leading global type 1 diabetes (T1D) research and advocacy charity. The charity is funded by supporters, corporate partnerships and foundations. We are part of a global organisation that invests in type 1 diabetes research.
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.	Sanofi, £22.5k for market research on type 1 diabetes and ageing and disease awareness work.

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?	Evidence from people living with type 1 diabetes. Evidence from those who have taken part in trials for the drug, as well as published research studies.

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?	Type 1 diabetes is complex and at times an all-encompassing condition. Those living with the condition report that it feels like a full-time job that they cannot ever quit, where every small decision can have a dramatic effect on their blood glucose levels. Indeed, there are over forty variables that can impact blood glucose and someone with the condition must be conscious of every single one day in, day out. For people living with type 1 diabetes, everything they do and everywhere they go their diabetes goes with them. The ever-present nature of the condition makes managing it exhausting and many will experience several episodes of burnout during their lifetime. Instances of depression, prolonged feelings of health anxiety and frustration are incredibly common. These feelings are often compounded by the knowledge that a diagnosis of type one diabetes puts you at elevated risk of a host of other complications. Often overlooked is the impact type 1 diabetes can have on the loved ones, particularly if they are partly or wholly responsible for managing the condition as parents of children with type 1 often are. The unpredictability of the condition can mean that the amount of support needed day to day can change radically which can be a very stressful experience. Carers must be as knowledgeable about the condition as the person they are caring for, knowing about carb counting, watching for signs of low blood glucose and knowing how to inject insulin. Both for the person with the condition and for those around them with a caring responsibility, type 1 diabetes is a distressing and isolating condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Technological progress in the realm of diabetes care has been staggering. Moving from finger prick tests to continuous glucose monitors and now with the increasing adoption of hybrid closed loop systems (HCL), managing diabetes is getting more convenient and allows those living with the condition to make more informed choices about their care. HCL in particular has been revolutionary, with surveys finding that they significantly improve management as well as alleviating some of the burden associated with the condition. They can also relieve pressure from a carer, helping to take away some of the strain of constantly having to be on top of someone else's type 1 diabetes. However, access to technology is still inequitable and there are profound inequalities with who gets told about new technologies, let alone offered them. As part of research conducted for Breakthrough T1D's 2024 access for all report, it was found that only 25% of respondents were aware of HCL and that those from lower socio-economic backgrounds or over the age of 65 were the least likely to have heard about HCL. Unfortunately, some of the people who would benefit most from new treatments are those who are least likely to have access to them. Currently, there is no treatment available on the NHS that can delay the onset of stage three type 1 diabetes.
8. Is there an unmet need for patients with this condition?	Currently, there is no treatment available on the NHS that can delay the onset of stage three type 1 diabetes. Teplizumab can delay the onset of stage 3 type 1 diabetes, leading to fewer acute complications and prolonged freedom from the burdens of managing type 1 diabetes with insulin.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Teplizumab has been shown to delay the development of type 1 in at-risk individuals by an average of three years. This is clinically significant as delaying the onset of symptoms offers patients reduced insulin usage, fewer hospital visits, fewer long-term complications, better long-term glucose control and an extended time to learn the essential skills needed to manage diabetes e.g. carb counting. The additional symptom-free years granted through the use of teplizumab are a lifeline, offering more time free from the burden of constantly managing diabetes. For children in the early stage of type 1 who are approaching adolescence, delaying type 1 would enable the pancreas to grow to adult size, giving better disease outcomes. Any time period that a person does not have to be dependent on insulin means they are avoiding important risks such as hypoglycaemia and the significant constant burdens of life with type 1. This can also play a key role in preventing complications such as eye, kidney, and heart diseases. Teplizumab can also help prevent traumatic and potentially fatal diabetic ketoacidosis (DKA) in individuals in the early stage of type 1. DKA is caused by a severe lack of insulin which leaves the body unable to use glucose for energy. As a result, it starts to use fat instead, releasing chemicals called ketones which turn the blood acidic. Currently, one in four children in the UK experience DKA when diagnosed.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Teplizumab is administered daily for a period of 14 days and we anticipate that this could be inconvenient for some families. Although the side effects are minor, research trials found that it can temporarily reduce white blood cell count which can put the patient at higher risk of infection. The administration of teplizumab can also result in a small rash. No long-term adverse reactions were observed.¹

¹ Herold, Kevan C., et al. "Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus." *New England Journal of Medicine* 346.22 (2002): 1692-1698.

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.	This treatment may be of particular benefit to children with stage 2 type 1 diabetes, in order to delay onset, potentially enabling the pancreas to grow to adult size, giving better disease outcomes. It can also provide a “softer landing” when the disease progresses, reducing the risk of DKA as patients and their families have had time to learn how to identify the symptoms and manage the condition.

Topic-specific questions

12. Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	The early stages of type 1 diabetes are identified through autoantibody screening. In the UK, this is currently available only in research settings, however we have heard some anecdotal evidence of a handful of HCPs screening in their clinics.

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Given that Teplizumab needs to be administered daily over a period of 14 days we anticipate that this could create some issues for families in insecure employment or with restricted access to transport. This could make accessing the treatment for those from lower socio-economic backgrounds more difficult than for those from more privileged backgrounds.

Other issues

14. Are there any other issues that you would like the committee to consider?	N/A

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Type 1 diabetes is complex and at times an all-encompassing condition with no cure. • Often overlooked is the impact type 1 diabetes can have on the loved ones, particularly if they are partly or wholly responsible for managing the condition as parents of children with type 1 often are. • Currently, there is no treatment available on the NHS that can delay the onset of stage three type 1 diabetes. • Teplizumab can delay the onset of stage three type 1 diabetes by an average of three years, leading to fewer acute complications and prolonged freedom from the burdens of managing type 1 diabetes with insulin. • Teplizumab may be of particular benefit to children with stage 2 type 1 diabetes, in order to delay onset, potentially enabling the pancreas to grow to adult size, giving better disease outcomes. It can also provide a “softer landing” when the disease progresses, reducing the risk of DKA as patients and their families have had time to learn how to identify the symptoms and manage the condition.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

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 over 5 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. 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.	Diabetes UK receives some funding from the pharmaceutical industry to support specific programmes of work and for conferences we run including: Sanofi - £98,334
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?	• Conversations with people living with type 1 diabetes • Conversations with parents and carers of children with type 1 diabetes • Conversations with parents and carers whose children have participated in trials screening for type 1 diabetes antibodies • Published research studies

	• National audits

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?	Type 1 diabetes can be relentless to live with. It is a serious condition that currently does not have a cure and requires intensive self-management. Incidence of type 1 diabetes is also rising. Most people living with type 1 diabetes make 180 more health-related decisions a day than someone without diabetes. That's an extraordinary number of extra decisions to be made – about once every 5 minutes when you are awake. Self-management of type 1 diabetes includes but is not limited to monitoring of blood glucose levels, carbohydrate counting and intensive insulin therapy. Where people living with diabetes find it a challenge to effectively self-manage their condition they are at risk of developing devastating short- and long-term complications. These include life-threatening diabetic ketoacidosis (DKA), severe hypoglycaemia, blindness, cardiovascular disease and amputations. Furthermore, a considerable number of people with type 1 diabetes are diagnosed when they are already acutely ill in DKA and this is a dangerous and potentially fatal outcome. Incidence of diagnosis in DKA has remained steady at around 25% for children and young people, despite consistent efforts to raise awareness of the risk factors of the condition, which shows the difficulty of identifying onset. For those diagnosed with diabetes as children and young people, adapting to manage the condition is particularly demanding whilst also navigating the challenges of growing up in general. The physiological impact of diabetes as people grow up can make managing glucose levels more difficult, and the

additional psychological burden of having a long-term condition for children and young people is also significant.

To demonstrate the impact for carers and parents, in responses to the National Paediatric Diabetes Audit's 2023/24 survey of patient reported outcomes for parents and carers of children and young people recently diagnosed with diabetes, 30% said they reduced working hours and 11% left work completely to provide care. Furthermore, 64% experience weekly sleep disruptions due to stress about their child's health – with frequency increasing for those with younger children who require more supervision.

As there is currently no cure for type 1 diabetes, people living with the condition have to self-manage for their whole life and even those able to reach treatment targets face a significant long-term burden. Many adults with type 1 diabetes highlight difficulty with balancing glucose levels, the resulting psychological impact and need to attend various healthcare appointments. Our 'It's Missing' report, which survey of 3,000 PWD, found that 7 in 10 people living with diabetes felt overwhelmed by the demands of their condition. Of these, three quarters said their self-management was affected by their emotional struggle.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People with type 1 diabetes require insulin therapy which is challenging and demands a high level of care and attention to optimise glucose levels and ensure safety. People with type 1 diabetes should receive structured education for training on carbohydrate counting to balance insulin delivery with food intake, regular essential checks for treatment targets and complications, and technology such as CGM, insulin pumps and hybrid closed loop to improve their self-management but these require ongoing support and a considerable time commitment.
8. Is there an unmet need for patients with this condition?	Yes, though there are potential methods to monitor the development of type 1 diabetes onset over a long-term – such as using continuous glucose monitoring (CGM) - there is currently no approved treatments available that can delay the onset of type 1 diabetes.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People with diabetes and their carers think that the main advantage of this technology is its ability to allow a more predictable “soft landing” of type 1 diabetes that enables them to manage it with more confidence and assurance. This means that people identified as having stage 2 type 1 diabetes can be given an opportunity to prepare for the many challenges that come with managing the condition, and where possible delay onset to a time when they are better placed to do so. This is important because it not only improves health and wellbeing in the present but sets a better beginning for a life with type 1 diabetes. There is a well-established link between improved management and reducing the risks of devastating long-term complications of diabetes like cardiovascular disease, neuropathy and retinopathy, and reducing the duration of diabetes can in turn reduce the risk of developing complications. A treatment to delay the onset of type 1 diabetes would have the advantage of both enabling people to adjust to the demands of managing the condition with more certainty, and reduce the timeframe for the risk of complications.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The potential of having to travel and be admitted as an inpatient for infusion of the treatment is a disadvantage as it may make it more difficult for some people to access the treatment.

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.	This treatment may have more benefit for younger children with stage 2 type 1 diabetes who are less able to self-manage independently and would benefit from delaying its onset until they are older and more able to. Additionally, children and young people experiencing major transitions in life – such as moving from primary school to secondary school or from home to university – could also greatly benefit from having additional time to manage this without the extra challenge of having type 1 diabetes. It may also be of particular benefit to people from disadvantaged backgrounds, those with mental health problems, learning disabilities, physical impairments or other reasons for finding engaging with insulin therapy difficult.

Topic-specific questions

12. Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	Pre-T1D is identified via autoantibody screening. In the UK, this is currently available only in research settings such as: • EarLy Surveillance for Autoimmune diabetes: The ELSA Study • The UK-Islet Antibody registry • Bart's-Oxford (BOX) family study • The Type 1 Diabetes Risk in Adults (T1DRA) study • T1D Early • European action for the Diagnosis of Early Non-clinical Type 1 diabetes (EDENT1FI) • INNODIA

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is a potential risk that people more likely to experience health inequalities, such as those from more deprived areas and from ethnic minority backgrounds, and have been slower to benefit from new technology and treatments in the past could face similar barriers to accessing Teplizumab.

Other issues

14. Are there any other issues that you would like the committee to consider?	As well as access to the treatment it is important to consider how people will be identified as having stage 2 type 1 diabetes and the availability of screening and clinical pathways to support them.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Type 1 diabetes is a serious, relentless condition with no available cure that significantly impacts the health and quality of life of those with it and their carers • Onset of type 1 diabetes can happen quickly, can result in hospitalisation that require urgent care and requires significant adaptations to daily life • Experiences of people with type 1 diabetes, or identified as having stage 2 type 1 diabetes, and their parent and carers highlight the enormous impacts of having a measure of control over the onset of the condition to manage its challenges more effectively • This treatment is innovative and unique in being the only one available currently that can potentially delay the onset of type 1 diabetes • Delaying the onset of type 1 diabetes has the potential to also reduce the risk of long-term complications, both because of shorter duration of type 1 diabetes and the individuals ability to psychologically prepare for the onset

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

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.

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 13 pages.

About you

1. Your name	
2. Name of organisation	British Society for Paediatric Endocrinology and Diabetes (BSPED)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians. Yes (Diabetes officer, BSPED) A specialist in the treatment of people with this condition? Yes (consultant paediatric endocrinologist) A specialist in the clinical evidence base for this condition or technology? Yes (screening for childhood type 1 diabetes is my research area at the University of Oxford) and I lead the BSPED pre-Type 1 diabetes Specialist Interest Group and the UK Islet autoantibody Registry.
5a. Brief description of the organisation (including who funds it).	The British Society for Paediatric Endocrinology and Diabetes aims to improve the care of children and young people with endocrine disorders or diabetes mellitus, by bringing together professionals from a range of disciplines. This includes tertiary paediatric endocrinologists and diabetologists, general paediatricians, researchers, nurses and other healthcare professionals involved in the care of these patients. The BSPED holds an annual scientific meeting; sends a monthly newsletter to its members; advises on best practice and guidance via its Clinical Committee; recognises excellences and funds research and represents the field of paediatric endocrinology and diabetes on a national level. The society is funded by membership subscriptions, meeting registrations and corporate sponsorship.
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.	BSPED has received sponsorship for its 2024 annual meeting from Sanofi, who exhibited at the event. (£13,000 + additional costs).

**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 delay progression from stage 2 (asymptomatic dysglycaemia) to stage 3 (symptomatic, hyperglycaemia) type 1 diabetes (T1D).

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.)	Delaying the onset of stage 3 T1D, which has several benefits: 1) Delaying the need for insulin. Treatment with insulin in stage 3 T1D is accompanied by significant demands on the child, young person and their caregivers, including school providers. This includes relentless treatment tasks and decision-making. Treatment is with insulin delivery by pump or injections and monitoring via regular fingerprick blood tests, or subcutaneous glucose sensors multiple times a day, to balance glucose levels with the goal of achieving levels that are in target. This interrupts daily functioning, and affects every aspect of a young person's (and their family's) life, including eating, exercise, sleep, education, friendships and relationships. This causes significant psychological burden on young people and their caregivers. Rates of depression and other psychiatric disorders such as eating, anxiety and behaviour disorders are higher in T1D, in part due to these excessive demands, <i>de Wit Ped Diab 2022</i>. Delaying the need for insulin provides additional years for a child or young person to live a life free of the burden of T1D treatment. This provides additional time to allow a young person to become more mature and pass through key developmental milestones, such as going to secondary school, going through puberty (where adherence and glycaemic control is a particular challenge) or taking GCSE's/ A-levels. 2) Reducing exposure to hyperglycaemia and potential diabetes-related complications. T1D is associated with long-term complications, broadly grouped into macrovascular (early heart disease, stroke), and microvascular (retinopathy, neuropathy, nephropathy), and a reduced life span. These complications are proportional to the duration of disease and glycaemic load (hyperglycaemia); <i>Nathan Diabetes Control and Complications Trial 2014</i>. A delay in T1D onset can be of particular benefit for young children who will have a longer duration of disease by the time they are young adults. The optimal current therapy (hybrid closed loop therapy, recently NICE approved) still only results in 34% achieving UK NICE targets of <6.5% (48mmol/mol) after 4 years of diagnosis; <i>Ware Diab Care 2024</i>. Young people who are delayed in reaching stage 3 T1D (should Teplizumab be approved and administered) will have additional years achieving this target, and therefore less exposure to hyperglycaemia. It is not known, with current treatment protocols, how much of an impact delaying T1DM by 3 years will have on long-term glycaemic control, but it is likely to have some benefit since there will be less cumulative glycaemic load (and therefore potentially less complications). One can extrapolate learnings from the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), which demonstrated the importance of optimising glycaemic control as early as possible in T1D for beneficial effects on long-term renal and cardiovascular outcomes – this so-called metabolic memory can last decades. The authors

	recommend “maintaining near-normal levels of glycemia, as early and as long as safely possible in order to limit the risk of complications.” <i>Lachin Diab Care 2021</i>. 3) Reducing the young person being exposed to hyperglycaemia and potential excess mortality. T1D has been associated with a 16-year reduced life expectancy, which was highest in children diagnosed under the age of 10 years; <i>Rawshani Lancet 2018</i>. The impact of delaying T1D onset on life expectancy is likely to most greatly impact children and adolescents, particularly those diagnosed under the age of 10 years, but potentially older children, if their T1D diagnosis is delayed. 4) Reducing the young person being exposed to severe hypoglycaemia and loss of consciousness. Hypoglycaemia is a key cause of admissions to hospital and of stress/anxiety/fear for those living with T1D and for their parents/caregivers/teachers. It can result in children being excluded from usual activities. Hypoglycaemia, and the fear of hypoglycaemia, affects sleep and therefore daily functioning in not only children but parents/caregivers. Hypoglycaemia does not occur if a child/young person is not requiring insulin and will therefore be delayed if the need for insulin therapy is delayed. 5) Reducing the young person being exposed to hyperglycaemia and hypoglycaemia, which are linked to poor school functioning and educational attainment via a combination of mechanisms including altered cognitive function and nonattendance for acute treatment; <i>de Wit Pediatric diabetes 2022</i>. 6) Through availability of teplizumab, T1D antibody screening is likely to increase which is known to reduce the risks of diabetic ketoacidosis (DKA); <i>Ziegler JAMA 2020</i>. Currently 38% of children and young people aged < 19 years present in DKA, <i>Report on hospital admissions of children and young people with diabetes, 2015-2020, NPDA</i>. DKA is a life-threatening emergency, requiring hospitalisation and often management on high dependency or intensive care, and can cause significant morbidity and less commonly, mortality. DKA is associated with neurocognitive deficits and structural changes to the developing brain. Emerging evidence suggests the association between DKA at onset and deterioration in glycated haemoglobin (HbA1c) over time; <i>Duca Diabetes Care 2017</i>. HbA1c is in turn associated with the risk of complications; <i>Nathan Diab Care 2014</i>, therefore availability of teplizumab could reduce the risk of diabetes-related complications through increasing screening and thereby reducing presentation in DKA. References: de Wit M, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes. <i>Pediatr Diabetes</i>. 2022 Dec;23(8):1373-1389. PMID: 36464988.

	• Duca LM, et al. Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Diabetes Care. 2017 Sep;40(9):1249-1255 PMID: 28667128. • Lachin JM, Nathan DM; DCCT/EDIC Research Group. Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care. 2021 Sep 21;44(10):2216–24. PMID: 34548284. • Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014;37(1):9-16. PMID: 24356592. • NPDA. Report on hospital admissions of children and young people with diabetes, 2015-2020, July 2023, <i>available at: https://www.hqip.org.uk/wp-content/uploads/2023/07/NPDA-report-on-Admissions-2015-2020v2.pdf</i> • Rawshani A, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug 11;392(10146):477-486. • Ziegler AG, et al; Fr1da Study Group. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. JAMA. 2020 Jan 28;323(4):339-351. PMID: 31990315. • Ware J, et al CLOuD Consortium. Effect of 48 Months of Closed-Loop Insulin Delivery on Residual C-Peptide Secretion and Glycemic Control in Newly Diagnosed Youth With Type 1 Diabetes: A Randomized Trial. Diabetes Care. 2024 Aug 1;47(8):1441-1448..PMID: 38924772.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – no treatment is available in the UK to delay T1D disease onset. Teplizumab would be the first disease modifying treatment for T1D.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is currently no treatment for stage 1 and stage 2 T1D – this would be the first treatment. Clinical stage 3 T1D is currently treated as part of routine NHS care. In children and young people, T1D is managed in the hospital setting, within multidisciplinary teams. Children and young people are seen in clinic every 3 months and they have a minimum of 8 additional contacts per year in England where the Best Practice Tariff is in use. A similar structure exists in Wales, Scotland and Northern Ireland. A diagnosis of stage 3 T1D currently occurs as an emergency, requiring same day insulin treatment, usually as an inpatient. Multidisciplinary team involvement is needed, for example for intensive counselling and education of insulin delivery, carbohydrate counting, hypoglycaemia and hyperglycaemia management, and sick day rules.

	Pre-clinical T1D (stage 1 and stage 2) is not routinely managed in the NHS, since general population children and adults are not routinely tested or screened for stage 1 and stage 2 T1D outside of a research setting. However a recent UK survey (presented at BSPED 2024 conference, abstract available here: https://www.endocrine-abstracts.org/ea/0103/ea0103p95) indicated that some children and young people are being identified in this pre-clinical stage. These children are managed in a variety of ways with no consistent approach, as, until recently, there was no clinical pathway of monitoring for stage 1 and stage 2 T1D. Children and young people with stage 2 T1D who transition to stage 3 T1D and who need insulin treatment, typically would not need insulin treatment as an emergency. Insulin could potentially be given in a planned way as an outpatient.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are international consensus pathways/recommendations for monitoring stage 1 and 2 T1D, listed below. The first reference, which is the most comprehensive, has recently been adapted for the UK setting for children and young people under the age of 18 years by the BSPED Pre-T1D Special Interest Group, and this has recently been ratified by the BSPED Clinical committee and is available for guidance for clinical teams in the UK. NICE guideline [NG18] [Overview Diabetes (type 1 and type 2) in children and young people: diagnosis and management Guidance NICE] is used for the management of symptomatic / stage 3 T1D. References • Phillip M, et al. Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes. Diabetes Care. 2024 Aug 1;47(8):1276-1298. PMID: 38912694. • Hendriks AEJ, et al.; INNODIA consortium, the Fr1da Study Group and the GPPAD Study Group. Clinical care advice for monitoring of islet autoantibody positive individuals with presymptomatic type 1 diabetes. Diabetes Metab Res Rev. 2024 Feb;40(2):e3777. PMID: 38375753. • Besser REJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2022 Dec;23(8):1175-1187. PMID: 36177823.
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.)	As mentioned above, should an individual be identified with one or more islet autoantibodies there is now a consensus and pathway of care as to how stage 1 and stage 2 T1D should be managed. However there is no formal care pathway for screening. There is also no treatment – Teplizumab would be the first treatment - so currently no pathway for treatment with Teplizumab currently exists. Importantly, there is no current funding for the clinical follow-up of islet autoantibody positive individuals outside of research. However some children, for example those who have been screened and who do not want to be followed in a research study (estimated 40-50% based on published literature) or, who have been identified as

	antibody positive as part of clinical care, are followed within current T1D clinics (at least around 60 suggested from our BSPED survey). There is no agreed mechanism for follow-up, creating pressure on existing T1D clinics. There are some dedicated but unfunded clinics in a few centres. There is lack of agreement amongst NHS professionals as to where stage 1 and 2 individuals should be managed – within a T1D service, as part of a specialist commissioned service or elsewhere e.g., primary care (less favourable). However, there is agreement that extra funding will be needed to follow stage 1 and stage 2 individuals if routine or more widespread screening were to be undertaken and also to follow children/adolescents after they are given teplizumab (should it be approved).
9c. What impact would the technology have on the current pathway of care?	A completely new clinical pathway will be needed and be fully funded, to include: 1) Eligibility assessment for teplizumab. This will be with multiple islet autoantibody confirmation, metabolic testing to confirm stage 2 T1D (the 2-hour oral glucose tolerance testing (OGTT), glycated haemoglobin (HbA1c), clinical assessment (including of vaccination status) and laboratory workup, <i>Mehta Horm Res Paed 2024</i>. The OGTT is the gold standard test but is lengthy and invasive. HbA1c has poor sensitivity and high specificity. If using HbA1c alone, this value can lag glucose values by 2-3 months, reducing the treatment window. 2) Administration of Teplizumab in secondary care, daily for 14 days; using either peripheral IV, or midline catheters) or central (peripherally inserted central catheter [PICC]) venous access. Administration can be arranged in day care units with weekend cover in secondary care, similar to monoclonal antibodies being administered for other autoimmune conditions in Paediatrics within a hospital setting. Home care delivery may also be possible in the second week of the treatment, until the risk of significant adverse events decreases, During the administration course, clinical assessments and blood tests are needed according to the recommended schedule <i>Mehta Horm Res Paed 2024</i>. 3) Follow up of individuals after teplizumab treatment administration. Individuals who respond will likely remain in stage 2 for an extended period of time, but all individuals will need long-term follow up and education to ensure a safe transition to stage 3 T1D. The follow up of children after receiving teplizumab should be in dedicated Early T1D clinics to ensure a safe transition to stage 3 T1D. Additional considerations: 1. Follow up of islet autoantibody positive individuals in stage 2 (stage 1 and those with a single islet autoantibody)– this group will increase as screening increases with access to the technology), to assess for hyperglycaemia according to Philip et al, above. This will include the need for education, psychological support, metabolic tests (HbA1c, continuous glucose monitoring, home glucose testing).

	2. NHS antibody assay standardisation. If Teplizumab is approved, more widespread testing/screening of individuals (in particular first-degree relatives of those with T1D) will increase. Antibody testing (type and method) currently varies amongst NHS labs. There are 4 different islet autoantibodies which can be tested. A requirement of screening is to adhere to the “rule of twos,” i.e., the presence of two different autoantibodies confirmed in two tests from two separate samples: <i>Phillip Diab Care & Diabetologia 2024</i>. Individuals who are initially screened and identified as islet autoantibody positive will then need islet antibody confirmation, with all 4 islet autoantibodies measured. There will be a need for standardisation of islet autoantibody assays for population-level screening for early-stage T1D and their thresholds of positivity, and a process for antibody confirmation, ideally in reference laboratories. There is a need to assess the sensitivity and predictive value of the available assays when used for confirmatory testing in populations with low islet autoimmunity prevalence, i.e. the general population, to assure high positive predictive value of assays used in confirmatory testing and limit the number of people falsely diagnosed with early-stage T1D and enrolled in unnecessary monitoring. The UK Islet autoantibody registry is established which offers confirmatory testing of all 4 antibodies in a reference lab on a research basis to address some of this unmet need (Besser et al, protocol available on request, funder: Diabetes UK). Reference: • Mehta S, et al. Pediatric Endocrine Society Statement on Considerations for Use of Teplizumab (Tzield™) in Clinical Practice. <i>Horm Res Paediatr.</i> 2024 Apr 30:1-12. PMID: 38663372.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Unlikely, it is expected that teplizumab will be given in specialist regional centres, whereas T1D is managed locally.
10a. How does healthcare resource use differ between the technology and current care?	The proposed technology would need to be completely funded akin to a new service, embedded within T1D care (for the situation of children and young people) both for monitoring and drug delivery.
10b. In what clinical setting should the technology be used? (For example,	Secondary care – possibly tertiary care (healthcare professionals would need specialist training to administer the drug safely) and have facilities for line insertion and will need to learn how to interpret antibody/metabolic tests and how to deliver the new pathway.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1) Training of healthcare professionals for how to manage the follow up of antibody positive individuals 2) Facilities and training for patient eligibility – based on antibody interpretation and metabolic tests (OGTT, HbA1c). 3) Delivery of teplizumab – facilities available for 14-day consecutive administration, resource for line insertion, staffing available for 14 days consecutive assessment. 4) Funding for the expansion of clinical services with adequate psychology, nursing and medical support, for the follow up of individuals who are antibody positive – not just those with 2 or more antibodies (stage 1 and stage 2) but also those with a single positive islet autoantibody. They will be followed with metabolic monitoring (including CGM) and education. 5) Development of materials for parents and children/young people for i. antibody positivity ii. drug delivery 6) Standardization of assays for the purposes of population screening (see above discussion). As discussed above, the availability and standardisation of islet autoantibody assays will be need as islet autoantibody testing increases in the situation of a therapeutic intervention.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In those who respond, yes. A median delay of 2-3 years is likely to be clinically very significant in terms of reducing the psychological burden of managing T1D for individuals, and their families, delaying the onset of complications and in terms of “metabolic memory”, as outlined in 6., above.
11a. Do you expect the technology to increase length of life more than current care?	It is known that a younger age at onset (particularly a diagnosis of T1D under age 10 years) is associated with worse survival. The Rashwani paper (reference above) suggests overall, being diagnosed with T1D before 10 years of age resulted in loss of 16.0 (95% CI 15.7, 16.4) life-years compared to patients diagnosed after 20 years of age who lost approximately 10 life-years. It is unknown whether delaying T1D by 2-3 years translates to an increase in life expectancy, however it may have a small effect, especially in children and young people diagnosed at a young age due to an effect on glycaemic load and other factors. It will not be any worse than current clinical care.
11b. Do you expect the technology to increase	Yes - people with T1D have been shown to score lower across all health-related Quality of Life measures than their unaffected peers, reporting difficulties including anxiety, depression, stress and worry.

health-related quality of life more than current care?	Therefore, for the duration that an individual is delayed from starting on insulin, quality of life is improved for the individuals, and their wider network of parents/caregivers and family members. However, psychological impact of being high risk for a condition and additional monitoring may need to be considered. Reference: Allen, V., Mahieu, A., Kasireddy, E. <i>et al.</i> Humanistic burden of pediatric type 1 diabetes on children and informal caregivers: systematic literature reviews. <i>Diabetol Metab Syndr</i> 16, 73 (2024). .
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, from the published paper it is suggested that certain subgroups are likely to respond better but the sample size was underpowered to adequately answer this question. Reference: Herold KC, et al Type 1 Diabetes TrialNet Study Group. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. <i>N Engl J Med</i>. 2019 Aug 15;381(7):603-613. . PMID: 31180194.

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.)	After administration, being free of the need to start insulin will be significantly easier for patients than starting on insulin – it will give children and teenagers time for a normal life without the daily demands and distress that comes with needing insulin therapy. However there may be expected barriers in marginalised or low-income groups e.g. problems taking 14 days from work, difficulties accessing a treatment centre. For healthcare professionals (HCPs), the technology will initially be more difficult to use as HCPs are untrained in its use, delivery, and follow up of individuals before and after its use. However that expertise will develop rapidly. Practical implications: 1. Confirming eligibility in stage 2 based on antibody and metabolic tests – extra resource is needed for confirming antibody status and undertaking OGTT and/or HbA1c measurement. 2. A monitoring pathway needs funding, education in its implementation and designated clinic allocation for the follow up. Stage 2 individuals will need education and monitoring before and after the drug is delivered. Extra resource is needed for, HbA1c, home glucose monitoring and continuous glucose monitoring for stage 2 T1D.

	3. Although the technology is for stage 2 individuals, as mentioned above, access to this technology will increase screening and therefore the numbers in stage 1 or with a single positive islet autoantibody– all need to be followed up with education, metabolic and repeat antibody tests. 4. Securing IV access to last 14 days in a child and delivering the infusion daily over 14 consecutive days will be challenging. The delivery centre may be far from the family requiring them to travel a distance each day or be admitted to the delivering centre. If there are no beds available, e.g., in secondary care over winter the family may have to pay to stay nearby if they live far away. Day case facilities do not function at weekends in many units (including tertiary units) - hence an additional impact on ward beds at weekends. 5. Standardisation of antibody assays are needed in NHS labs for this technology, as discussed above.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, this is expected. The Pediatric Endocrine Society (<i>Mehta Horm Res Paed 2024</i>) has published a consensus on when to stop drug therapy and when to hold.
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?	Yes – the QALY calculation will not account adequately for use of the technology. Additional health-related benefits may be seen, including: improvement in mental health due to reduction of psychological burden/distress to patients and families, following delay of insulin requirement and avoidance of DKA due to being in a monitoring pathway; improved functioning with daily activities, e.g. education, exercise and sleep without limitations of T1D treatment and monitoring burden; and avoiding the need for time off work and school to live with and manage T1D adequately, such as during illness.
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	Yes, this would be the first disease modifying therapy and a major step forward in addressing the paradigm whereby currently we generally only pick up patients when they present with osmotic symptoms whereas the evolution of clinical T1D can over many months and years. It is an autoimmune process that we can potentially address before the stage where individuals require insulin.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes – if approved, it will be the first drug to be administered to delay T1D onset.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – to delay T1D. There is no other technology that currently does this.
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 frequently seen (especially rash and transient lymphopenia day 5). However these are typically minor and self-limiting. Lymphocyte counts typically normalise by day 28. This is a one-off treatment with no ongoing burden of care

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The trials have been undertaken in first degree relatives, whereas >85% children/young people with T1D do not have a first degree relative with T1D.
18a. If not, how could the results be extrapolated to the UK setting?	It is unlikely that general population at risk individuals respond differently to first degree relatives, but this should be monitored.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Time to starting insulin and adverse events of the drug. Both were measured.
18c. If surrogate outcome measures were used, do	

they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real world use of teplizumab, for example in the United States.
20. How do data on real-world experience compare with the trial data?	None available to our knowledge.

Topic-specific questions

21 Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	Some individuals are identified from routine clinical care – see BSPED 2024 abstract. It is likely that if Teplizumab is made available as in the USA that first-degree relative (in whom the risk of T1D is around 1 in 20) would be the group most likely to be identified in the initial stages of implementation- they will have greatest knowledge of its benefit and will be the easiest to identify from routine paediatric diabetes clinics. A record of islet autoantibody individuals is being collected by the UK Islet autoantibody registry.

Equality

22a. Are there any potential <u>equality issues</u> that should be taken into account when considering this treatment?	There are significant equality issues. If approved teplizumab would initially only be available to those identified through research trials, none of which offer universal coverage. Available research trials offer screening of certain ages (ELSA 3-13y; T1DRA: adults), often advertised through social media; or regionally (GPPAD – Thames Valley, Newcastle), or through first degree relatives (INNODIA, BOX, previously TrialNet [now closed]). This means those who are better educated, first-degree relatives, or in certain regions, are more likely to be screened. However this could be mitigated by encouraging screening of siblings and offspring within clinic populations (if the screening of first-degree relatives is decided). This would limit the numbers and the majority of individuals who would benefit, because whilst first degree relatives of a person with T1D have a 15 times higher risk than someone from the general population (1 in 20), familial type 1 diabetes only accounts for around 10-15% of the T1D population, with the majority coming from the general population (1 in 300). To ensure full equality, population screening would be required but further data generated by implementation of the technology would be required to support such a case.
22b. Consider whether these issues are different from issues with current care and why.	In current care, everyone who gets T1D should be treated to a minimum standard of care. National benchmarking is reported, through the National Paediatric Diabetes Audit (for England and Wales), and equivalent Scottish registry (Sci-Diabetes).

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Teplizumab will benefit those who respond – delaying onset of clinical stage 3 T1D and the need for insulin management, the burden of the disease and buying additional time during key paediatric and adolescent development. • There are major equity issues as universal screening for T1D is currently not available • If approved, additional resource is needed to fund the pathway end to end i.e. antibody confirmation, metabolic confirmation for eligibility of stage 2, follow up, drug delivery, and follow up post drug delivery • Training will be needed for HCPs to deliver the pathway.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

NHS organisation submission (ICBs and NHS England)

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.

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	
2. Name of organisation	RCGP
3. Job title or position	

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify): Academic GP; RCGP National Clinical Advisor
5a. Brief description of the organisation (including who funds it).	Royal College of General Practice
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NG17 – Last Updated Aug 2022 NG18 – Last Updated May 2023
7. 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.)	Yes
8. What impact would the technology have on the current pathway of care?	New treatment option in the population with the intention to delay progression of diabetes. There is no current such treatment.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Proposed for people with stage 2 type 1 diabetes aged 8 or older. Not currently being used outside of clinical trials.
10. Will the technology be used (or is it already used) in the same way	No

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The use of OGTT as a screen to diagnose Stage 2 Type 1 diabetes would be needed. HBA1c could be normal in these. Stage 2 diagnosis would also require antibody screening which may already be taking place amongst high risk individuals. The infusion would need to be given in either a hospital setting (best) or a community setting with facilities and staff able to give and monitor intravenous infusions. There would need to be consideration of testing for transient lymphopenia as an expected side effect as well as evaluation of practical impact on a patient e.g. if they acquired an infection during this time. There may need to be a helpline similar to that which is provided in most areas for oncology patients or this support could be a joint effort between primary and secondary care nursing teams.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We would suggest secondary care initially due to the practicalities discussed above in order to establish safe practice before handing onto or sharing with community settings.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for clinicians across the MDT including medical staff, pharmacists and other prescribers across the board as well as resources for patients; training around additional monitoring requirements, impact on operating machinery including driving as well as any known short-term and long-term sequelae; public health awareness which could be delivered in conjunction with charities, royal colleges and the faculty of public health
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Yes as detailed above.
11. What is the outcome of any evaluations or	NEJM published initial results 2019 Aug

audits of the use of the technology?	Lancet comments - Published Online January 6, 2023 https://doi.org/10.1016/S2213-8587(22)00390-4 Further study in larger grouper of patients with a different treatment protocol – NEJM 2023 N Engl J Med 2023;389:2151-61. DOI: 10.1056/NEJMoa2308743

Topic-specific questions

12. Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	Not routinely; there may be research into identifying these populations outside of a national screening programme

Equality

13a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not every area in the country has easy access to OGTTs.
13b. Consider whether these issues are different from issues with current care and why.	This may exacerbate current problems however may also highlight an area requiring more investment; There is a potential research area here for patients with PCOS for whom OGTT would be the best way to assess diabetes risk.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

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.

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 13 pages.

About you

1. Your name	
2. Name of organisation	United Kingdom Clinical Pharmacy Association (UKCPA)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? <u>Yes</u> or No A specialist in the treatment of people with this condition? Yes or <u>No</u> A specialist in the clinical evidence base for this condition or technology? Yes or <u>No</u> Other (please specify):
5a. Brief description of the organisation (including who funds it).	UKCPA is a not-for-profit organisation that connects thousands of practitioners with a broad range of specialties, professions and sectors, to enable the delivery of outstanding pharmaceutical care, ensuring that patients receive the best possible outcome from their medicines. Self-funded through memberships.
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.)	Disease prevention/delay.
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.)	A clinically significant treatment response in the context of stage 2 Type 1 Diabetes (T1D) would involve measurable outcomes such as delaying the progression to stage 3 T1D, preserving beta-cell function, and improving metabolic markers.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need for a drug that delays the onset of type 1 diabetes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In the NHS, Type 1 diabetes is primarily managed through insulin therapy to regulate blood glucose levels. Patients are educated on carbohydrate counting to adjust insulin doses appropriately. Regular blood glucose monitoring is essential, with some individuals using continuous glucose monitoring systems. Structured education programmes, such as DAFNE (Dose Adjustment For Normal Eating), are offered to enhance self-

	management skills. Additionally, the NHS provides access to multidisciplinary teams, including dietitians and diabetes specialist nurses, to support comprehensive care.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	• NICE guidelines – NG17 for type 1 diabetes in adults and NG18 for type 1 diabetes in children/adolescents. • International Society for Paediatric and Adolescent Diabetes (ISPAD)
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 by NICE guidance: • Diagnosis and initial management: Prompt initiation of insulin therapy upon diagnosis. • Education: Access to structured education programmes like DAFNE for self-management. • Ongoing support: Regular reviews by multidisciplinary teams including endocrinologists, diabetes nurses, dietitians, and psychologists. • Access to technology: Provision of continuous glucose monitors (CGM) or insulin pumps for eligible patients. There may still be differences in practice depending on: - Access to technology: Differences in funding and availability of advanced technologies like CGMs and insulin pumps can vary by region. - Professional opinions: Variations may arise in transitioning children to adult services, the use of adjunctive therapies, or the timing of interventions like immunotherapy. - Local resources: Some regions may offer more frequent specialist reviews than others due to resource constraints.

9c. What impact would the technology have on the current pathway of care?	Early intervention: Teplizumab, if adopted, would introduce a new step for individuals in Stage 2 Type 1 Diabetes. This would shift the focus from reactive management (post-diagnosis) to proactive prevention of Stage 3 progression. Screening and monitoring: The need for widespread autoantibody screening and glycaemic monitoring would expand the diagnostic pathway, requiring additional resources and training for primary and secondary care providers. Delaying onset: By delaying progression to clinical diabetes, teplizumab could reduce immediate reliance on insulin therapy and mitigate early disease burden, altering long-term care strategies. Resource allocation: There may be an increase in initial costs due to immunotherapy administration, but long-term benefits might include reduced complications, hospital admissions, and emergency care. Care coordination: Multi-disciplinary teams may need to adapt to integrate immunotherapies, adding complexity to care pathways but potentially improving patient outcomes.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	- The technology would not be used in the same way as current care as it would focus on targeting stage 2 T1D to delay onset of stage 3, thereby focusing on preventative therapy. - At present the NHS does not routinely screen at-risk individuals for autoantibodies. The use of teplizumab would necessitate the identification of individuals with multiple islet autoantibodies and dysglycaemia, requiring new infrastructure and protocols. - Teplizumab involves intravenous infusion over 14 days, a method not typically used in standard diabetes care, which relies on subcutaneous insulin and oral medications. - Use of teplizumab would require close monitoring for adverse effects such as lymphopenia and cytokine release syndrome, adding layers to the existing care framework.

10a. How does healthcare resource use differ between the technology and current care?	Screening and Identification: • Teplizumab: Requires population-wide or targeted autoantibody screening to identify Stage 2 Type 1 Diabetes. This adds significant upfront resource needs, such as testing facilities, personnel training, and repeat follow-ups for confirmation. • Current Care: Focuses on managing symptomatic patients with Stage 3 diabetes, without routine early-stage screening. Administration: • Teplizumab: Administered intravenously over 14 consecutive days, requiring infusion facilities, healthcare staff for administration, and pre-treatment assessments (e.g., liver function, CBC). • Current Care: Primarily involves insulin therapy delivered via pens or pumps, managed by patients themselves with support from diabetes teams. Monitoring: • Teplizumab: Needs close monitoring for side effects such as lymphopenia or cytokine release syndrome. Regular follow-up is essential to evaluate progression to Stage 3. • Current Care: Focuses on ongoing blood glucose monitoring and management of complications like hypoglycaemia or DKA. Cost Implications: • Teplizumab: Higher initial costs due to infusion protocols, infrastructure for screening, and management of adverse effects. • Current Care: Long-term costs revolve around insulin provision, glucose monitors, and treating diabetes-related complications.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist clinics.
10c. What investment is needed to introduce the technology? (For example,	There is an investment required for: - education for clinicians to integrate teplizumab into the diagnostic pathway. - education for pharmacists to appropriately screen prescriptions.

for facilities, equipment, or training.)	- education for nursing staff to appropriately administer teplizumab. - investment into clinical units to have beds available to administer teplizumab. - staff costs to account for the new service provision.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Data shows that teplizumab has been shown to delay T1D from stage 2 to stage 3 by 32.5 months. However, there are no long-term studies to demonstrate whether there is a long-term benefit or quality of life given the potential cost of teplizumab.
11a. Do you expect the technology to increase length of life more than current care?	Unknown.
11b. Do you expect the technology to increase health-related quality of life more than current care?	By delaying Stage 3 Type 1 Diabetes for a median of 32.5 months, teplizumab reduces the immediate burden of daily insulin administration, frequent glucose monitoring, and the risk of acute complications like hypoglycaemia or diabetic ketoacidosis. However, it is unknown whether this will be offset by the need for a 14-day hospital admission. Early intervention may alleviate stress and anxiety associated with managing a chronic condition, particularly in children and their families. Parents may feel reassured about postponing the need for intensive disease management. Families, particularly those of younger children, benefit from fewer immediate caregiving responsibilities associated with full-blown diabetes management.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Limited data exist on adults over 45 years with Stage 2 T1D. Older individuals may have slower disease progression, reducing the immediate benefit of delaying Stage 3. Individuals with active infections, significant immunosuppression, or conditions like chronic viral infections (e.g., Epstein-Barr virus) may face risks outweighing the benefits.

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.)	Teplizumab is likely to be more difficult to use for both patients and healthcare professionals compared to current care due to its unique administration and monitoring requirements. Below are the practical implications: For Patients: Administration: - Teplizumab is delivered as a 14-day intravenous infusion, requiring daily visits to a clinical setting, which contrasts with the self-administered nature of insulin therapy. - This may impact patient acceptability, particularly for families with logistical challenges such as travel or time constraints. Concomitant Treatments: Patients may need supportive (e.g., nonsteroidal anti-inflammatory drugs, antihistamines, antiemetics) before each infusion to reduce the risk of adverse effects like cytokine release syndrome. For Healthcare Professionals: Screening and Selection: - o Identifying eligible patients requires testing for multiple islet autoantibodies and dysglycaemia, introducing additional diagnostic complexity. - o These tests are not currently routine in NHS care, requiring new infrastructure and training. Administration:

	- Administering intravenous therapy demands specialised clinical facilities and trained staff, potentially straining NHS resources. - Regular patient monitoring during the infusion period for adverse reactions adds to the workload. Monitoring: - Requires ongoing laboratory tests to monitor for side effects such as lymphopenia, elevated liver enzymes, and other immune-modulatory complications.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	- There should be a strict patient criterion to ensure eligibility for usage of teplizumab. - Patients should undergo baseline blood testing. - Patients must be fit and well and not have any active infections or immunosuppression during the administration process. - Patients should be monitored for adverse effects.
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?	Psychosocial benefits - Delaying the onset of Stage 3 Type 1 Diabetes can alleviate the psychological burden on patients and families, such as stress, anxiety, and the lifestyle disruptions caused by intensive diabetes management. These aspects may not be fully captured in QALY models. Reduced caregiver burden: For children with Type 1 Diabetes, parents often take on significant caregiving responsibilities, including insulin administration and continuous glucose monitoring. Delaying

	these tasks provides families with extended periods of normalcy, which is difficult to quantify in QALY terms. Educational and social impacts: Children who avoid the challenges of managing clinical diabetes during critical developmental years (e.g., school transitions, social interactions) may experience better educational and social outcomes, which are unlikely to be reflected in traditional QALY metrics.
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?	Teplizumab is the first therapy to target the immune basis of T1Dj by delaying progression from stage 2 to stage 3.
16a. Is the technology a 'step-change' in the management of the condition?	Yes – teplizumab represents a step-change in the management of T1D. It defers from the conventional approach of treating to preventing or delaying T1D.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – there is an unmet need to delay the progression or diagnosis of T1D which teplizumab fills.

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?	- Reduced lymphocyte counts are common and typically temporary, but they require monitoring during and after treatment. This adds a layer of complexity to care management. - Symptoms like fever, fatigue, nausea, and elevated liver enzymes may occur, particularly in the early days of infusion. These side effects necessitate premedication with anti-inflammatory drugs and antihistamines, increasing the treatment burden. The impact of adverse effects may lead to treatment cessation or increase length of hospital stay.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No the clinical trials do not reflect current UK clinical practice as routine screening for T1D without symptoms is not standard practice.
18a. If not, how could the results be extrapolated to the UK setting?	Introduce population-based or targeted screening for islet autoantibodies and dysglycaemia, focusing on high-risk groups (e.g., first-degree relatives of Type 1 Diabetes patients). This would identify individuals with Stage 2 Type 1 Diabetes, a prerequisite for teplizumab treatment.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	- Delaying disease progression from stage 2 to stage 3 T1D. - Preservation of beta-cell function. - Adverse events, including cytokine release syndrome, lymphopenia, and liver enzyme elevations.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A
20. How do data on real-world experience compare with the trial data?	N/A

Topic-specific questions

21 Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	Patients may be identified as part of research but not in clinical practice.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to screening: Identifying individuals with Stage 2 Type 1 Diabetes requires screening for islet autoantibodies and dysglycaemia. In areas with limited healthcare resources, patients may have reduced access to these tests, creating inequities in identifying eligible candidates for teplizumab. Socioeconomic barriers: The logistics of a 14-day infusion course may disproportionately affect individuals (e.g. parents) from lower socioeconomic backgrounds who may struggle with transportation, time off work, or childcare. Awareness and education: Disparities in health literacy may lead to unequal understanding of the benefits of early screening and preventive treatments, particularly in underrepresented or disadvantaged communities. Ethnic and genetic diversity: Most clinical trials for teplizumab were conducted on predominantly Caucasian populations. Differences in autoimmune disease progression across ethnic groups may influence the treatment's effectiveness or uptake.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Innovative prevention or disease delaying therapy. • Fills a gap at the moment which currently focuses on treatment only. • Challenges in administration by requiring a 14-day infusion. • The long term benefits or cost of teplizumab are currently unknown. • Screening for T1D is currently not standard practice. If this changes there is likely to be a significant cost implication on the NHS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - **YES** or **NO**

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

NHS organisation submission (ICBs and NHS England)

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.

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	
2. Name of organisation	NHS England
3. Job title or position	

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes or No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? Yes or No An expert in treating the condition for which NICE is considering this technology? Yes or No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is responsible for providing unified, national leadership for the NHS. NHS England is a single regulatory body responsible for overseeing the funding, planning, delivery, transformation, and performance of NHS healthcare in England. It also oversees the commissioning, planning, and buying of services and commissions some services itself nationally but passes on the majority of its money to ICSs. NHS England is government funded.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NICE guidelines for identification and management of stage 1 or stage 2 type 1 diabetes. We are aware of the following international clinical guidelines: • ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents • JDRF I Consensus Guidance for Monitoring Individuals With Islet Autoantibody–Positive Pre-Stage 3 Type 1 Diabetes These are international guidelines, not designed specifically for the NHS, and not widely used in practice within the NHS.

7. 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.)	Whilst there are well established diagnosis and treatment pathways for symptomatic stage 3 type 1 diabetes, the pathway of care for the identification and treatment of stage 1 and stage 2 type 1 diabetes is not yet defined. For example: • No commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes. Screening programs are only available via research trials. • No provision for psychosocial assessment / support following positive screening, which may lead to anxiety and disease monitoring burden. • No education or monitoring programs for people identified as stage 1 / stage 2. • No provision for self-monitoring of blood glucose to inform disease progression in those identified at risk of type 1 diabetes where OGTT is impractical or not available. • No pathway and new additional demand for glycaemic staging and surveillance in individuals identified as stage 1 / stage 2. • Both monitoring and treatment require paediatric and adult healthcare professional understanding of early-stage type 1 diabetes. All levels of medical and nursing education will require development to support competencies. This is applicable to secondary / specialist care, but also primary care healthcare professionals who will be required to support people identified with autoantibodies. • No provision for management of pregnant women identified as having stage 1 / stage 2 diabetes, with evidence on treatment limited. • New demand on secondary care services in the management of stage 1 / stage 2 • Increases in demand on secondary care infusion services and additional IV capacity requirements, including over the weekend as the technology is delivered daily for 14 consecutive days. With the exception of centres participating in research studies, the absence of a defined pathway is an NHS wide issue.

8. What impact would the technology have on the current pathway of care?	The introduction of the technology will have multiple impacts across the pathway, for example: • Local screening and treatment services could be established in an ad hoc way and without clear evidence-based guidance, leading to geographical variation and potentially exacerbating health inequality. • Increased caseloads for specialist teams and a lack of capacity to deliver safe, effective screening, monitoring and treatment. • Unmet need for trained healthcare professionals, including primary care, nursing, medical and psychology HCPs, leading to suboptimal care and workforce pressure.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	There are several research studies offering screening for type 1 diabetes in the UK, for example ELSA in children, T1DRA in adults and INNODIA for individuals with a first-degree relative with T1D. Immunotherapy treatment for delaying onset of stage 3 type 1 diabetes is not routinely available within the NHS.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – the technology will not be used in the same way as current care in the NHS as currently screening for early-stage type 1 diabetes is not available, nor are immunotherapy drugs for delaying onset of type 1 diabetes.
10a. How does healthcare resource use differ between the technology and current care?	Additional healthcare resources will be required in multiple parts of the clinical pathway, as set out at Q2 above.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The international guidelines suggest that the technology would be used in secondary care specialist clinics, although there will be a need for some aspects of clinical monitoring in primary care.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	In addition to the investment required for the treatment, there is also a need for substantial staffing, training and infrastructure investment to deliver the new technology. This is because this is a new patient group currently not known to services, the workforce is not yet trained in the new technology and full pathway development is required. Please refer to point 2 for further details. It is likely that commissioning would fall under ICB responsibility (specialised service or standard diabetes care), however, we are not aware of the mechanism for ensuring ICBs receive increased funding to cover the costs of the new treatment, or the additional staffing, training and infrastructure costs. Until clarity is gained on this, a recommendation of teplizumab as a treatment option is highly likely to lead to an unfunded cost pressure for ICBs.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	We are not aware of rules for stopping / starting treatment and any additional testing.
11. What is the outcome of any evaluations or audits of the use of the technology?	In a clinical trial¹, teplizumab delayed the onset of stage 3 type 1 diabetes in people with stage 2 aT1D by a median 2 years. We are not aware of other evidence. ¹ Herold K C et al. An Anti-CD-3 Antibody, Teplizumab, in relatives at Risk for Type-1 Diabetes. <i>New England Journal of Medicine</i> 2019; 381: 603-613

Topic-specific questions

12. Are people with stage 2 type 1 diabetes currently identified in NHS practice, and if so, how?	Not routinely, only via the research studies referenced at Q4.

¹ Herold K C et al. An Anti-CD-3 Antibody, Teplizumab, in relatives at Risk for Type-1 Diabetes. *New England Journal of Medicine* 2019; 381: 603-613

Equality

13a. Are there any potential <u>equality issues</u> that should be taken into account when considering this treatment?	An EHIA would need to be undertaken, but potential inequalities that may emerge are as follows: • The absence of a national screening programme is likely to mean that geographical variation in the availability of treatment. Individuals that are well resourced and educated will be more likely to find ways to access the treatment, for example through research and travelling to relevant centres. • It is not clear how patients would be clinically prioritised if demand for the technology is greater than the NHS capacity to deliver treatment. • There may be poorer access to treatment in health systems / hospitals with lower resource availability. • The treatment is a 14-day infusion and costs of travel and accommodation may be prohibitive for some people and their families.
13b. Consider whether these issues are different from issues with current care and why.	The issues are different because the technology is not routinely offered in the NHS at present thus the cohort of patients that would be eligible for this technology are currently not managed in routine NHS care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or **NO**

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259] 1 of 3

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Fulya Mehta
2. Name of organisation	NHS England
3. Job title or position	National Speciality Advisor Children and Young Adults Diabetes, NHS England Consultant Paediatrician, Alder Hey Children's hospital, Liverpool
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes? ☐ A specialist in the clinical evidence base for type 1 diabetes or technology? ☒ Other (please specify): National Speciality Advisor Children and Young Adult Diabetes, NHS England
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes

Clinical expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259] 3 of 3

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with type 1 diabetes or caring for a patient with type 1 diabetes. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
1 of 10

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
2 of 10

Part 1: Living with this condition or caring for a patient with type 1 diabetes

Table 1 About you, type 1 diabetes, current treatments and equality

1. Your name	Amy Norman
2. Are you (please tick all that apply)	☒ A patient with type 1 diabetes? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with type 1 diabetes? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with type 1 diabetes? If you are a carer (for someone with type 1 diabetes) please share your experience of caring for them	Our daughter was identified as being at stage 2 of type 1 diabetes through the ELSA study. She is currently undergoing regular testing and monitoring to track the progression of the condition. In addition to being her parent and carer, I also live with type 1 diabetes myself, having been diagnosed at the age of 13. I know firsthand how the condition affects every aspect of life. While I live a full and active life, it requires constant attention, planning, and thought to manage my health and ensure I do things safely. Because of my own lived experience, I'm especially aware of the challenges type 1 diabetes can bring—not just physically, but emotionally and socially as well. That's why I'm so motivated to support efforts that might delay the onset of the condition in our daughter. I want to give her as much time as possible before she has to take on the daily demands of managing type 1 diabetes
7a. What do you think of the current treatments and care available for type 1 diabetes on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Our daughter was identified at stage 2 of type 1 diabetes through the ELSA study. Now that her participation in the study is concluding, she has been placed under the care of the Early Type 1 Diabetes Clinic at Birmingham Children's Hospital. She has six-monthly reviews with a consultant via video call. As part of her monitoring, we test her blood glucose once a month, two

Patient expert statement

	hours after a carbohydrate-rich meal, using a blood glucose meter and testing strips provided by the NHS. Personally, I was diagnosed with type 1 diabetes at age 13 and currently manage it using closed-loop insulin therapy. I wear both an insulin pump and a continuous glucose monitor (CGM), which are funded by the NHS along with all necessary consumables. I attend six-monthly appointments with my local hospital's type 1 diabetes clinic. I'm very grateful for the care we receive through the NHS—it provides access to advanced technology and regular specialist support, which makes a significant difference in our day-to-day lives. That said, there are limitations, particularly in terms of capacity and consistency in care, especially when it comes to newer technology to treat the condition, which are still developing. Because of my lived experience, I understand how deeply type 1 diabetes impacts every part of life. It takes constant thought, planning, and adjustment. While I live a full life, the condition is always present. That's why I'm so motivated to support efforts to delay its progression in our daughter for as long as possible.
8. If there are disadvantages for patients of current NHS treatments for type 1 diabetes (for example, how they are given or taken, side effects of treatment, and any others) please describe these	One of the key challenges is learning how to use medical equipment such as insulin pumps and continuous glucose monitors (CGMs), which can be overwhelming, especially at the start. There is a learning curve that requires time, support, and confidence to manage effectively.

Patient expert statement

	Wearing medical devices on the body can also have a psychological impact. For some, the visibility of these devices can affect body image, confidence, and overall mental wellbeing, particularly in social or public settings. Managing fluctuating blood glucose levels—both high and low—can be unpredictable and stressful. It not only affects the person with type 1 diabetes but also has a significant impact on family life. For individuals who are still adjusting to managing their condition or who are struggling with control, this can be a constant source of worry and emotional strain for both them and their loved ones.
9a. If there are advantages of type 1 diabetes over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does teplizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	I've always lived by the mantra, "<i>I control it; it doesn't control me.</i>" That mindset has helped shape my understanding of type 1 diabetes and has been important in how I approach daily life with the condition. That said, if I had been given the option at 13 to delay the onset of type 1 diabetes, I would have taken it. Developing the condition during adolescence is incredibly challenging. I had to learn how to manage a complex medical condition while also navigating the usual pressures of growing up and trying to find my place in the world. It can have a real impact on a young person's mental health and emotional wellbeing. Type 1 diabetes hasn't stopped me from working or reaching my goals, but it does take more time, planning, and energy to get there. Every achievement

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
6 of 10

	comes with an added layer of effort that many people don't see—but it's always there
10. If there are disadvantages of teplizumab over current treatments on the NHS please describe these. For example, are there any risks with teplizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	One of the minor disadvantages was the time commitment required. Our daughter needed to attend hospital as a day case over a 14-day period. Some of the days were quite long, which understandably led to some boredom for her. Despite the length of the visits, she felt well throughout and did not experience any side effects. Her T-cell levels did drop during treatment, but this was within the expected range and gradually recovered over the course of the therapy. Subsequent blood tests have confirmed that all her levels have fully returned to normal.
11. Are there any groups of patients who might benefit more from teplizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	As someone living with type 1 diabetes, I strongly believe that all children identified as being at risk should be offered the opportunity to delay the onset of the condition. Giving them the chance to experience a more typical childhood—and to navigate adolescence without the added burden of managing type 1 diabetes—can make a meaningful difference to their overall wellbeing and development.
12. Are there any potential equality issues that should be taken into account when considering type 1 diabetes and teplizumab? Please explain if you think any groups of people with this condition are particularly disadvantage	As part of our daughter's treatment, we needed to stay close to the hospital in case of any complications. This meant spending two weeks in Birmingham, with both myself and my husband taking time off work. For

Patient expert statement

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.	some families, this could present a significant financial challenge, especially when factoring in travel, accommodation, and lost income.
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
8 of 10

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- All children within stage 2 of prediabetes should be given the opportunity to receive Teplizumab to delay the onset of Type 1 diabetes.
- The treatment should be offered in more NHS locations so it can be delivered universally to all – thus reducing the financial and time burden on families.
- Children who start treatment early helps protect their pancreas and keeps some natural insulin production going. This could make their future diabetes easier to manage and possibly prevent long-term complications.
- Often children are only diagnosed after a frightening health crisis like DKA (diabetic ketoacidosis). If we already know they're at risk, giving teplizumab can help prevent that traumatic experience altogether.
- If there's a treatment that can slow this disease and buy us more time as a family, it should be available on the NHS. Every child deserves the best chance at a healthy start, especially when science gives us that chance.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
9 of 10

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
10 of 10

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with type 1 diabetes or caring for a patient with type 1 diabetes. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
1 of 7

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
2 of 7

Part 1: Living with this condition or caring for a patient with type 1 diabetes

Table 1 About you, type 1 diabetes, current treatments and equality

1. Your name	Rachael Chrisp
2. Are you (please tick all that apply)	☐ A patient with type 1 diabetes? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with type 1 diabetes? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breakthrough T1D UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with type 1 diabetes? If you are a carer (for someone with type 1 diabetes) please share your experience of caring for them	
7a. What do you think of the current treatments and care available for type 1 diabetes on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for type 1 diabetes (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of type 1 diabetes over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does teplizumab help to overcome or address any of the listed disadvantages of current treatment that	

Patient expert statement

you have described in question 8? If so, please describe these	
10. If there are disadvantages of teplizumab over current treatments on the NHS please describe these. For example, are there any risks with teplizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from teplizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering type 1 diabetes and teplizumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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	

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
5 of 7

[Find more general information about the Equality Act and equalities issues here.](#)

13. Are there any other issues that you would like the committee to consider?

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
6 of 7

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]
7 of 7



in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Marie Westwood, Reviews Manager, KSR Ltd, United Kingdom (UK) Isaac Corro Ramos, Health Economics Researcher, Institute for Medical Technology Assessment (iMTA), EUR, the Netherlands (NL) Seamus Kent, Assistant Professor Health Technology Assessment (HTA), Erasmus School of Health Policy & Management (ESHPM), EUR, NL Kevin McDermott, Systematic Reviewer, KSR Ltd, UK Jiongyu Chen, Systematic Reviewer, KSR Ltd, UK Xiaoyu Tian, Systematic Reviewer, KSR Ltd, UK Caro Noake, Senior Information Specialist, KSR Ltd, UK Maiwenn Al, Associate Professor HTA, ESHPM, EUR, NL Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Correspondence to	Kleijnen Systematic Reviews Ltd. FAO Nigel Armstrong Unit 6, Escrick Business Park Riccall Road, Escrick York, YO19 6FD United Kingdom
Date completed	12/02/2025

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 17/07/83.

Declared competing interests of the authors

None.

[REDACTED]

Copyright belongs to Kleijnen Systematic Reviews Ltd.

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.

This report should be referenced as follows:

Westwood M, Corro Ramos I, Kent S, McDermott K, Chen J, Tian X, Noake C, Al M, Armstrong N. Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2025.

Contributions of authors

Marie Westwood and Nigel Armstrong acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Seamus Kent acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott, Jiongyu Chen and Xiaoyu Tian acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Marie Westwood and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADA	American Diabetes Association
AdViSHE	Assessment of the Validation of Health-Economic decision models
AE	Adverse events
AESI	Adverse events of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCinf	AUC extrapolated to infinity
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSPED	British Society for Paediatric Endocrinology and Diabetes
CADTH	Canadian Agency for Drugs and Technologies in Health
CD3	Cluster of differentiation 3
CDER	Center for Drug Evaluation and Research
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CGM	Continuous glucose monitoring
CI	Confidence interval
CMV	Cytomegalovirus
CRD	Centre for Reviews and Dissemination
CRS	Cytokine release syndrome
CS	Company submission
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
CYP	Children and young people
DKA	Diabetic ketoacidosis
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EBV	Epstein-Barr virus
ECM	Established clinical management
EOT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions-3-Levels
ESHPM	Erasmus School of Health Policy and Management
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GoF	Goodness-of-fit
Hb1Ac	Glycosylated haemoglobin
HCL	Hybrid closed loop
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health technology assessment
IA2	Tyrosine phosphatase islet antigen-2
ICA	Islet-cell antibody
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
INR	International normalisation ratio
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LYs	Life years
LYG	Life years gained
mAB	Monoclonal antibody
MDT	Multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
mIAA	Micro insulin autoantibody
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
NSC	National Screening Committee
OGTT	Oral glucose tolerance test
ONS	Office for National Statistics
PAS	Patient access scheme
PH	Proportional hazards
PK	Pharmacokinetic
PLGS	Predictive low-glucose suspend
PMN	Polymorphonuclear neutrophils
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RoB2	Cochrane risk of bias assessment tool
SAE	Serious adverse event
SE	Standard error
SES	Socioeconomic status
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Systems Organ Class
STA	Single technology appraisal
T1D	Type 1 diabetes
TA	Technology appraisal

TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
YHEC	York Health Economics Consortium
ZnT8	Zinc transporter protein 8

Table of Contents

Abbreviations	3
Table of Contents	6
Table of Tables	8
Table of Figures	10
1. Executive summary	11
1.1 Overview of the EAG's key issues	11
1.2 Overview of key model outcomes	12
1.3 The decision problem: summary of the EAG's key issues	12
1.4 The clinical effectiveness evidence: summary of the EAG's key issues	14
1.5 The cost effectiveness evidence: summary of the EAG's key issues	16
1.6 Summary of the EAG's view	18
2. Critique of company's definition of decision problem	20
2.1 Population	25
2.2 Intervention	27
2.3 Comparators	28
2.4 Outcomes	29
2.5 Other relevant factors	29
3. Clinical effectiveness	30
3.1 Critique of the methods of review	30
3.1.1 Searches	30
3.1.2 Inclusion criteria	31
3.1.3 Critique of screening and data extraction	33
3.1.4 Study retrieval	33
3.1.5 Quality assessment	35
3.1.6 Evidence synthesis	36
3.2 Critique of TN-10, its analysis and interpretation	37
3.2.1 Details of TN-10	37
3.2.2 Statistical analysis for the TN-10 trial	43
3.2.3 Baseline characteristics	44
3.2.4 Efficacy results of the TN-10 trial	47
3.2.5 Adverse events of the TN-10 trial	50
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison	62
3.4 Critique of the indirect comparison and/or multiple treatment comparison	62
3.5 Additional work on clinical effectiveness undertaken by the EAG	62
3.6 Conclusions of the clinical effectiveness section	62
4. Cost effectiveness	64
4.1 EAG comment on company's review of cost effectiveness evidence	64
4.1.1 Searches performed for CE Section	64
4.1.2 Inclusion/exclusion criteria	65
4.1.3 Conclusions of the CE review	65
4.2 Summary and critique of company's submitted economic evaluation by the EAG	66

4.2.1	NICE reference case checklist	66
4.2.2	Model structure	66
4.2.3	Population	68
4.2.4	Interventions and comparator.....	68
4.2.5	Perspective, time horizon and discounting.....	69
4.2.6	Treatment effectiveness and extrapolation.....	70
4.2.7	Health-related quality of life data identified in the review	83
4.2.8	Resources and costs	89
5.	Cost effectiveness results	98
5.1	Company's cost effectiveness results	98
5.1.1	Original company's CE results	98
5.1.2	Updated company's CE results	99
5.2	Company's sensitivity analyses.....	99
5.2.1	Probabilistic sensitivity analysis	99
5.2.2	Deterministic sensitivity analysis.....	101
5.2.3	Scenario analysis.....	102
5.3	Model validation and face validity check.....	105
5.3.1	Validation of the conceptual model	105
5.3.2	Input data validation.....	106
5.3.3	Validation of the computerised model (technical verification).....	106
5.3.4	Operational validation (validation of model outcomes).....	107
6.	External Assessment Group's additional analyses.....	112
6.1	Exploratory and sensitivity analyses undertaken by the EAG.....	112
6.1.1	Explanation of the EAG adjustments.....	112
6.1.2	EAG base-case	112
6.1.3	EAG exploratory scenario analyses	113
6.1.4	EAG subgroup analyses	114
6.2	Impact on the ICER of additional clinical and economic analyses undertaken by the EAG	116
6.2.1	Results of the EAG preferred base-case scenario	116
6.2.2	Results of the EAG PSA	117
6.2.3	Results of the EAG additional exploratory scenario analyses	118
6.3	EAG's preferred assumptions.....	121
6.4	Conclusions of the CE section.....	121
7.	References	126

Table of Tables

Table 1.1: Summary of key issues	11
Table 1.2: Key issue 1: Identification of people with Stage 2 T1D and definition of the population eligible for treatment with teplizumab	13
Table 1.3: Key issue 2: Appropriateness of ‘established clinical management’ as a comparator for treatment with teplizumab.....	13
Table 1.4: Key issue 3: Recruitment and generalisability of the teplizumab TN-10 trial population...	14
Table 1.5: Key issue 4: Treatment-emergent adverse events of special interest (AESI)	15
Table 1.6: Key issue 5: The EAG disagrees with the company’s approach of modelling progression to Stage 3 T1D	16
Table 1.7: Key issue 6: The EAG disagrees with the company’s approach of estimating a decline in disutility based on years lived with Stage 3 T1D.....	17
Table 1.8: Key issue 7: The EAG disagrees with the company’s approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs	18
Table 1.9: Individual impact of EAG preferred assumptions	18
Table 2.1: Statement of the decision problem (as presented by the company).....	20
Table 3.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence	31
Table 3.2: Risk of bias assessment of TN-10 using Cochrane RoB 2	35
Table 3.3: Summary of TN-10 methodology	37
Table 3.4: Eligibility criteria for TN-10.....	39
Table 3.5: Disposition of participants in the primary analysis of TN-10.....	41
Table 3.6: Baseline characteristics of participants in the primary analysis of TN-10	44
Table 3.7: Time from randomisation to onset of Stage 3 T1D (primary analysis)	47
Table 3.8: Sensitivity analysis of time to onset of Stage 3 T1D (TN-10; ITT population; sensitivity analysis at 5 years)	48
Table 3.9: C-peptide AUC at 6 months after enrolment (TN-10; ITT population).....	49
Table 3.10: ANCOVA analysis of C-peptide AUC slope over first 6 months in TN-10.....	49
Table 3.11: Insulin interval secretion (2 hours) at 6 months after enrolment (TN-10; ITT population)	50
Table 3.12: Summary of TEAEs at a median follow-up of 745 days (TN-10; safety population; primary analysis)	50
Table 3.13: Study design of trials included in the integrated safety analysis	51
Table 3.14: Treatment-emergent AESIs: Events by SOC and PTs (integrated safety population).....	52
Table 3.15: TEAEs by preferred term occurring in $\geq 5\%$ of participants in the teplizumab or placebo group at a median follow-up of 745 days (TN-10; safety population; primary analysis).....	54
Table 3.16: Treatment-emergent SAEs in TN-10 by PT/SOC	54
Table 3.17: Grade 3 TEAEs in the teplizumab and placebo groups of TN-10 by PT/SOC.....	55
Table 3.18: TEAEs by preferred term occurring in $\geq 5\%$ of participants in the teplizumab or placebo group in the integrated safety analysis.....	56
Table 3.19: Treatment-emergent SAEs in the integrated safety analysis by PT/SOC	58
Table 4.1: NICE reference case checklist	66
Table 4.2: Key baseline patient characteristics used in the economic model	68
Table 4.3: AIC and BIC statistics for time to onset of Stage 3 T1D using individual curves (ITT population)	73
Table 4.4: AIC and BIC goodness-of-fit criteria using individual curves (ITT population)	73
Table 4.5: Proportion of individuals in Stage 2 T1D by parametric fitting in placebo arm.....	76

Table 4.6: Proportion of individuals in Stage 2 T1D by parametric fitting in teplizumab arm	77
Table 4.7: AIC and BIC statistics for time to onset of Stage 3 T1D using joint curves (ITT population)	78
Table 4.8: AIC and BIC goodness-of-fit criteria using a joint model (ITT population).....	79
Table 4.9: HRs stratified by age at onset of Stage 3 T1D.....	81
Table 4.10: Adjusted HRs for all-cause mortality stratified by age at onset of Stage 3 T1D.....	82
Table 4.11: Meta-regression model for excess mortality.....	82
Table 4.12: AEs (and excess proportion) included in the economic model.....	83
Table 4.13: EQ-5D-3L utilities for the UK general population.....	84
Table 4.14: Multiple regression analysis on EQ-5D _{index} from Sparring et al. 2013	85
Table 4.15: Disutility values for people with Stage 3 T1D based on time since onset of Stage 3.....	86
Table 4.16: Number of carers/parents in families with dependent children in the UK.....	87
Table 4.17: Costs of administering teplizumab	90
Table 4.18: Use and costs of pre-infusion medications	90
Table 4.19: Costs of laboratory tests related to teplizumab treatment.....	91
Table 4.20: Costs of confirmatory tests prior to teplizumab treatment.....	91
Table 4.21: Annual healthcare resource use and costs for Stage 2 T1D.....	92
Table 4.22: Monthly costs for Stage 2 T1D.....	93
Table 4.23: Regression models for Stage 3 T1D healthcare costs.....	94
Table 4.24: Original regression models and EAG calibrated regression models for trend in Stage 3 T1D costs over time	96
Table 4.25: Adverse event frequency and management costs	97
Table 5.1: Company base-case deterministic CE results (teplizumab, PAS price, discounted)	98
Table 5.2: Disaggregated QALY results (teplizumab, discounted).....	98
Table 5.3: Disaggregated cost results (teplizumab, PAS price, discounted).....	98
Table 5.4: Updated company base-case deterministic CE results (teplizumab, PAS price, discounted)	99
Table 5.5: Company base-case probabilistic CE results (teplizumab, PAS price, discounted)	100
Table 5.6: Company scenario analysis results (teplizumab, PAS price, discounted)	104
Table 5.7: Comparison vs. NICE TA943 EAG Stage 3 T1D model	108
Table 5.8: Comparison vs. Roze et al. 2021 ⁴⁵ Stage 3 T1D model.....	109
Table 5.9: Comparison vs. Mital et al. 2020 ⁸³ Stage 3 T1D model.....	110
Table 5.10: Risk of progression to Stage 3 T1D onset in individuals diagnosed with Stage 2 T1D ..	110
Table 5.11: Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis).....	111
Table 6.1: Overview of key issues related to the CE	115
Table 6.2: EAG base-case deterministic CE results (teplizumab PAS price, discounted).....	116
Table 6.3: Disaggregated QALYs results (EAG base-case, discounted).....	116
Table 6.4: Disaggregated cost results (EAG base-case, teplizumab PAS price, discounted)	116
Table 6.5: EAG PSA results (teplizumab PAS price, discounted)	117
Table 6.6: Results of exploratory scenario analyses by the EAG (teplizumab PAS price, discounted)	119
Table 6.7: Individual impact of EAG preferred assumptions	121

Table of Figures

Figure 3.1: Flow chart of evidence identification	34
Figure 3.2: Trial design of TN-10 in the primary analysis and extended follow-up analysis.....	38
Figure 3.3: CONSORT diagram of participant disposition in TN-10.....	43
Figure 3.4: KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis).....	48
Figure 4.1: Model structure.....	67
Figure 4.2: Observed KM curves (ITT population).....	70
Figure 4.3: Log-cumulative hazard plot (ITT population).....	71
Figure 4.4: Schoenfeld residuals plot (ITT population).....	71
Figure 4.5: KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis).....	72
Figure 4.6: Time to Stage 3 T1D using individual curves (ITT population) – teplizumab arm	75
Figure 4.7: Time to Stage 3 T1D using individual curves (ITT population) – placebo arm.....	75
Figure 4.8: Observed hazard functions over time	77
Figure 4.9: Time to Stage 3 T1D parametric fits for individuals on teplizumab using a joint parametric distribution (ITT population)	79
Figure 4.10: Time to Stage 3 T1D parametric fits for individuals on placebo using a joint parametric distribution (ITT population)	80
Figure 4.11: Linear regression model for Stage 3 T1D disutilities according to time from onset.....	86
Figure 4.12: Trends in healthcare costs over time from Ou et al 2016. ²	94
Figure 4.13: Stage 3 T1D healthcare costs regression models versus observed data	95
Figure 4.14: Estimates of Stage 3 T1D healthcare costs from the company versus EAG estimates	96
Figure 5.1: PSA CE-plane (teplizumab, PAS price, discounted).....	100
Figure 5.2: PSA CEAC (teplizumab, PAS price, discounted)	101
Figure 5.3: DSA tornado diagram for incremental costs (teplizumab, PAS price, discounted)	102
Figure 5.4: DSA tornado diagram for incremental QALYs (teplizumab, PAS price, discounted).....	102
Figure 5.5: DSA tornado diagram for ICER (teplizumab, PAS price, discounted)	102
Figure 6.1: EAG probabilistic CE-plane (teplizumab PAS price, discounted).....	117
Figure 6.2: EAG base-case CEAC (teplizumab PAS price, discounted)	118

1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID6259	Summary of issue	Report Sections
1	Identification of people with Stage 2 T1D and definition of the population eligible for treatment with teplizumab; it is unclear how people with Stage 2 T1D, who are asymptomatic, would be identified in clinical practice in England.	2.1
2	Appropriateness of 'established clinical management' as a comparator for treatment with teplizumab: Given that people with Stage 2 T1D are not currently routinely identified in the NHS in England, the EAG questions the appropriateness of 'established clinical management' as a comparator for treatment with teplizumab in this population	2.3
3	Recruitment and generalisability of the teplizumab TN-10 trial population	3.2.1 and 3.2.3
4	Treatment-emergent adverse events of special interest (AESI)	3.2.5
5	The EAG disagrees with the company's approach of modelling progression to Stage 3 T1D	4.2.6
6	The EAG disagrees with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D	4.2.7
7	The EAG disagrees with the company's approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs	4.2.8
AESI = adverse events of special interest; EAG = External Assessment Group; NHS =National Health Service; T1D = type 1 diabetes		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- Using a multiplicative approach to the disutilities associated with Stage 3 type 1 diabetes (T1D), to be in line with the NICE reference case. However, as two of the three company defined

disutilities for this stage were set to zero in the EAG base-case, the additive and the multiplicative approach yielded the same results.

- Assuming a gamma distribution for both arms to model time to progression to Stage 3 T1D.
- Using life tables from before the coronavirus disease 2019 (COVID-19) pandemic (2017-2018) to estimate mortality in the general population.
- Forgoing the extra utility decline as function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point.
- Removing the one-off disutility for progressing to Stage 3 T1D.
- Applying the average monthly cost from Hex et al. 2024 as a fixed Stage 3 T1D health state cost.¹

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.

Overall, the technology is modelled to affect QALYs by:

- Increasing total QALYs by delaying the onset of Stage 3 T1D.
- Slightly improving caregiver quality of life.
- Slightly reducing the QALYs due to experiencing treatment-related adverse events (AEs).

Overall, the technology is modelled to affect costs by:

- Reducing costs due to Stage 3 T1D (by delaying its onset), which is more costly than Stage 2 T1D.
- Increasing costs due to treatment acquisition, administration and testing.
- Slightly increasing costs due to experiencing treatment-related AEs.

The modelling assumptions that have the greatest effect on the ICER are:

- The selection of different parametric curves to model progression to Stage 3 T1D.
- Forgoing extra utility decline depending on years since onset of Stage 3 T1D and retaining the decline in utility per year resulting from the general population.
- Applying the average monthly cost from Hex et al. 2024 as a fixed health state cost.¹

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, it is unclear how people with Stage 2 T1D would be identified for treatment in the National Health Service (NHS) in England (Table 1.2); because people with Stage 2 T1D are not routinely identified in the NHS in England, there is no established clinical management and this has implications for the comparators and costs of comparators included in the economic model (Table 1.3).

Table 1.2: Key issue 1: Identification of people with Stage 2 T1D and definition of the population eligible for treatment with teplizumab

Report Section	2.1
Description of issue and why the EAG has identified it as important	The population defined in the final NICE scope and in the CS is people aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia). However, given that people with Stage 2 T1D are asymptomatic and that, according to the submission from NHS England, there is currently ' <i>no commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes,</i> ' it is unclear how people with Stage 2 T1D would be identified such that people who could benefit from teplizumab would have equitable access to treatment.
What alternative approach has the EAG suggested?	The EAG has suggested that either screening/testing should be included in the intervention and the proposed screening/testing process should be included and appropriately costed (i.e. costs for the number of people tested per individual treated) in the economic model or the population should be limited to people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Either screening/testing should be included in the intervention and the proposed screening/testing process should be included and appropriately costed (i.e., costs for the number of people tested per individual treated) in the economic model or the population should be limited to people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected.
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; T1D = type 1 diabetes	

Table 1.3: Key issue 2: Appropriateness of 'established clinical management' as a comparator for treatment with teplizumab

Report Section	2.3
Description of issue and why the EAG has identified it as important	The comparator defined in the final NICE scope and in the CS scope is ' <i>established clinical management without teplizumab</i> ', with monitoring of blood glucose, psychosocial support and education listed as examples. However, since, as noted in Key issue 1, people with Stage 2 T1D are not currently routinely identified in the NHS in England. The EAG considers that if a condition is not routinely identified there cannot be established clinical management for that condition. This is consistent with the submission from NHS England which stated that there are no education or monitoring programmes, no provision for self-assessment of blood glucose and no provision for psychosocial assessment/support for people with people with Stage 2 T1D.

Report Section	2.3
What alternative approach has the EAG suggested?	The EAG has suggested that the comparator is no screening/ testing and no management and that this means that the cost of Stage 2 T1D in the comparator arm of the economic model should be zero.
What is the expected effect on the cost effectiveness estimates?	The ICER would probably increase.
What additional evidence or analyses might help to resolve this key issue?	The cost of Stage 2 T1D in the comparator arm of the economic model should be zero if the patients to be treated would be identified by a screening programme. If patients are identified incidentally, i.e., as appears to be currently the case, then the cost could be that of any management for such patients.
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; T1D = type 1 diabetes	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified two major concerns with the evidence presented on the clinical effectiveness of teplizumab. Participants in the teplizumab TN-10 trial were identified through another, ongoing, research study (the TrialNet Natural History/Pathway to Prevention study [TN-01; NCT00097292]); both the recruitment process and the generalisability of participants to the population, in the NHS in England, who may be eligible for treatment are unclear (Table 1.4). The potential impact of adverse events of special interest (AESIs) is unclear, in relation to the immunosuppressive effects of teplizumab (Table 1.5). ■ **Table 1.4: Key issue 3: Recruitment and generalisability of the teplizumab TN-10 trial population**

Report Section	3.2.1 and 3.2.3
Description of issue and why the EAG has identified it as important	Section B.2.3.1 of the CS states that: <i>'Participants in TN-10 were identified through the ongoing TrialNet Natural History/Pathway to Prevention study (TN-01; NCT00097292) that included relatives of people with Stage 3 T1D who were diagnosed with Stage 2 T1D.'</i> The number of participants in TN-10 appears to be very small, relative to the number of potentially eligible participants from TN-01 and the process of recruitment/selection is unclear. Together with the uncertainty about how people with Stage 2 T1D could be identified in the NHS in England (see Key issue 1), the EAG considers this means that the generalisability of the TN-10 trial population the population of people who are relatives of people with Stage 3 T1D and who have been diagnosed with Stage 2 T1D, and to clinical practice in the NHS in England is uncertain.
What alternative approach has the EAG suggested?	In addition to the alternative approaches suggested in Table 1.2, the EAG requested: A detailed description of how participants in TN-10 were selected from the eligible TN-01 population (participants in TN-01 who were autoantibody positive and who had dysglycaemia on OGTT)

Report Section	3.2.1 and 3.2.3
	- The number of participants in TN-01 met the eligibility criteria specified for TN-10 - A CONSORT diagram for TN-10. This diagram should include the steps for selecting participants from the eligible TN-01 population - Justification for how data from TN-10 can be generalised to a relevant clinical population in England
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Evidence to assess the generalisability of the trial patients to those who would be treated in UK clinical practice.
CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; OGTT = oral glucose tolerance test; T1D = type 1 diabetes; UK = United Kingdom	

Table 1.5: Key issue 4: Treatment-emergent adverse events of special interest (AESI)

Report Section	3.2.5
Description of issue and why the EAG has identified it as important	The EAG is concerned that the potential impact of AESIs is unclear, in relation to the immunosuppressive effects of teplizumab. Table 17 in the CS includes the overall number of treatment-emergent AESIs observed in the TN-10 trial (██████ in the teplizumab arm and █ in the placebo arm). AESIs are listed as including: Grade ≥ 3 infections (including all opportunistic infections), acute mononucleosis-like illness, lymphomas or other malignancies, major hypoglycaemia, Grade ≥ 3 liver function abnormalities (AST, ALT, bilirubin), Grade ≥ 3 thrombocytopenia, Grade ≥ 3 neutropenia, Grade ≥ 4 allergic/hypersensitivity reaction (through Study Day 365), Grade ≥ 3 rash, Grade ≥ 4 cytokine release syndrome (through Study Day 365), lymphocyte count $<500 \text{ mm}^3$ for 7 days or longer. No details of which of the listed AESIs occurred in TN-10 trial are reported. In addition, TN-10 is a small trial with only n=44 participants exposed to teplizumab treatment. Although other potential sources of safety data were briefly explored (integrated safety analysis [teplizumab n=773, placebo n=245], Section B.2.10.1.4 of the CS), AESI rates were not fully reported (only rates of cytokine release syndrome were provided).
What alternative approach has the EAG suggested?	The EAG requested: - Clarification on whether any participant in TN-10 experienced >1 treatment-emergent AESI - Details of each treatment-emergent AESI event (type, grade, time to resolution, whether hospitalisation was required) observed in TN-10 - Provision of any data for treatment-emergent AESI (as specified in Table 17 of the CS) collected for teplizumab, in its anticipated licensed dosing regimen or

Report Section	3.2.5
	the equivalent dose (e.g., as used in TN-10), in any study. Additional data were provided (see Section 3.2.5) and the EAG notes that treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular severe (≥ 3) neutropenia.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Provision of those AESI data mentioned above.
AESI = adverse events of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's cost effectiveness results are presented in Section 5, and the EAG's amendments to the company's model and results are in Section 6. The key issues in the cost effectiveness evidence are discussed below.

Table 1.6: Key issue 5: The EAG disagrees with the company's approach of modelling progression to Stage 3 T1D

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company assumed: • Different types of parametric distributions for the intervention and comparator arms (log-normal for teplizumab and exponential for ECM), which in general is not recommended. • An exponential distribution for ECM, where non-constant hazard functions are observed. • An exponential distribution for ECM results in the lowest long-term extrapolations compared to other choices. • A log-normal distribution for teplizumab results in the long-term extrapolations at the upper end compared to other choices. The EAG considers that this approach does not completely follow best practices and there is uncertainty about the long-term effects assumed for teplizumab.
What alternative approach has the EAG suggested?	The EAG assumed: • Same type of parametric distributions for both treatment arms (gamma). • Parametric distributions with non-constant hazard functions.

Report Section	4.2.6
	A more conservative approach for long-term extrapolations.
What is the expected effect on the cost effectiveness estimates?	The ICER increases.
What additional evidence or analyses might help to resolve this key issue?	Additional data to validate long-term projections. Fitting more complex models to the available data. Clearer and more detailed elicitation of expert opinion.
EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; T1D = type 1 diabetes	

Table 1.7: Key issue 6: The EAG disagrees with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company modelled QoL in Stage 3 T1D by applying three types of disutilities to the age dependent utility estimates of the general population after onset of Stage 3 T1D: - A disutility during the cycle of onset of Stage 3 T1D to reflect the adjustment of the patient to the next stage of the disease. - A disutility during all cycles in Stage 3 T1D to reflect the impact of having symptomatic T1D compared to the general population and patients in Stage 2 T1D. - A disutility that increases (becomes more negative) with time spent in Stage 3 T1D to reflect the accumulation of diabetes-related complications over time and their impact of HRQoL. Whilst the EAG considers this conceptually sound, the actual approach to estimating the time-dependent complication-related disutility appears to lead to double counting of the age-related decline in HRQoL associated to Stage 3 T1D.
What alternative approach has the EAG suggested?	The EAG considers that in the estimation of the time-dependent complication-related disutility the impact of age as observed in the general population should be taken into account. For the current data, the EAG preferred forgoing the extra utility decline depending on years since onset of Stage 3 T1D as the rate of decline was almost the same as the rate of decline in the general population.
What is the expected effect on the cost effectiveness estimates?	The ICER increases.
What additional evidence or analyses might help to resolve this key issue?	Re-analyse available (or new) data to ensure that no double counting of age-related decline in HRQoL occurs.
EAG = External Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QoL = quality of life; T1D = type 1 diabetes	

Table 1.8: Key issue 7: The EAG disagrees with the company's approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company assumed: - Average monthly cost per person from Hex et al. 2024 as the initial cost for individuals transitioning to Stage 3 T1D.¹ However, these costs are based on the prevalent population, including patients who developed Stage 3 T1D many years ago. - These initial costs were then extended over time according to modelled data from Ou et al. 2016 such that costs increase over time with the Hex et al. 2024 used for the initial costs. The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data,² is incorrect and substantially overestimates healthcare costs for Stage 3 T1D.
What alternative approach has the EAG suggested?	The EAG applied the average monthly cost from Hex et al. 2024 as a fixed health state cost of Stage 3 T1D. ¹
What is the expected effect on the cost effectiveness estimates?	The ICER increases.
What additional evidence or analyses might help to resolve this key issue?	Re-analyse available or new data to ensure that no overestimation of Stage 3 T1D costs occurs.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; T1D = type 1 diabetes	

1.6 Summary of the EAG's view

The step-by-step changes made by the EAG to derive its base-case, using the CS base-case and the model submitted after clarification as starting point, can be seen in Table 1.9. The change with the largest impact on the results was applying the average monthly cost from Hex et al. 2024 as a fixed health state cost.¹ Assuming a gamma distribution (individual fitting) for both treatment arms to model time to Stage 3 T1D onset, and forgoing extra utility decline depending on years since onset of Stage 3 T1D also had a major impact on the model results. The other two changes included in the EAG base-case (using 2017-2018 life tables and removing the one-off disutility for progressing to Stage 3 T1D) had an almost negligible impact on the results.

Table 1.9: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Teplizumab	██████	██████	██████	██████	27,534
ECM	██████	██████			
Time to Stage 3 T1D onset – individual fitting gamma (both arms)					
Teplizumab	██████	██████	██████	██████	61,078
ECM	██████	██████			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Life tables 2017-2018					
Teplizumab	██████	██████	██████	██████	27,368
ECM	██████	██████			
Extra utility decline depending on years since onset of Stage 3 T1D forgone					
Teplizumab	██████	██████	██████	██████	46,208
ECM	██████	██████			
One-off disutility for progressing to Stage 3 T1D removed					
Teplizumab	██████	██████	██████	██████	27,601
ECM	██████	██████			
Average monthly cost from Hex et al. 2024 for Stage 3 T1D					
Teplizumab	██████	██████	██████	██████	75,114
ECM	██████	██████			
EAG's base-case					
Teplizumab	██████	██████	██████	██████	165,387
ECM	██████	██████			
Based on the model submitted following the clarification phase. CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1D = type 1 diabetes					

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia).	People aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia).	NA – in line with the NICE final scope.	The clinical pathway, illustrated in Figure 2 in the CS, starts with people already diagnosed with Stage 2 T1D. However, as indicated in the submission from NHS England: <i>'There are no NICE guidelines for identification and management of stage 1 or stage 2 type 1 diabetes' and 'No commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes. Screening programs are only available via research trials.'</i> The EAG, therefore, considers that it is important to establish how, in practice, individuals eligible for treatment with teplizumab in the NHS in England would be identified.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				The EAG also notes that the evidence for the clinical effectiveness of teplizumab, included in the CS, was limited to people aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia), who were relatives of people with Stage 3 T1D.
Intervention	Teplizumab	Teplizumab	NA – in line with the NICE final scope.	The intervention is in line with the NICE scope.
Comparator(s)	Established clinical management without teplizumab including, but not limited to: • monitoring blood glucose • psychosocial support • education.	Table 1 in the CS states ' <i>As per final scope</i> ' and Figure 2 in the CS includes such management following diagnosis of Stage 2 T1D.	NA – in line with the NICE final scope.	The EAG notes that, as indicated above, there is currently no routine process to identify eligible patients in the NHS in England, and therefore it would seem that there is currently no established clinical management.
Outcomes	The outcome measures to be considered include: • progression from Stage 2 to Stage 3 T1D • time to starting insulin treatment • levels of stimulated C-peptide	The following outcomes have been included within this submission: • progression from Stage 2 to Stage 3 T1D (specifically time to progression and rate of progression) • time to starting insulin treatment	Table 1 in the CS states that the outcome ' <i>time to progression to Stage 3 T1D</i> ' (<i>measured in the teplizumab TN-10 trial</i>) is largely the same as ' <i>time to starting insulin treatment</i> ,' because insulin therapy is usually initiated immediately in children with newly diagnosed Stage 3 T1D, after presentation with symptoms and hyperglycaemia. ³ Table 1 further notes	None.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• symptoms and complications of T1D including incidence of DKA • mortality • adverse effects of treatment • HRQoL.	• levels of stimulated C-peptide • mortality • adverse effects of treatment HRQoL • impact on the patient • impact on caregiver.	that: <i>'Teplizumab is not expected to have a direct impact on the symptoms, complications or incidence of DKA at diagnosis. The longer-term effect of teplizumab on DKA has not been fully elucidated.'</i> Table 1 in the CS also provides references in support of the inclusion of the outcomes, 'impact on the individual'⁴⁻⁷ and 'impact on caregiver.'⁸	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into	The economic analysis will be carried out in line with the NICE reference case. The costs associated with diagnostic testing for pancreatic islet autoantibodies in people who would not otherwise have been tested are not included in the economic modelling.	In line with the anticipated marketing authorisation, the population of interest will already have received testing for autoantibodies and be diagnosed with Stage 2 T1D when considered for treatment with teplizumab. The economic analysis accounts for the cost of confirmatory tests in line with the SmPC prior to administration of teplizumab.■	As per the reference case. Note that if the population is all those who have been identified by screening then the cost of the diagnostic test should be included.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	account. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for pancreatic islet autoantibodies in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Subgroups to be considered	If evidence allows, consideration may be given to subgroups based on age. If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations.	Table 1 in the CS states: <i>'No subgroups to be considered.'</i>	Table 1 in the CS states: <i>'Given the small number of people diagnosed with Stage 2 T1D and the limited evidence on patient subgroups, the entire eligible patient population should be considered. In particular, the effect of teplizumab was consistent by age, and subgroups are therefore not considered. We would advise caution in interpreting data for subgroups given the small size of the TN-10 trial population.'</i>	Appendix E in the CS reports results from exploratory subgroups analyses.
Special considerations including issues related to equity or equality	None specified.	Table 1 in the CS states that: <i>'Potentially relevant equality considerations related to factors such as SES, ethnicity and age should be taken into account.'</i>	Table 1 in the CS states that: <i>'Potential equality issues have been identified by NICE in previous T1D assessments, including those related to SES, ethnicity, age, having cystic fibrosis-related T1D, and having</i>	The EAG notes that there may be potential inequalities in relation to the approach taken to identifying people eligible for treatment with teplizumab, e.g., treatment of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			<i>other conditions that prevent or hinder optimal use of an HCL device (e.g., skin conditions or allergies, learning difficulties, vision or hearing impairments, blood clotting disorders).'</i>	people identified through research studies could favour groups who are more likely to participate in research.
Based on Table 1 of the CS⁹ CE = cost effectiveness; CS = company submission; DKA = diabetic ketoacidosis; EAG = External Assessment Group; HCL = hybrid closed loop; HRQoL = health-related quality of life; NA = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SES = socioeconomic status; T1D = type 1 diabetes				

2.1 Population

The population defined in the final National Institute for Health and Care Excellence (NICE) scope¹⁰ is people aged 8 and over with Stage 2 type 1 diabetes (T1D) (2 or more pancreatic islet autoantibodies and dysglycaemia); this is consistent with the decision problem addressed by the company.⁹ The clinical pathway, proposed in the company submission (CS) (Figure 2), is consistent with this specification and starts with people already diagnosed with Stage 2 T1D.⁹ However, as indicated in the submission from National Health Service (NHS) England: *'There are no NICE guidelines for identification and management of stage 1 or stage 2 type 1 diabetes' and 'No commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes. Screening programs are only available via research trials.'*¹¹

Although the population included in the teplizumab TN-10 trial, the only trial included in the clinical effectiveness section (B.2) of the CS, was broadly consistent with that specified in the decision problem, all participants in TN-10 were relatives of people with Stage 3 T1D¹² and were participants in a research study (TrialNet natural History Study, TN-01).¹³

EAG comment: The EAG notes that, although the populations in the decision problem and scope appear to be the same, the method of identifying the patients for treatment with teplizumab could have profound implications for both the prognosis and treatment effect versus no teplizumab. If all patients eligible for teplizumab are to be identified then this raises the question as to whether the population is consistent with an intervention, which is, in fact, teplizumab plus screening/testing. Alternatively, if the intervention does not include a method of identifying the specified asymptomatic population and the costs of testing are not included in the economic model, the definition of the population should be *'people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected.'*

At clarification (Question A6), the EAG requested details of how patients eligible for treatment with teplizumab would be identified, in the NHS in England (including an estimate of how many people would be eligible to receive testing or screening for Stage 2 T1D annually and what proportion of these would be eligible to receive treatment with teplizumab). The company were also asked (Question A7) to consider the implications of this for the definition of the intervention and for the cost-effectiveness analysis (CEA).¹⁴ The company declined to provide a response to these questions, stating that: *'In summary, it would be inappropriate for Sanofi to respond to how early detection of T1D is delivered in the NHS in England, and we respectfully decline to answer these questions at this time.'*¹⁵ In support of this conclusion, the company noted that: *'The assessment and recommendation of population screening programmes is a responsibility of the National Screening Committee (NSC) and we believe it falls outside of NICE's remit.'* The company further stated that: *'The patient population in the final scope has also been defined in a way that reflects how eligible individuals are currently identified, through UK clinical practice and clinical research programmes,' and that: 'As described in the submission and aligned with the final scope, people over 8 years old are eligible for teplizumab if they have been diagnosed with Stage 2 T1D. This is identified by positive tests for ≥ 2 pancreatic islet autoantibodies and dysglycaemia (i.e., abnormal blood glucose levels, without overt hyperglycaemia).'*¹⁵

The EAG acknowledges that the recommendation of screening programmes is the responsibility of the NSC. However, the EAG maintains that where (as would be the case for the population described in the scope) diagnostic testing (pancreatic islet autoantibodies and/or blood glucose levels) is being applied in an asymptomatic population, it is necessary to define the criteria by which people will be identified

and selected for testing (since, by definition, people will not present with symptoms and hence, without selection criteria, there would be no way of knowing who should be tested). Irrespective of whether the process of identifying patients who are eligible for treatment is described as screening, it remains essential to define the selection criteria for diagnostic testing (pancreatic islet autoantibodies and/or blood glucose levels) in order for testing and treatment to be applied in practice.

The EAG further notes that, whilst the recommendation of screening programmes is the responsibility of the NSC, decisions to recommend treatments for asymptomatic patients (i.e., people who would not naturally present for testing and diagnosis) have the potential to affect prioritisation and resource use in the NSC.

In its response to clarification questions,¹⁵ the company stated that: *'that individuals are being identified outside of those (research) screening programme settings in the UK,'* citing recent research by the British Society for Paediatric Endocrinology and Diabetes (BSPED).¹⁶ This conference abstract reported findings from a survey of paediatric diabetes units in the United Kingdom (UK), with 76/84 responses from units in England and Wales, which collected information on the identification and management of children and young people (CYP) with ≥ 1 islet autoantibodies, who are not on insulin. Thirty-six percent (30/84) responding units reported managing a total of 111 CYP with ≥ 1 islet autoantibodies, who were not on insulin. The company noted that this abstract reported that CYP were identified from secondary (47%) and primary care (6%), as well as research platforms (47%). Importantly, the abstract additionally reported the reasons for early identification, which were listed as family screening (42%), clinical symptoms suggestive of new-onset diabetes (37%) and following an autoimmune screen (21%); since symptomatic patients are outside the scope of this assessment, all reported methods of early identification, used in the UK, involved some form of targeted screening. With respect to the testing of relatives of patients with T1D (the method used to identify patients for inclusion in the teplizumab TN-10 trial), the abstract noted that: 'Clinicians reported that if requested to test an unaffected sibling's diabetes risk, 17% would organise islet autoantibody testing in clinical care, 61% would refer to a research study and 17% would not test and reassure.'¹⁶

The EAG notes that, in the summary report of the company's advisory board meeting (provided at the EAG's request), it is stated that:¹⁷

[REDACTED] and
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Whether the population eligible for teplizumab i.e., in the decision problem are screened or identified incidentally, the EAG notes that it is not clear what proportion of the population in the decision problem, people aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia), have a relative with Stage 3 T1D. Furthermore, if testing of relatives of people with Stage 3 T1D (the most common route to early identification reported in the UK study cited by the company¹⁶) were to be considered as the pathway for identifying people with Stage 2 T1D, no information has been provided

about either the number of people who would be eligible for testing or the proportion of those tested who would be eligible for treatment with teplizumab.

In conclusion, there is uncertainty as to the nature of the population, which depends on how Stage 2 T1D patients are to be identified in clinical practice. This has implications for the generalisability of the trial data, where all patients were relatives of those with T1D, and it has implications for the nature of the intervention i.e., whether screening is included (see Section 2.2). Also, if screening is to be used then this would also have implications for the comparator (see Section 2.3). This is therefore a key issue.

2.2 Intervention

The intervention is teplizumab (Tziel[®]), as specified in the final NICE scope.¹⁰

Participants in the TN-10 trial received teplizumab via intravenous (IV) infusion, over 14 days, in an outpatient setting, according to the following regimen:¹²

- a dose of 51 mcg/m² of body surface area (BSA) on day 1
- a dose of 103 mcg/m² of BSA on day 2
- a dose of 207 mcg/m² of BSA on day 3
- a dose of 413 mcg/m² of BSA on day 4
- followed by a dose of 826 mcg/m² of BSA on each of days 5 through 14

The CS (Section B.2.3.4.1) notes that changes to the manufacturing process for teplizumab in 2018 resulted in a new drug product being manufactured (referred to as the commercial product).⁹ To demonstrate the pharmacokinetic (PK) comparability between the clinical trial product and the planned commercial product, a single dose comparability study and a PK sub-study was conducted which noted lower drug exposure (AUC extrapolated to infinity (AUCinf)) of the commercial product versus the clinical trial product. This resulted in the validation of an alternative 14-day dosing regimen of the commercial product with a higher cumulative dose to match the drug exposure of the TN-10 clinical trial product:

- A dose of 65 mcg/m² BSA on day 1
- A dose of 125 mcg/m² BSA on day 2
- A dose of 250 mcg/m² BSA on day 3
- A dose of 500 mcg/m² BSA on day 4
- A dose of 1,030 mcg/m² BSA on days 5 through 14

In a review by the US Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology (BLA761183), the adjusted dosing regimen for the commercial product matched the total exposure (AUCinf), peak concentration (C_{max} after the last dose) as well as trough concentrations after the last dose (C_{trough} after the last dose) in comparison to the clinical trial product during the 14-day regimen.¹⁸

EAG comment: The EAG agrees that the intervention is as specified in the NICE scope and that the dosing regimen reported for the commercial product is pharmacokinetically equivalent to that evaluated in the TN-10 trial.

However, the EAG considers that, given that people with Stage 2 T1D are asymptomatic and that there is currently *'no commissioned targeted or general population screening and monitoring programme to*

identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes,’ if the population is as defined in the decision problem and in Section 2.1 and includes all people aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) then it could be argued that the intervention should be defined as teplizumab plus screening. As noted in Section 2.1, a possible alternative would be to limit the population to people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected.

2.3 Comparators

The NICE final scope specifies *‘established clinical management without teplizumab’* as the comparator, with monitoring of blood glucose, psychosocial support and education listed as examples.¹⁰ The decision problem addressed in the CS and the clinical pathway illustrated in Figure 2 are consistent with this specification. However, as noted above, it is unclear how people with Stage 2 T1D would be identified for treatment in the NHS in England.

EAG comment: The EAG notes that, according to the submission from NHS England, *‘the pathway of care for the identification and treatment of stage 1 and stage 2 type 1 diabetes is not yet defined,’* specifically:¹¹

- *‘No commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes. Screening programs are only available via research trials.’*
- *‘No provision for psychosocial assessment / support following positive screening, which may lead to anxiety and disease monitoring burden.’*
- *‘No education or monitoring programs for people identified as stage 1 / stage 2.’*
- *‘No provision for self-monitoring of blood glucose to inform disease progression in those identified at risk of type 1 diabetes where OGTT is impractical or not available.’*
- *‘No pathway and new additional demand for glycaemic staging and surveillance in individuals identified as stage 1 / stage 2.’*
- *‘No provision for management of pregnant women identified as having stage 1 / stage 2 diabetes, with evidence on treatment limited.’*

With consideration to this submission, at clarification, the EAG sought confirmation that the comparator is no screening and no management and that this means that the cost of Stage 2 T1D in the comparator arm of the economic model would be zero.¹⁴ The company response stated that: *‘established clinical management for Stage 2 T1D consists of routine monitoring of blood glucose, psychosocial support and education on the management of T1D,’* and that: *‘This is aligned with the final scope, as well as current UK clinical management, international guidelines and UK expert opinion.’* The company further stated that: *‘Recent data published by BSPED indicates that more than half of children and young people with early-stage T1D are being identified in the NHS setting.’*¹⁶

The EAG notes that the BSPED data do not indicate that more than half of CYP with early-stage T1D are being identified in the NHS setting, but rather that of a total of 111 CYP with ≥ 1 islet autoantibody who were reported as being managed (across 84 units in the UK) and who were not on insulin (early-stage T1D), 53% (fewer than 60 patients) were identified in an NHS setting (either through targeted screening or clinical symptoms). The EAG therefore retains the view that, currently in England, most people with Stage 2 T1D are not being identified in the NHS and hence are not receiving any management (i.e., the cost of the comparator arm of the economic model should be zero).

There is therefore uncertainty as to the nature of the comparator: if Stage 2 T1D patients are to be identified by screening, then, for these patients, there cannot be any established clinical management (ECM), and so the comparator is no management. Only if Stage 2 T1D are continued to be detected incidentally can ECM resemble what is in the scope and the decision problem. This is therefore a key issue.

2.4 Outcomes

The CS included data for all outcomes listed in the NICE scope, with the exception of time to starting insulin treatment and symptoms and complications of T1D. The majority of these data were derived for the TN-10 trial; TN-10 did not include any measure to assess effects of teplizumab treatment on health-related quality of life (HRQoL).

Table 1 of the CS includes the following statements, with respect to outcome measures:

- *‘time to progression to Stage 3 T1D’* (measured in the teplizumab TN-10 trial) is largely the same as *‘time to starting insulin treatment’*
- *‘Teplizumab is not expected to have a direct impact on the symptoms, complications or incidence of DKA at diagnosis. The longer-term effect of teplizumab on DKA has not been fully elucidated.’*

EAG comment: The EAG agrees that time to starting insulin treatment is likely to be very similar to time to progression to Stage 3 T1D. The EAG notes that the CS does not include any assessment of possible long-term effects of teplizumab treatment on symptoms and complications of T1D that might potentially arise from delayed progression from Stage 2 to Stage 3 T1D. Diabetic ketoacidosis (DKA) was included in the adverse events (AEs) recorded in the TN-10 trial.

2.5 Other relevant factors

Table 1 in the CS states that: *‘Potentially relevant equality considerations related to factors such as SES, ethnicity and age should be taken into account.’*⁹

EAG comment: The EAG notes that there may be potential inequalities in relation to the approach taken to identifying people eligible for treatment with teplizumab, e.g., treatment of people identified through research studies could advantage groups who are more likely to participate in research.

3. Clinical effectiveness

A systematic literature review (SLR), reported in Appendix D of the CS,¹⁹ was conducted to identify evidence on the efficacy and safety of treatments which aim to delay the onset of Stage 3 T1D in children (≥ 8 years old) and adults.

3.1 Critique of the methods of review

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.^{9, 19} The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.²⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SLR conducted to identify evidence on the clinical efficacy and safety of treatments for the delay of Stage 3 T1D in children (≥ 8 years old) and adults at risk (e.g., familial risk) of developing T1D, and the delay of Stage 3 T1D in those people with Stage 2 T1D.¹⁹ Searches were conducted on 2 May 2023 and updated on 27 June 2024.

EAG comment:

- Searches were undertaken to identify clinical evidence on the clinical efficacy and safety of treatments for the delay of Stage 3 T1D in children (≥ 8 years old) and adults at risk (e.g., familial risk) of developing T1D, and the delay of Stage 3 T1D in those people with Stage 2 T1D. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{9, 15, 19, 21}
- The following databases were searched via the Ovid interface from inception on 2 May 2023: Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR). Update searches were conducted on 27 June 2024.
- Additional grey literature sources were also searched, including seven key conference proceedings which were manually searched where not available on Embase. Both ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) clinical trials registries were searched. Five health technology assessment (HTA) sources were also searched. These searches were limited from 2021 onwards.
- The database searches for the clinical effectiveness SLR combined facets for T1D and terms for the concepts of prevention or high risk, with a facet containing search terms for teplizumab and its comparators. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Animal-only studies were excluded, only conference proceedings were limited by date to those published since 2021.
- The EAG queried a disparity between the search results reported in the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart and those reported in the individual search tables in Appendix D.¹⁹ The company confirmed that the searches provided in the CS contained an early search conducted in February 2023 rather than those conducted in May 2023 which were used to inform the submission. The correct searches were provided in a revised Appendix D at clarification.^{15, 21}

- Both the MEDLINE and Embase search contained a limit to remove the following: “(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.”¹⁹ When queried the company explained that “These limits were included to remove papers where the singular use of these words only appeared in the title, with the goal of reducing the number of case studies brought in. We would expect that articles that met other criteria for capture would not have been eliminated.”¹⁵ Whilst the EAG understands the rationale for wanting to limit the number of unwanted case studies, the inclusion of the terms *male and female* may have been overly restrictive, but without rerunning the searches the EAG cannot say what impact this may have had on the overall recall of results.
- All searches were well structured, transparent and reproducible. Full details of the search terms used for the grey literature searches, not originally included in the CS, were provided in response to clarification.¹⁵
- All clinical effectiveness searches contained a good range of search terms, synonyms and subject headings. Where appropriate a search filter based on that developed by the Cochrane Collaboration was applied to identify clinical trials. The EAG considers these searches adequate and fit for purpose.
- The EAG queried whether any separate searches for AEs had been conducted. The company confirmed that no separate searches were undertaken to retrieve information regarding AEs for safety outcomes for teplizumab. Given that the main clinical effectiveness searches were restricted to randomised controlled trials (RCTs), guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.²²

3.1.2 Inclusion criteria

The CS¹⁹ states that an SLR was conducted on 2 May 2023 and updated on 27 June 2024 to identify clinical evidence on the efficacy and safety of treatments for the delay of Stage 3 T1D in children (≥ 8 years old) and adults with Stage 2 T1D or who are at risk (e.g., familial risk) of developing T1D. Five records related to one study were identified. The eligibility criteria used to select relevant studies are detailed in Table 3.1.

Table 3.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults and children (aged ≥ 8 years) at risk for developing T1D ^a OR those diagnosed with Stage 2 T1D	Studies not evaluating people at risk for T1D
		Studies not evaluating those with Stage 2 T1D

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	Mixed populations of people with results reported separately for the population of interest or at least 80% of the overall population has the indication of interest Subgroups: age (8 to <18 years, ≥18 years); sex (male, female); BMI z score (<median; ≥median); presence of autoantibodies (anti-GAD65, micro insulin, anti-IA2, ICA, anti-ZnT8); HLA-DR3 (absent, present); HLA-DR4 (absent, present); glucose level (<median, ≥median); C-peptide level (<median, ≥median)	Study participants are younger than 8 years of age
Intervention	Teplizumab or any treatment aimed at preventing/delaying the onset of Stage 3 T1D.	Treatments that are not licenced or recommended for the prevention/delay of T1D.
Comparators	Any approved treatment Placebo Best standard of care None (in the case of single-arm trials).	NA
Outcomes	Clinical Outcomes Rate of new diabetes cases For those at risk of diabetes: Time from randomisation/study enrolment to T1D diagnosis For those with Stage 2 T1D: Time from randomisation/study enrolment to onset of Stage 3 T1D T1D diagnosis C-peptide levels (including AUC and ratio values) Safety and Tolerability Outcomes Overall AEs Serious AEs (including grade 3 and 4 AEs) Treatment-emergent AEs Individual AEs occurring in ≥5% of the population in any treatment arm Treatment discontinuations (any reason or due to AE).	Relevant outcomes are not reported, or data are not extractable (i.e., only available from figures needing to be digitised).
		Studies evaluating a mixed population, but results are not reported separately for population of interest.
Study design	Clinical trials, including randomised-controlled, single-arm trials.	Editorial, letters to the editor, erratum, trial protocol, guideline, case reports, narrative reviews.

Clinical effectiveness	Inclusion criteria	Exclusion criteria
		In vitro, ex vivo, animal, or pharmacokinetic studies, phase I trials, gene studies, observational studies.
		SLRs/NMAs in T1D published since 2019 to be used for manual reference checks but will not be eligible for inclusion in the SLR
Timeframe	No time limit for full-text articles April 2021 to April 2023 for conference abstracts	Conference abstracts presented prior to 2021.
Language restrictions	English language	Full-text articles not published in English.
Adapted from Table 6, CS appendices¹⁹ ^a Including but not limited to (1) having a relative with T1D—if first degree, relative must be 8 to 45 years old (brother, sister, parent, or offspring) and if second degree, relative must be 8 to 20 years old (niece, nephew, aunt, uncle, grandchild, or cousin); (2) abnormal glucose tolerance by OGTT; or (3) presence of at least two confirmed diabetes autoantibodies. AE = adverse event; AUC = area under the concentration–time curve; BMI = body mass index; CS = company submission; GAD = glutamic acid decarboxylase; HLA = human leukocyte antigen; IA2 = tyrosine phosphatase islet antigen-2; ICA = islet-cell antibody; NA = not applicable; NMA = network meta-analysis; OGTT = oral glucose tolerance test; RCT = randomised controlled trial; SLR = systematic literature review; T1D = type 1 diabetes; ZnT8 = zinc transporter protein 8		

3.1.3 Critique of screening and data extraction

All studies identified were screened at title and abstract level (phase 1) by two independent reviewers against the inclusion/exclusion criteria. Where any disputes regarding eligibility arose, these were resolved through discussion or referred to a third reviewer. The CS states that phase 2 screening involved the assessment of any full-text articles that could not be excluded on the basis of title and abstract (phase 1),¹⁹ however, it was unclear how many reviewers were involved in phase 2 inclusion screening.

The CS provides no information on the processes for data extraction, however, in response to clarification questions, the company stated that: *‘Quality assessments were conducted by the initial team member during the extraction phase and then validated by a second team member as part of the validation step. Disagreements were resolved by a third reviewer.’* This statement appears to imply a common process for data extraction and quality assessment.

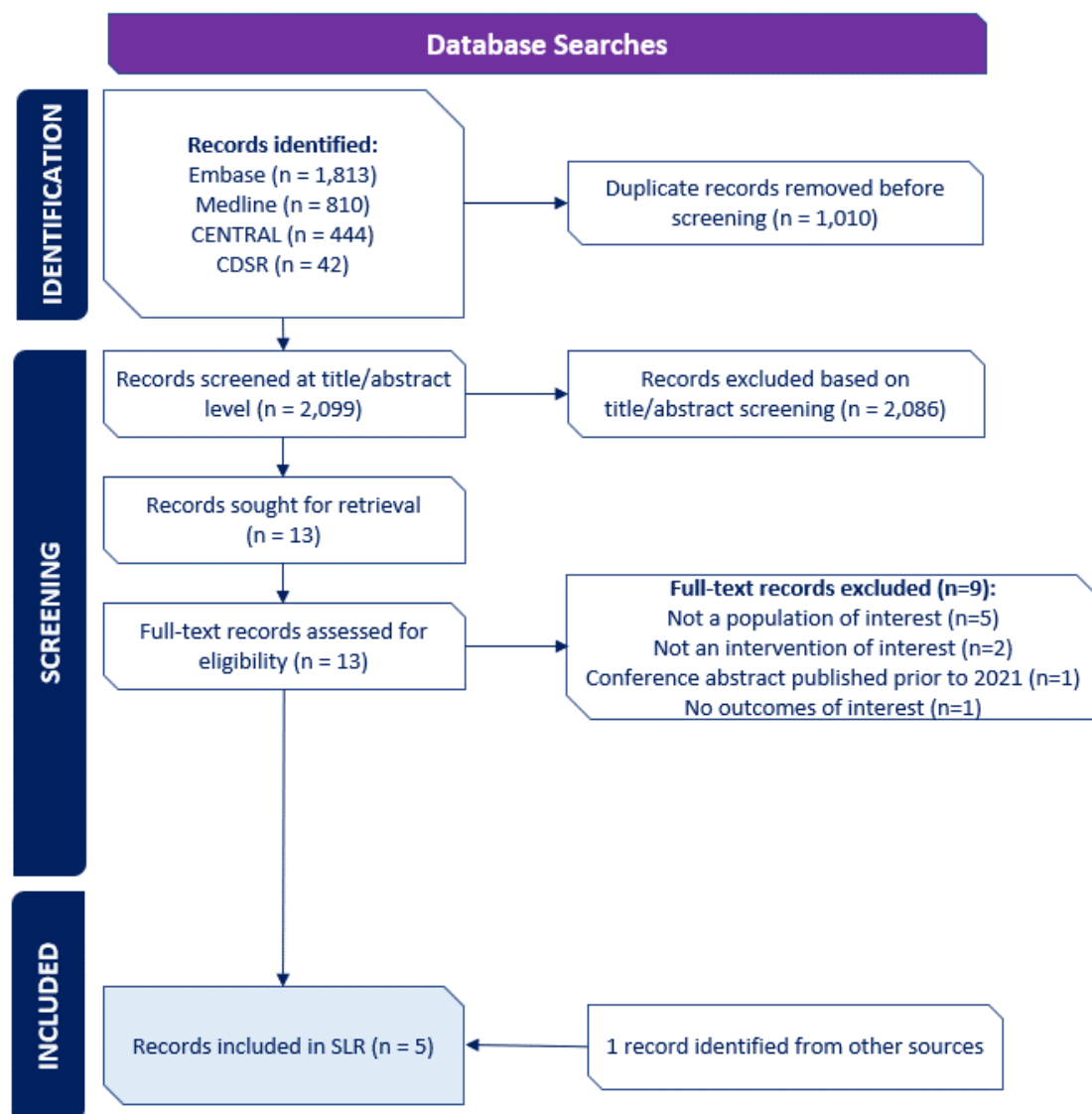
EAG comment: The EAG emphasises that adherence to standard SLR processes is important to ensure minimisation of error and bias. Full transparency and clarity in reporting is an essential part of the SLR process.

3.1.4 Study retrieval

A total of 3,109 titles and abstracts were identified from database searches; after deduplication, 2,099 unique titles/abstracts were screened. Of these, 13 records progressed to full-text screening, from which four records related to the same parent trial (Sanofi TN-10) met the inclusion criteria. Further

unpublished data were also identified in the TN-10 clinical study report (CSR) provided by Sanofi. This resulted in a total of five included records reporting on the one included RCT. Figure 3.1 illustrates the flow of studies through the SLR process.

Figure 3.1: Flow chart of evidence identification



Adapted from Figure 1, Appendix D in the CS¹⁹

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; SLR = systematic literature review

3.1.5 Quality assessment

The CS states that the Cochrane risk of bias assessment tool (RoB 2) as used, in accordance with NICE recommendations, to assess quality of the included trial (TN-10).⁹

The risk of bias assessment was conducted, based on the primary publication for TN-10 (Herold 2019),²³ and is reproduced in Table 3.2. TN-10 was rated low risk of bias on all domains of RoB 2 and hence low overall risk of bias.

Table 3.2: Risk of bias assessment of TN-10 using Cochrane RoB 2

Bias Domain	Questions	Response Options	Herold 2019 ²³
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	Y
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y / PY / PN / N / NI	Y
	1.3 Were there baseline imbalances that suggest a problem with the randomisation process?	Y / PY / PN / N / NI	N
	Risk-of-bias judgement	Low / High / Some concerns	Low
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	N
	2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	N
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA/ Y / PY / PN / N / NI	NA
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA/ Y / PY / PN / N / NI	NA
	2.5 Were any participants analysed in a group different from the one to which they were assigned?	Y / PY / PN / N / NI	N
	2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA/ Y / PY / PN / N / NI	NA
	Risk-of-bias judgement	Low / High / Some concerns	Low
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomised?	Y / PY / PN / N / NI	Y

Bias Domain	Questions	Response Options	Herold 2019 ²³
	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA/ Y / PY / PN / N / NI	NA
	3.3 If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	NA/ Y / PY / PN / N / NI	NA
	Risk-of-bias judgement	Low / High / Some concerns	Low
Bias in measurement of the outcome	4.1 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	N
	4.2 If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA/ Y / PY / PN / N / NI	NA
	Risk-of-bias judgement	Low / High / Some concerns	Low
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from...		
	5.1... multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	N
	5.2... multiple analyses of the data?	Y / PY / PN / N / NI	N
	Risk-of-bias judgement	Low / High / Some concerns	Low
Overall bias	Risk-of-bias judgement	Low / High / Some concerns	Low
Adapted from Table 8, CS appendices ¹⁹ Note: Responses in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used. N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; RoB2 = Cochrane risk of bias 2 assessment tool; SLR = systematic literature review; Y = yes			

EAG comment: The EAG agrees with the company's assessment that TN-10 has low risk of bias.

3.1.6 Evidence synthesis

The SLR identified one relevant RCT, TN-10,¹² the details of which are summarised in Section 3.2. Results from TN-10 have been reported in four publications.²³⁻²⁶

3.2 Critique of TN-10, its analysis and interpretation

3.2.1 Details of TN-10

Only one study¹² with four related publications²³⁻²⁶ met inclusion criteria. This study, entitled “*Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus*” (Provention Bio TrialNet [TN]-10 trial; NCT01030861), was a multicentre, phase II, randomised, placebo-controlled, double-blind trial evaluating the efficacy and safety of treatment with teplizumab in people with Stage 2 T1D. Included participants were people with Stage 2 T1D (≥ 8 years old) who were relatives of people with Stage 3 T1D with ≥ 2 or more diabetes-related autoantibodies detected in two samples obtained within six months before randomisation, and evidence of dysglycaemia during an OGTT. Participants in TN-10 were identified through the ongoing TrialNet Natural History/Pathway to Prevention study (TN-01; NCT00097292) that included relatives of people with Stage 3 T1D who were diagnosed with Stage 2 T1D.¹³ Seventy-six eligible participants were randomised 1:1 to receive either teplizumab or placebo via IV infusion (Figure 3.2).

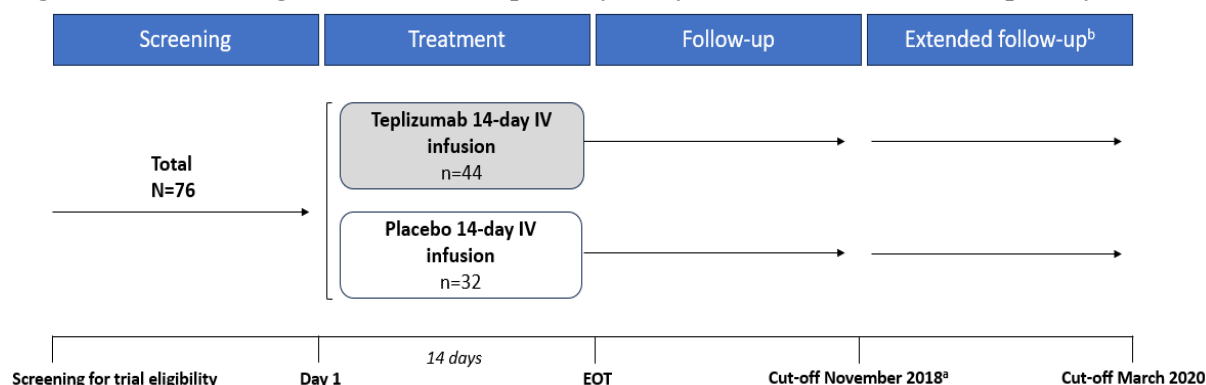
The CS notes that TN-10 was conducted at sites in the United States (US), Canada, Australia and Germany. The primary analysis was conducted based on data from July 2011 through November 2018.⁹ When the TN-10 trial ended in June 2019, participants who had not progressed to Stage 3 T1D continued to receive follow-up oral glucose tolerance test (OGTT) monitoring. An extended follow-up analysis was conducted based on data through March 2020 for these participants. Table 3.3 provides an overview of TN-10 methodology.

Table 3.3: Summary of TN-10 methodology

Trial number (acronym)	NCT01030861 (TN-10)
Location	US, Canada, Australia, Germany
Trial design	Phase II, randomised, placebo-controlled, double-blind
Eligibility criteria for participants	People with Stage 2 T1D (≥ 8 years old) who were relatives of people with Stage 3 T1D at the time of randomisation Presence of ≥ 2 or more diabetes-related autoantibodies detected in two samples obtained within 6 months before randomisation Evidence of dysglycaemia during an OGTT
Settings and locations where the data were collected	Outpatient sites
Trial drugs	Intervention: Teplizumab (n=44) Comparator: Placebo (n=32)
Permitted and disallowed concomitant medication	Prophylactic medications: Ibuprofen and antihistamine prior to infusion on the first 5 days of treatment; further dosing of ibuprofen, antihistamines and/or acetaminophen as needed Prohibited medications: Steroids or other immunosuppressive agents for the duration of the trial; live vaccinations for one year after treatment; killed virus vaccine < 4 weeks after treatment
Primary outcomes (including scoring methods and timings of assessments)	Time from randomisation to the onset of Stage 3 T1D (per ADA criteria), based on glucose testing, or the presence of unequivocal hyperglycaemia with acute metabolic decompensation (DKA); one of the following criteria must have been met on two occasions ≤ 1 day apart:

Trial number (acronym)	NCT01030861 (TN-10)
	- Symptoms of diabetes plus casual plasma glucose concentration >200 mg/dL (11.1 mmol/l), regardless of the time since last meal FPG ≥ 126 mg/dL (7 mmol/l) 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/l) Glucose testing (e.g., OGTT) was performed 3 months and 6 months after the infusions and every 6 months thereafter, with random screening glucose levels evaluated at 3-month intervals.
Other outcomes specified in the scope	Mortality
Pre-planned subgroups	Age Sex BMI z score HLA type Baseline C-peptide level Baseline glucose level Autoantibodies
Analyses	Primary analysis (data cut-off of 30 November 2018; median follow-up of 745 days) Extended follow-up analysis (data cut-off of March 2020; median follow-up of 923 days)
Adapted from table 6, CS ⁹ ADA = American Diabetes Association; BMI = body mass index; CS = company submission; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; HLA = human leukocyte antigen; OGTT = oral glucose tolerance test; T1D = type 1 diabetes	

Figure 3.2: Trial design of TN-10 in the primary analysis and extended follow-up analysis



Adapted from Figure 3, CS⁹

^a Data cut-off date for the primary analysis of TN-10

^b Data cut-off date for the extended follow-up analysis of TN-10

CS = company submission; EOT = end of treatment; IV = intravenous; T1D = type 1 diabetes

Randomisation of participants was stratified according to TrialNet site, age (<18 years or ≥ 18 years) and second OGTT results prior to treatment, and follow-up continued in the TN-10 trial until at least 40 participants were confirmed to have Stage 3 T1D. This point was selected as this cut-off provides 80% power to detect a reduction of 60% in the risk of Stage 3 T1D. Those who had not progressed to Stage 3 T1D by the end of the TN-10 trial continued to receive follow-up OGTT monitoring. Eligibility

for participation in the TN-10 trial included people with Stage 2 T1D (≥ 8 years old) who were relatives of people with Stage 3 T1D to facilitate identification of participants given the lack of a general population early detection programme. Participants were required to have ≥ 2 diabetes-related autoantibodies detected in two samples obtained within six months before randomisation, as well as evidence of dysglycaemia during an OGTT within 52 days before enrolment into the trial. Prior use of anti-CD3 treatment was prohibited at any time prior to randomisation and throughout the trial period.⁹ The eligibility criteria for TN-10 are summarised in Table 3.4.

Table 3.4: Eligibility criteria for TN-10

Inclusion criteria	Exclusion criteria
People with Stage 2 T1D who were relatives of people with Stage 3 T1D Aged ≥ 8 years Weight ≥ 26 kg at randomisation OGTT demonstrating abnormal glucose^a tolerance within 7 weeks (52 days) of the baseline visit (visit 0). Abnormal glucose tolerance was defined as: - FPG ≥ 110 mg/dL and < 126 mg/dL (6.1 to 6.9 mmol/L), or 2-hour plasma glucose ≥ 140 mg/dL and < 200 mg/dL (7.8 to 11.1 mmol/L), or 30, 60, or 90-minute value on OGTT ≥ 200 mg/dL Positive for ≥ 2 diabetes-related autoantibodies in two separate samples - The autoantibodies to be confirmed were anti-GAD65, IA2 or ICA512, mIAA, ZnT8 antibody and/or ICA	Participants aged ≥ 18 years with a diagnosis of diabetes or has a screening OGTT in which: - FPG was ≥ 126 mg/dL, or 2-hour plasma glucose was ≥ 200 mg/dL Participants aged < 18 years with a diagnosis of diabetes or has a screening random glucose ≥ 200 mg/dL Abnormal blood counts or laboratory chemical values including: - Lymphopenia ($< 1,000$ lymphocytes/μL) - Neutropenia ($< 1,500$ PMN/μL) - Thrombocytopenia ($< 150,000$ platelets/μL) - Anaemia (haemoglobin < 10 g/dL) - AST or ALT > 1.5 x ULN - Total bilirubin > 1.5 x ULN with the exception of subjects with the diagnosis of Gilbert's syndrome who might be eligible if they had no other causes leading to hyperbilirubinemia - INR > 0.1 above ULN Vaccination with a live virus within 8 weeks or a killed virus within 4 weeks Positive purified protein derivative test Any of the following conditions: - Current or past HIV, hepatitis B or hepatitis C infection - History of asthma or atopic disease requiring chronic treatment - Untreated hypothyroidism or active Graves' disease - Chronic active infection other than localised skin infections - Clinical evidence of acute infection with EBV or CMV - Infectious mononucleosis within the prior 3 months - Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject Current pregnancy/lactation or anticipated pregnancy Chronic use of steroids or other immunosuppressive agents Prior anti-CD3 treatment Administration of an mAb within the year before randomisation

Inclusion criteria	Exclusion criteria
	Current use of non-insulin pharmaceuticals that affect glycaemic control
Adapted from table 7 of the CS⁹ ^a In this study, fasting glucose levels of 110-125 mg/dL qualified subjects as having abnormal glucose tolerance, as it reflects the criteria used for entry into the DPT-1 study (National Diabetes Data Group 1979), which was used for the calculation of Stage 3 T1D risk in TN-10. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CD3 = cluster of differentiation 3; CMV = cytomegalovirus; CS = company submission; EBV = Epstein-Barr virus; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; HIV = human immunodeficiency virus; IA2 = islet antigen 2 antibody; ICA = islet cell antibodies; INR = international normalisation ratio; mAb = monoclonal antibody; mIAA = micro insulin autoantibody; OGTT = oral glucose tolerance test; PMN = polymorphonuclear neutrophils; T1D = type 1 diabetes; ULN = upper limit of normal; ZnT8 = zinc transporter 8	

Participants were randomised to receive teplizumab or placebo (saline) via IV infusion for 14-days in the outpatient setting. Teplizumab was administered according as follows:

- a dose of 51 mcg/m² of BSA on day 1
- a dose of 103 mcg/m² of BSA on day 2
- a dose of 207 mcg/m² of BSA on day 3
- a dose of 413 mcg/m² of BSA on day 4
- followed by a dose of 826 mcg/m² of BSA on each of days 5 through 14.

The company noted (CS Section B.2.3.4.1) that: *‘the manufacturing process for teplizumab was updated and moved to a new facility in 2018. This resulted in a new drug product being manufactured, further referred to as the commercial product. To demonstrate the pharmacokinetic (PK) comparability between the clinical trial product and the planned commercial product, a single dose comparability study and a PK sub-study was conducted. It highlighted the lower drug exposure (AUC_{inf}) of the commercial product vs. the clinical trial product. This resulted in the validation of an alternative 14-day dosing regimen of the commercial product with a higher cumulative dose to match the drug exposure of the TN-10 clinical trial product.’*⁹

Based on this, the anticipated licensed dosing regimen for teplizumab is:

- A dose of 65 mcg/m² BSA on day 1
- A dose of 125 mcg/m² BSA on day 2
- A dose of 250 mcg/m² BSA on day 3
- A dose of 500 mcg/m² BSA on day 4
- A dose of 1,030 mcg/m² BSA on days 5 through 14

The company go on to state that *‘In a review by the US Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology (BLA761183), the adjusted dosing regimen for the commercial product matched the total exposure (AUC_{inf}), peak concentration (C_{max} after the last dose) as well as trough concentrations after the last dose (C_{trough} after the last dose) in comparison to the clinical trial product during the 14-day regimen.’*⁹

Concomitant medications were assessed and recorded during the TN-10 trial. There was prophylactic administration of ibuprofen and antihistamine prior to teplizumab/placebo infusion on the first five days of treatment.¹² Additional dosing of ibuprofen, antihistamines and/or acetaminophen could be used as required for fever, malaise, headache, arthralgia or rash. To reduce the risk of infection and prevent impact on progression to Stage 3 T1D steroids or other immunosuppressive agents were prohibited for

the duration of the trial. Participants were instructed to not receive live vaccinations for one year after treatment or vaccinations with a killed virus vaccine <4 weeks after treatment.⁹

The primary outcome in TN-10 was the time from randomisation (day 0) to the onset of Stage 3 T1D. The TN-10 primary outcome is the key outcome in the CEA. C-peptide levels, in response to glucose load (OGTT) were assessed as a secondary, metabolic outcome; C-peptide levels were assessed as a surrogate marker beta-cell function and endogenous insulin production. Additionally, insulin data from the OGTT were used to measure insulin secretion in TN-10.⁹

One hundred and forty-six participants were identified from TN-01 trial and assessed for inclusion. Seventy participants were excluded as they were '*screening failures*' and 76 participants were randomised 1:1 to receive teplizumab (n=44) or placebo (n=32).^{12, 23} All 76 participants received the study treatment and were included in the intention-to-treat (ITT), full analysis set and safety populations.⁹ The 14-day treatment course had a completion rate of 97.7% for teplizumab and 93.8% for placebo (93.8%). Treatment discontinuation in all instances was due to protocol-specified drug withholding e.g., special circumstances, laboratory abnormalities or AEs (3.9%).⁹ 43.2% of participants in the teplizumab group and 65.6% of participants in the placebo group had completed the study (median follow-up: 745 days) by the primary analysis cut-off date 30 November 2018.⁹ The study was discontinued by six participants from both arms: lost to follow-up (n=1 in the placebo arm) and other (n=3 in the teplizumab group and n=2 in the placebo arm). However, three of these participants progressed to Stage 3 T1D prior to discontinuation (one in the teplizumab group and two in the placebo arm) and these progression events were included in the primary analysis.⁹ Table 3.5 summarises participant disposition for the primary analysis.

Table 3.5: Disposition of participants in the primary analysis of TN-10

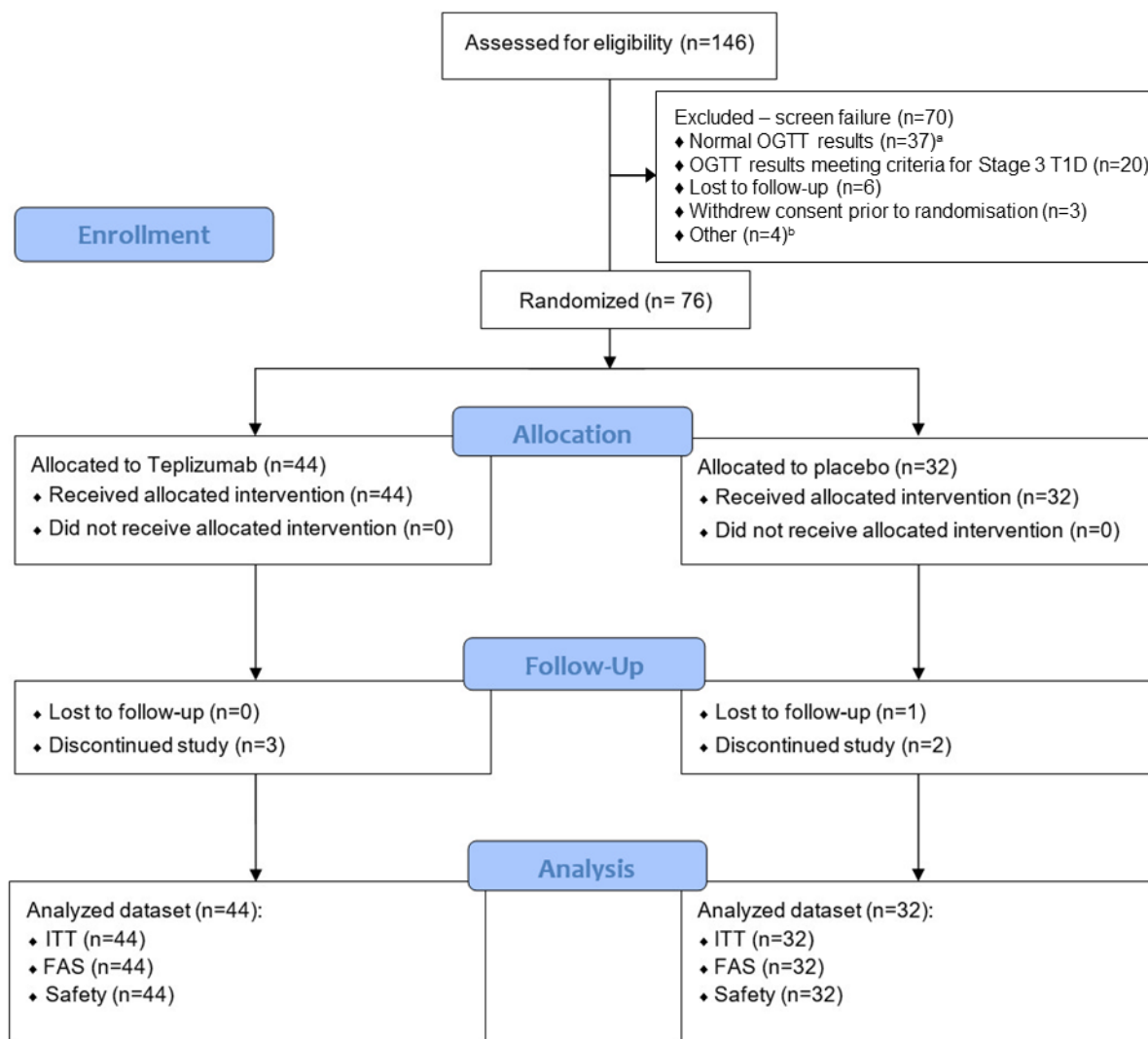
	Teplizumab	Placebo	Total
Screened	NA	NA	146
Randomised	44	32	76
Status at day 14			
Completed 14-day treatment course, n (%)	43 (97.7)	30 (93.8)	73 (96.1)
Discontinued from treatment course, n (%)	1 (2.3)	2 (6.3)	3 (3.9)
Protocol-specified drug withholding, n (%)	1 (2.3)	2 (6.3)	3 (3.9)
Status at time of primary analysis			
Completed study at cut-off date ^a , n (%)	19 (43.2)	21 (65.6)	40 (52.6)
Ongoing at cut-off date ^a , n (%)	22 (50.0)	8 (25.0)	30 (39.5)
Discontinued from study ^b , n (%)	3 (6.8)	3 (9.4)	6 (7.9)
Lost to follow-up, n (%)	0	1 (3.1)	1 (1.3)
Other, n (%)	3 (6.8)	2 (6.3)	5 (6.6)
Adapted from Table 9, CS ⁹			
^a TN-10 primary analysis cut-off date: 30 November 2018.			
^b Of the six participants who discontinued from the study, onset of Stage 3 T1D occurred in two participants in the placebo group and one in the teplizumab group (i.e., the primary endpoint was met) and were therefore already included in the primary endpoint analysis before discontinuing.			
CS = company submission; NA = not applicable; T1D = type 1 diabetes			

EAG comment: The EAG notes that the number of participants in TN-10 appears to be very small, relative to the number of potentially eligible participants from TN-01 and the process for

selecting/recruiting eligible participants from TN-01 is unclear. Taken together with the uncertainty about how people with Stage 2 T1D could be identified in the NHS in England, the EAG considers that there may be questions about the generalisability of the TN-10 trial population to clinical practice in the NHS in England. The EAG requested clarification on how participants in TN-10 were selected from the eligible TN-01 population (participants in TN-01 who were autoantibody positive and who had dysglycaemia on OGTT), the number of participants in TN-01 met the eligibility criteria specified for TN-10, and provision of a CONSORT diagram for TN-10 (specifically to include the steps for selecting participants from the eligible TN-01 population).

The company's response did not provide the total number of participants in TN-01 who met the eligibility criteria specified for TN-10, stating only that: *'A total of 146 individuals who were identified through the TrialNet Natural History/Pathway to Prevention study and gave informed consent for this study were assessed for eligibility in TN-10.'*¹⁵ A CONSORT diagram was provided (Figure 3.3), which started with the 146 TN-01 participants assessed for TN-10 eligibility.¹⁵

The EAG therefore considers that the extent to which participants in TN-10 are representative of the population of people who are relatives of people with Stage 3 T1D and who have been diagnosed with Stage 2 T1D remains unclear.

Figure 3.3: CONSORT diagram of participant disposition in TN-10

Adapted from Figure 1, Response to clarification questions¹⁵

^a Did not meet criteria for dysglycaemia on OGTT

^b Failed screening secondary to chronic steroid use (n=2), T1D autoantibody count not meeting criteria (n=1) and lymphopenia (n=1)

FAS = full analysis set; ITT = intention-to-treat; OGTT = oral glucose tolerance test; T1D = type 1 diabetes

3.2.2 Statistical analysis for the TN-10 trial

The primary analysis assessed the effect of teplizumab versus placebo on the risk of Stage 3 T1D onset in the ITT population. The cumulative incidence of Stage 3 T1D onset over time since randomisation within each treatment group was estimated using the Kaplan-Meier (KM) method (proportion surviving Stage 3 T1D-free as a function of time). The difference between groups in the cumulative incidence curves, and the associated hazard functions, were tested with a one-sided Wald test at the 0.025 significance level using the Cox proportional hazards model with discrete time intervals at the 6-month OGTT intervals. The treatment effect (hazard ratio, HR) of Stage 3 T1D onset between treatment arms was estimated from the proportional hazards model. The primary test of treatment effect was adjusted for design strata and any covariates identified as improving the log-likelihood at 0.10 level (two-sided). The candidate covariates tested for inclusion in the model were: sex, body mass index (BMI), HbA1c,

human leukocyte antigen (HLA) (DR3/4 versus others), baseline C-peptide (fasting, peak, area under the concentration–time curve [AUC]), baseline OGTT glucose (fasting, 2-hour, AUC), and autoantibody presence (mIAA, GADA, IA2A, ZnT8) at study entry. Sensitivity analyses of the primary endpoint conducted at five years evaluated three scenarios (Table 3.8).⁹

The primary analysis was planned for after 40 or more events (i.e., cases of Stage 3 T1D) had been reported in the full analysis set population, which included all participants who received any study drug and who participated in at least one post-baseline assessment.⁹

Participants who had not progressed to Stage 3 T1D by the end of TN-10 continued to be followed up and were included in the extended follow-up analysis of the primary endpoint, which was conducted after participants had been followed for a median of 923 days.⁹

Safety analyses were conducted in the safety population, which included all participants who received any study treatment.⁹

3.2.3 Baseline characteristics

The CS states that baseline characteristics of participants in the primary analysis of TN-10 were generally well-balanced between treatment groups (Table 3.6).⁹ However, typically where a difference of >5% exists in any characteristic, this should be highlighted as worthy of consideration. It is apparent that there were more participants <18 years in the placebo group than in the teplizumab group (81% versus 66%). There were more white participants in the teplizumab group compared to placebo (100% versus 93.8%) and more Asian participants in the placebo group (6.2% versus 0%). The relationships to a person with Stage 3 T1D also differed between arms with more sibling relationships in the teplizumab group (64% versus 50%). There were differences of >5% in rates of antibody positivity between the groups with higher rates of micro insulin positivity in the teplizumab group (45% versus 34%), and higher rates of anti-tyrosine phosphatase islet antigen-2 (IA2), harmonised, and islet-cell antibody (ICA) positivity in the placebo group (75% versus 61% and 88% versus 66%, respectively). Additionally the distribution of participants between groups who were positive for multiple autoantibodies also differed between the teplizumab and placebo groups.⁹

Table 3.6: Baseline characteristics of participants in the primary analysis of TN-10

	Teplizumab	Placebo
N	44	32
Age²³		
Median (IQR)	14 (12, 22)	13 (11, 16)
Range	8.5, 49.5	8.6, 45.0
Age <18 years (n, %)	29 (66)	26 (81)
Male sex (n, %)	25 (57)	17 (53)
Race (n, %)²³		
White	44 (100)	30 (93.8)
African American	0	0
Asian	0	2 (6.2)
Ethnicity (n, %)¹²		
Hispanic or Latino	1 (2.3)	1 (3.1)

	Teplizumab	Placebo
Non-Hispanic or Latino	43 (97.7)	29 (90.6)
Unknown	0	2 (6.3)
Relationship to person with Stage 3 T1D (n, %)²³		
Sibling ^a	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies^b (n, %)²³		
Anti-GAD65, harmonised	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti-IA2, harmonised	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median autoantibodies titre (IQR) ²³		
Anti-GAD65, harmonised	240 (76.8, 464)	221 (42.3, 520)
Micro insulin	0.0070 (0.0020, 0.028)	0.0040 (0.0020, 0.0168)
Anti-IA2, harmonised	52 (0, 310)	187 (26, 253)
ICA	20 (0, 200)	80 (20, 160)
Anti-ZnT8	0.157 (0.0133, 0.496)	0.096 (0.028, 0.386)
Number of autoantibodies positive^c (n, %)²³		
1	1 (2.4)	0
2	11 (25.0)	7 (21.9)
3	12 (27.3)	5 (15.6)
4	11 (25.0)	14 (43.8)
5	9 (20.5)	6 (18.8)
Median HbA1 _c (IQR) ²³	5.2 (4.9, 5.4)	5.3 (5.1, 5.4)
C-peptide AUC Mean, Median OGTT (nmol/L) ²³	1.76 (1.47, 2.18)	1.73 (1.44, 2.36)
HLA alleles present (n, %)²³		
Neither DR3 or DR4	5 (11.6)	3 (9.4)
DR3 only	10 (23.3)	8 (25.0)
DR4 only	17 (39.5)	14 (43.8)
Adapted from Table 10, CS ⁹		
^a Participants in this category may have had more than one sibling with Stage 3 T1D.		
^b Shown are the autoantibodies for which participants were positive at the time of randomisation. All participants were positive for at least two autoantibodies before randomisation.		

	Teplizumab	Placebo
^c This was at the time of randomisation. All subjects were positive for at least two autoantibodies prior to randomisation. AUC = area under the concentration–time curve; CCS = company submission; GAD = glutamic acid decarboxylase; HbA _{1c} = glycosylated haemoglobin; HLA = human leukocyte antigen; IA2 = tyrosine phosphatase islet antigen-2; ICA = islet cell antibodies; IQR = interquartile range; OGTT = oral glucose tolerance test; T1D = type 1 diabetes; ZnT8 = zinc transporter 8		

EAG comment: The EAG notes that no UK patients were included in TN-10. Further, it is unclear how asymptomatic people would be identified for testing (pancreatic islet autoantibodies and dysglycaemia) to diagnose Stage 2 T1D, in the NHS in England; it is not clear whether people would be tested on the basis of a familial relationship with someone with T1D (as was the case in TN-01). The EAG requested justification of how these data can be generalised to a relevant clinical population in England and Wales. In their response to clarification, the company stated that *‘the effectiveness of teplizumab demonstrated in TN-10 is likely to be generalisable to English and Welsh populations with Stage 2 T1D as these populations are expected to have a similar prognosis in terms of progressing from Stage 2 to Stage 3 T1D as the participants in TN-10.’* The EAG notes that no evidence was provided to this statement. The company further stated that: *‘evidence from observational studies and UK clinical expert opinion suggests that their progression through the T1D continuum would be comparable to European populations that include both relatives and non-relatives of individuals with Stage 3 T1D.’* Two sources were cited in support of this statement: The first is a German study (Fr1da) which the company state found that the risk of progression in children with presymptomatic T1D is not significantly associated with having a first-degree relative.²⁷ The second source was described as advice from UK clinicians at a Sanofi advisory board who indicated that they did not expect the mechanism of T1D to be dissimilar for those who do and do not have a relative with Stage 3 T1D, however, no source document for this advice was provided with the initial submission; where clinical opinion is used we would expect this to be accompanied by a justification of why clinical opinion is applicable to the question (it is not clear how questions about the underlying mechanism of a disease would be informed by clinical experience), details of the clinicians providing the opinion and their experience, as well as details of how questions were framed and in what setting opinion was sought. The company also stated that: *‘Further supporting this expectation, the recently published 2025 guidance from the American Diabetes Association (ADA) also highlights that findings from a study of cohorts from Germany, Finland, and the US suggest ‘that the same sequence of events led to clinical disease in both “sporadic” and familial cases of T1D’ (insert cs response).’* The EAG notes that, whilst some evidence has been provided to support the view that having a first degree relative with T1D does not affect risk of progression from pre-symptomatic T1D to Stage 3 T1D, this is not the same as evidence that there is no variation in the mechanism of progression and that any such variation would not result in variation in the effects of teplizumab.

The source clinical expert opinion (a summary report of a UK advisory board meeting, organised and funded by Sanofi) was provided following a request by the EAG.

█; details of the disciplines and experience of the participants in this advisory board were provided separately in Appendix M of the CS.¹⁷ The text of the advisory board summary report indicates where opinion is based on assumptions rather than experience/evidence:¹⁷

[REDACTED]

[REDACTED]

With respect to generalisability to the UK, the advisory board summary report notes that:¹⁷

[REDACTED]

3.2.4 Efficacy results of the TN-10 trial

3.2.4.1 Time from randomisation to the onset of Stage 3 T1D (primary outcome)

The median time from randomisation to onset of Stage 3 T1D, the primary endpoint of TN-10, was 49.5 months in the teplizumab group and 24.9 months in the placebo group, with a difference of 24.6 months. Onset of Stage 3 T1D occurred in 45% (20/44) of the individuals treated with teplizumab and in 72% (23/32) of the individuals treated with placebo as of the data cut-off date of 30 November 2018.⁹ Results of the primary analysis are provided in Table 3.7 and Figure 3.4.

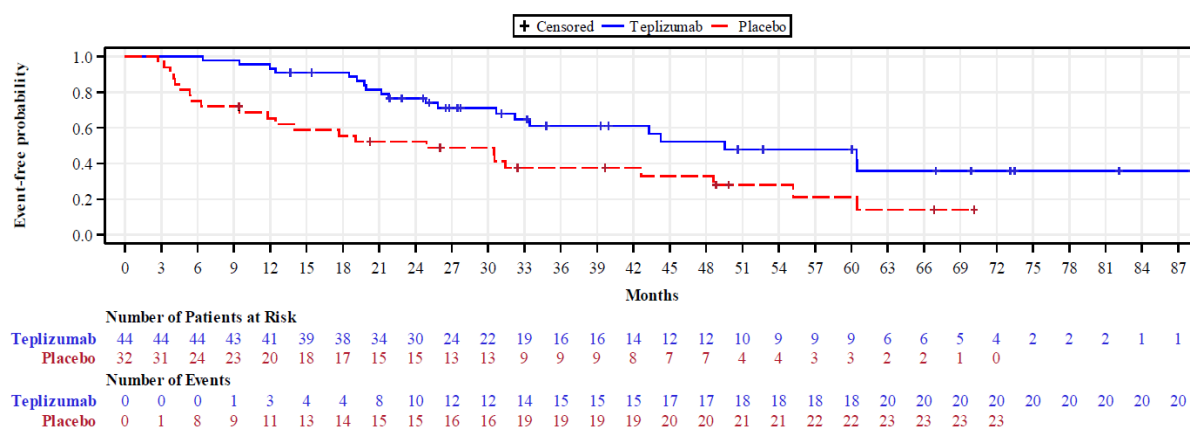
Table 3.7: Time from randomisation to onset of Stage 3 T1D (primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Primary analysis		
Median (95% CI)	49.5 months (32.2, NE)	24.9 months (9.5, 48.6)
Median difference (95% CI)	24.6 months (NE, NE)	
HR (95% CI); p value	0.41 (0.22, 0.78); p=0.0066	
Extended follow-up analysis		
Median (95% CI)	59.6 months ██████████	27.1 months ██████████
Median difference (95% CI)	32.5 months ██████████	
HR (95% CI); p value	0.457 (NR); p=0.01	
Based on Table 2 in the response to clarification questions ¹⁵ CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; T1D = type 1 diabetes		

In their response to clarification questions, the company stated that: ‘In the primary analysis of the TN-10 trial, the median follow-up time was [REDACTED] days (approximately [REDACTED] months; range: [REDACTED] days) for the teplizumab group and [REDACTED] days (approximately [REDACTED] months; range: [REDACTED] days) for the placebo group, with the follow-up period ending at the time of Stage 3 T1D onset.’¹⁵

At a median follow-up time of 745 days (range: 74, 2,683), treatment with teplizumab resulted in a statistically significant delay in the progression to Stage 3 T1D (HR: 0.41; 95% confidence interval [CI]: 0.22 to 0.78; $p=0.0066$ by adjusted Cox PH model), see Figure 3.4.⁹

Figure 3.4: KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis)



Based on Figure 4 in the CS⁹

CS = company submission; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

The results of the 5-year sensitivity analysis of the primary endpoint, indicating consistent results across three scenarios are summarised in Table 3.8.

Table 3.8: Sensitivity analysis of time to onset of Stage 3 T1D (TN-10; ITT population; sensitivity analysis at 5 years)

Scenario	HR (95% CI); p value
1: Stage 3 T1D onset was delayed from <12 months to 1 year for participants in the placebo group^a	0.43 (0.22, 0.81); $p=0.0089$
2: Participants with early withdrawal considered^b	0.42 (0.22, 0.78); $p=0.0065$
3: Combined assumptions for scenarios 1 and 2	0.43 (0.23, 0.81); $p=0.0086$
Based on Table 14 in the CS ⁹	
^a Stage 3 T1D onset was delayed to 1 year for 13 participants who had a follow-up duration <12 months and had onset of Stage 3 T1D.	
^b Stage 3 T1D onset was assumed at last evaluation for 3 participants who prematurely withdrew from the study or were lost to follow-up, including 1 participant in the placebo group and 2 participants in the teplizumab arm.	
CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; T1D = type 1 diabetes	

3.2.4.2 Time from randomisation to the onset of Stage 3 T1D (extended follow-up analysis)

In the extended follow-up analysis, the median follow-up time was 923 days (range: 74, 3,119). At follow-up, 50% (22/44) of teplizumab-treated individuals had not progressed to Stage 3 T1D, compared to 22% (7/32) of placebo group. Teplizumab significantly delayed the median time to onset of Stage 3 T1D by 2.7 years compared with placebo (59.6 versus 27.1 months, respectively; HR: 0.457; $p=0.01$ by adjusted Cox PH model).⁹

In their response to clarification questions, the company stated that: *'In the extended follow-up analysis, the reported median follow-up time for all participants was 923 days (approximately 30.3 months;*

range: 74 to 3,119). The median follow-up times for each treatment arm are not available for the extended follow-up analysis, and thus Sanofi are unable to provide these data.¹⁵

EAG comment: The EAG note that there is a discrepancy in median survival between the Primary analysis and the Extended follow-up analysis in that the median survival increases (Table 3.7). An increase in the median would suggest that some of those patients who were censored turned out not to have experienced onset of Stage 3 T1D until later than the time that they were censored.

3.2.4.3 C-peptide response (secondary outcome)

C-peptide, a marker of beta-cell function and endogenous insulin production, was better preserved with teplizumab. The average on-study C-peptide AUC was significantly higher with teplizumab versus placebo (1.94 versus 1.72 pmol/ml, $p=0.006$). Teplizumab also reversed the decline seen with placebo in the first six months ($p=0.0015$) (Table 3.9).

At six months, mean C-peptide AUC was 2.06 pmol/ml with teplizumab versus 1.68 pmol/ml with placebo. The difference in pre- versus post-treatment slopes was significant for teplizumab ($p=0.04$). C-peptide preservation remained significant at 24 months (██████ overall; ██████ in those progressing to Stage 3 T1D).⁹ In response to clarification questions, the company stated that: '24-month C-peptide AUC data were available for 30/44 participants in the teplizumab arm and 15/32 participants in the placebo arm' and '24-month C-peptide AUC data were available for 9/44 participants in the teplizumab arm and 8/32 participants in the placebo arm who progressed to Stage 3 T1D during the study'.¹⁵

Table 3.9: C-peptide AUC at 6 months after enrolment (TN-10; ITT population)

	Teplizumab (n=44)	Placebo (n=32)
C-peptide AUC at 6 months (pmol/ml), mean (IQR)	2.06 (1.55, 2.58)	1.68 (1.20, 2.15)
Difference between pre- versus post-treatment slopes	p=0.04	p>0.05
Difference between post-treatment slopes ^a	p=0.0015	
Based on Table 15 in the CS ⁹		
^a ANCOVA comparison corrected for age and pre-treatment slope		
ANCOVA = analysis of covariance; AUC = area under the concentration–time curve; CS = company submission; IQR = interquartile range; ITT = intention-to-treat		

The EAG requested confirmation that all study participants had a 6-month OGTT that contributed to this analysis to which the company responded that 'All participants in the teplizumab arm (n=44/44) and all except four participants in the placebo arm (n=28/32) were analysed for C-peptide response at 6 months.' The EAG also requested confirmation that only one OGTT per participant was included in this analysis, or details on how multiple OGTTs per participant were handled. The company stated that 'Since TN-10 was designed as a time-to-event protocol, the variable time in the study for each participant made it a challenge to analyse the metabolic responses from the multiple OGTTs available per participant.¹⁷ Therefore, average on-study C-peptide, glucose and glycosylated haemoglobin (HbA1c) AUCs were used, which included all the available data for each participant.'¹⁵

The EAG requested full numerical results, not just p values, for all comparisons of slope presented in Table 3.9, to which the company provided additional detail, summarised in Table 3.10.

Table 3.10: ANCOVA analysis of C-peptide AUC slope over first 6 months in TN-10

Covariate	Coefficient	Standard Error	t-test	p-value

Intercept	-0.0234	0.00715	-3.27	0.00166
Pre-slope	-0.078	0.0438	-1.78	0.0795
Age	0.000469	0.000284	1.65	0.103
Teplizumab treatment	0.0219	0.00662	3.31	0.00149
Based on Table 3 of the response to clarification questions ¹⁵ ANCOVA = analysis of covariance; AUC = area under the concentration-time curve				

3.2.4.4 Insulin secretion (secondary outcome)

Insulin secretion, measured via OGTT, was significantly higher with teplizumab at six months ($p=0.01$), and the change from baseline was greater versus placebo ($p=0.0004$) (Table 3.11).

Table 3.11: Insulin interval secretion (2 hours) at 6 months after enrolment (TN-10; ITT population)

	Teplizumab (n=44)	Placebo (n=32)
Pre-treatment slope	-1,024.0	-1,245.0
Post-treatment slope	1,085.8	-1,037.4
Difference between pre- and post-treatment slope ^a	p=0.01	p=0.80
Difference between post-treatment slopes ^a	p=0.0004	
Based on Table 16 in the CS ⁹		
^a Wilcoxon signed-rank (paired) test		
AUC = area under the concentration-time curve; CS = company submission; ITT = intention-to-treat		

3.2.5 Adverse events of the TN-10 trial

3.2.5.1 Overview of TEAEs

The company reported the incidence of treatment-emergent adverse events (TEAEs) and treatment discontinuations in the teplizumab and placebo arms of TN-10, which can be found in Table 3.12.

Table 3.12: Summary of TEAEs at a median follow-up of 745 days (TN-10; safety population; primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Any TEAE, n (%)	██████	██████
Any treatment-emergent AESI, n (%) ^a	██████	█
Any treatment-emergent SAE, n (%)	7 (15.9) ^b	1 (3.1)
TEAE leading to treatment interruption, n (%)	██████	█
TEAE leading to treatment withdrawal, n (%)	1 (2.3)	2 (6.3)
TEAE related to study drug, n (%)	██████	██████
Death	0	0

Based on Table 17 of CS⁹

^aAESI included the following: Grade ≥ 3 infections (including all opportunistic infections), acute mononucleosis-like illness, lymphomas or other malignancies, major hypoglycaemia, Grade ≥ 3 liver function abnormalities (AST, ALT, bilirubin), Grade ≥ 3 thrombocytopenia, Grade ≥ 3 neutropenia, Grade ≥ 4

	Teplizumab (n=44)	Placebo (n=32)
allergic/hypersensitivity reaction (through Study Day 365), Grade ≥ 3 rash, Grade ≥ 4 cytokine release syndrome (through Study Day 365), lymphocyte count < 500 mm ³ for 7 days or longer		
^b Eight SAEs occurred in 7 participants in the teplizumab arm		
ALT = aspartate aminotransferase; AST = alanine aminotransferase; AESI = adverse event of special interest; CS = company submission; SAE = serious adverse event; TEAE = treatment-emergent adverse event		

3.2.5.2 treatment-emergent adverse events of special interest (AESI)

For treatment-emergent adverse events of special interest, the EAG requested clarification as to whether any participant experienced more than one AESI to which the company responded that '██████████ participants in the teplizumab group each had one AESI; ██████████'. The EAG also requested details of each AESI event (type, grade, time to resolution, whether hospitalisation was required) to which the company responded that: 'The AESIs were ██████████ events of ██████████ for each event) ██████████. ██████████, was considered ██████████ to the study drug. The other ██████████ were considered ██████████. ██████████ resolved by the end of the study.' The EAG was concerned that the small number of patients included in TN-10 may not be sufficient to adequately assess the risk of AESI associated with teplizumab treatment and requested that the company provide any data for AESI (as specified in Table 17 of the CS)⁹ collected for teplizumab, in its anticipated licensed dosing regimen or the equivalent dose (e.g., as used in TN-10), as described in section B.2.3.4.1 of the CS; this should include data from any study over the entire development of the product, regardless of anticipated indication during this period. The company provided additional AESI data from an 'integrated safety analysis' combining data from five trials (AbATE, Protégé, Encore, DELAY and TN-10), which evaluated three different teplizumab dosing regimens.^{15, 28} Details of the studies included in the integrated safety analysis are provided in Table 3.13 and AESI data from the integrated safety analysis are summarised in Table 3.14.

Table 3.13: Study design of trials included in the integrated safety analysis

	AbATE	Protégé	Encore	DELAY	TN-10
Population	Individuals aged 8 to 30 years with Stage 3 T1D	Individuals aged 8 to 35 years with Stage 3 T1D	Individuals aged 8 to 35 years with Stage 3 T1D	Individuals aged 8 to 30 years with Stage 3 T1D	Individuals aged 8 to 45 years with Stage 2 T1D
Treatment groups	Teplizumab: 52 Standard of care: 25	Teplizumab: 453 Placebo: 98	Teplizumab: 192 Placebo: 62	Teplizumab: 31 Placebo: 27	Teplizumab: 44 Placebo: 32
Teplizumab dose and dosing schedule, n	9,034 mcg/m ² over 14 days	9,034 mcg/m ² (full) over 14 days (n=245) 2,985 mcg/m ² (1/3) over 14 days (n=102) 2,426 mcg/m ² (6-day) over 6 days (n=106)	9,034 mcg/m ² over 14 days (n=63) 2,985 mcg/m ² (1/3) over 14 days (n=66) 2,426 mcg/m ² over 6 days (n=63)	9,034 mcg/m ² over 14 days	9,034 mcg/m ² over 14 days
Teplizumab regimen	2 courses: Baseline	2 courses: Baseline	2 courses: Baseline	1 course: Baseline	1 course: Baseline

	AbATE	Protégé	Encore	DELAY	TN-10
	12 months	6 months	6 months		
Follow-up timepoints	Baseline Month 6 Month 12 Month 18 Month 24	Baseline Day 140 Month 12 Month 18 Month 24	Baseline Day 140 Month 12 Month 18 Month 24	Baseline Month 6 Month 12	Baseline Month 3 Month 6 Every 6 months thereafter
Based on Table 6 of the response to clarification questions ¹⁵ mcg = microgram; T1D = type 1 diabetes					

Table 3.14: Treatment-emergent AESIs: Events by SOC and PTs (integrated safety population)

SOC^c PT	Teplizumab N=791^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a			
Blood and lymphatic system disorders			
Neutropenia			
Lymphadenopathy			
Lymphopenia			
Thrombocytopenia			
Infections and infestations			
Epstein-Barr viremia			
Cellulitis			
Infectious mononucleosis			
Gastroenteritis viral			
Herpes zoster			
Gastroenteritis			
Infection			
Pneumonia			
Anal abscess			
Appendicitis			
Arthritis infective			
Conjunctivitis			
Dengue fever			
Epstein-Barr virus infection			
Hepatic amoebiasis			
Liver abscess			
Malaria			
Mononucleosis syndrome			
Pilonidal cyst			

SOC ^c PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Staphylococcal sepsis			
Tuberculosis			
Wound infection			
Wound infection staphylococcal			
Investigations			
Epstein-Barr virus antibody positive			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Cytomegalovirus test positive			
Gamma-glutamyl transferase increased			
Epstein-Barr virus test positive			
Blood bilirubin increased			
Nervous system disorders			
Hypoglycaemic seizure			
Hypoglycaemia unconsciousness			
Hypoglycaemic coma			
Skin and subcutaneous tissue disorders			
Pruritus			
Rash			
Based on Table 9 of the response to clarification questions¹⁵ ^a Subjects who had more than one AE or SAE for a treatment were counted once. ^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count. ^c Only SOC with subject count meeting threshold are included. SOCs and PTs are based on MedDRA version 23.0 AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TESAE = treatment-emergent serious adverse event			

The following additional information was provided:¹⁵

- **‘Grade ≥3 infections:** Reported in [REDACTED] of the teplizumab group and [REDACTED] of the control group
- **Acute mononucleosis-like illness:** [REDACTED]
- **Lymphomas or other malignancies:** [REDACTED]
- **Major hypoglycaemia:** [REDACTED]
- **Grade ≥3 liver function abnormalities:** [REDACTED]
- **Grade ≥3 thrombocytopenia:** [REDACTED]
- **Grade ≥3 neutropenia:** [REDACTED]

- **Grade ≥ 4 allergic/hypersensitivity reaction:** [REDACTED]
- **Grade ≥ 3 rash:** [REDACTED]
- **Grade ≥ 4 CRS:** [REDACTED]
- **Severe lymphopenia (lymphocyte count $<500 \text{ mm}^3$ for ≥ 7 days):** [REDACTED]

EAG comment: The EAG notes that treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular ≥ 3 neutropenia.

3.2.5.3 TEAEs by preferred term

The company reported that “The most common TEAEs in the teplizumab group were lymphopenia (72.7%), leukopenia (20.5%), rash pruritic ([REDACTED]%) and nasopharyngitis ([REDACTED]%).” Further details can be found in Table 3.15.

Table 3.15: TEAEs by preferred term occurring in $\geq 5\%$ of participants in the teplizumab or placebo group at a median follow-up of 745 days (TN-10; safety population; primary analysis)

Preferred term, n (%)	Teplizumab (n=44)	Placebo (n=32)
Any TEAE	[REDACTED]	[REDACTED]
Leukopenia	9 (20.5)	0 [REDACTED]
Lymphopenia	32 (72.7)	2 (6.3)
Neutropenia	[REDACTED]	[REDACTED]
Nasopharyngitis	[REDACTED]	[REDACTED]
Pneumonia	[REDACTED]	[REDACTED]
Sinusitis	[REDACTED]	[REDACTED]
Upper respiratory tract infection	[REDACTED]	[REDACTED]
Rash	[REDACTED]	[REDACTED]
Rash pruritic	[REDACTED]	[REDACTED]
Headache	5 (11.4)	[REDACTED]
Vomiting	[REDACTED]	[REDACTED]
Bronchospasm	[REDACTED]	[REDACTED]
Cough	[REDACTED]	[REDACTED]
Hypertension	[REDACTED]	[REDACTED]
Hyperbilirubinemia	[REDACTED]	[REDACTED]
Based on Table 18 of the CS ⁹		
CS = company submission; TEAE = treatment-emergent adverse event		

EAG comment: The EAG requested that the company provide a breakdown of all treatment-emergent SAEs and grade ≥ 3 TEAEs by preferred term (PT), for the teplizumab group and for the placebo group, to which the company provided detail in Tables 3.16 and 3.17.

Table 3.16: Treatment-emergent SAEs in TN-10 by PT/SOC

PT/SOC	Severity	Causality	Action	Reason for SAE	Outcome
Teplizumab					

PT/SOC	Severity	Causality	Action	Reason for SAE	Outcome
Pneumonia/ Infections and Infestations	■	■	■	■	■
Dizziness/ Nervous system disorders	■	■	■	■	■
Ankle fracture/ Injury, poisoning and procedural complications	■	■	■	■	■
Serum sickness/ Immune disorders	■	■	■	■	■
Musculoskeletal chest pain/ Musculoskeletal and connective tissue disorders	■	■	■	■	■
Cellulitis/ Infections and infestations	■	■	■	■	■
Wound infection/ Infections and infestations	■	■	■	■	■
Gastroenteritis/ Infections and infestations	■	■	■	■	■
Placebo					
Pelvi-ureteric obstruction/ Renal and urinary disorders	■	■	■	■	■
Based on Table 4 of the response to clarification questions ¹⁵ PT = preferred term; SAE = serious adverse event; SOC = System Organ Class					

Table 3.17: Grade 3 TEAEs in the teplizumab and placebo groups of TN-10 by PT/SOC

Grade 3 TEAEs, n (%)	Teplizumab (n=44)	Placebo (n=32)
≥1 Grade 3 TEAE ^{a,b}	■	■
Blood and lymphatic system disorders	■	■
Lymphopenia	■	■
Leukopenia	■	■
Infections and infestations^a	■	■
Pneumonia	■	■
Cellulitis	■	■
Gastroenteritis	■	■

Wound infection		
Nervous system disorders		
Peripheral motor neuropathy		
Peripheral sensory neuropathy		
Syncope		
Gastrointestinal disorders		
Oesophageal food impaction		
Injury, poisoning and procedural complications		
Ankle fracture		
Post-traumatic pain		
Tendon rupture		
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain		
Immune system disorders		
Serum sickness		
Renal and urinary disorders		
Nephrolithiasis		
Pelvi-ureteric obstruction		
Based on Table 5 of the response to clarification questions ¹⁵		
^a Data was missing for one participant in the placebo group.		
^b		
PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event		

EAG comment: The EAG requested that the above safety data also be provided for the integrated safety analysis population. The company provided data on TEAEs occurring in $\geq 5\%$ of the integrated safety population and on treatment-emergent SAEs; these data are summarised in Tables 3.18 and 3.19. The company further noted that breakdown of all Grade ≥ 3 TEAEs is not available for this population.

In the integrated safety analysis, TEAEs occurring in $\geq 5\%$ of participants occurred in individuals () and individuals () in the teplizumab and control groups, respectively.¹⁵

Table 3.18: TEAEs by preferred term occurring in $\geq 5\%$ of participants in the teplizumab or placebo group in the integrated safety analysis

SOC ^c PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a			
Blood and lymphatic system disorders (total)			
Lymphopenia			
Leukopenia			
Neutropenia			
Thrombocytopenia			

SOC^c PT	Teplizumab N=791^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Anaemia			
Eosinophilia			
Investigations			
Blood bicarbonate decreased			
Haemoglobin decreased			
Aspartate aminotransferase increased			
Alanine aminotransferase increased			
Blood sodium decreased			
Blood alkaline phosphatase increased			
Blood calcium decreased			
Blood potassium increased			
Blood albumin decreased			
Blood bilirubin increased			
Gamma-glutamyl transferase increased			
Blood creatinine increased			
Blood potassium decreased			
Infections and infestations			
Upper respiratory tract infection			
Nasopharyngitis			
Pharyngitis			
Skin and subcutaneous tissue disorders			
Rash			
Pruritus			
Metabolism and nutrition disorders			
Hyponatraemia			
Hypocalcaemia			
Hyperkalaemia			
Hypoalbuminemia			
Hypoglycaemia			
Hypokalaemia			
Hypercalcaemia			
General disorders and administration site conditions			
Pyrexia			
Fatigue			
Chills			
Gastrointestinal disorders			

SOC ^c PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Nausea			
Vomiting			
Diarrhoea			
Abdominal pain			
Abdominal pain upper			
Nervous system disorders			
Headache			
Respiratory, thoracic, and mediastinal disorders			
Oropharyngeal pain			
Cough			
Renal and urinary disorders			
Proteinuria			
Immune system disorders			
Cytokine release syndrome	46 (5.8)	3 (1.2)	49 (4.8)
Hepatobiliary disorders			
Hyperbilirubinemia			
Based on Table 7 of the response to clarification questions ¹⁵ ^a Subjects who had more than one AE or SAE for a treatment were counted once. ^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count. ^c Only SOC with subject count meeting threshold are included. SOCs and PTs are based on MedDRA version 23.0 AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.			

At least one type of treatment-emergent serious adverse event (TESAE) occurred in [REDACTED] individuals ([REDACTED]) and [REDACTED] individuals ([REDACTED]) in the teplizumab and control groups, respectively.¹⁵

Table 3.19: Treatment-emergent SAEs in the integrated safety analysis by PT/SOC

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Subjects with at least one type of event of interest^a			
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
Hyperglycaemia			
Hypoglycaemia			
Diabetes mellitus inadequate control			
Dehydration			
Diabetic ketosis			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Ketoacidosis			
Ketosis			
Infections and infestations			
Gastroenteritis			
Cellulitis			
Gastroenteritis viral			
Infection			
Pneumonia			
Anal abscess			
Appendicitis			
Arthritis infective			
Bronchitis			
Dengue fever			
Epididymitis			
Gastritis viral			
Hepatic amoebiasis			
Hepatitis A			
Infectious mononucleosis			
Paronychia			
Pharyngotonsillitis			
Pilonidal cyst			
Pulmonary tuberculosis			
Pyelonephritis			
Renal abscess			
Sepsis			
Staphylococcal sepsis			
Tuberculosis			
Urinary tract infection			
Wound infection			
Nervous system disorders			
Hypoglycaemic seizure			
Hypoglycaemia unconsciousness			
Hypoglycaemic coma			
Central nervous system haemorrhage			
Dizziness			
Gastrointestinal disorders			
Gastritis			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Abdominal pain			
Abdominal pain upper			
Diarrhoea			
Intestinal obstruction			
Nausea			
Vomiting			
Immune system disorders			
Cytokine release syndrome			
Drug hypersensitivity			
Hypersensitivity			
Serum sickness			
Injury, poisoning and procedural complications			
Splenic rupture			
Ankle fracture			
Concussion			
Facial bones fracture			
Fall			
Fibula fracture			
Foot fracture			
Skull fracture			
Upper limb fracture			
Blood and lymphatic system disorders			
Neutropenia			
Lymphopenia			
General disorders and administration site conditions			
Non-cardiac chest pain			
Pyrexia			
Pain			
Psychiatric disorders			
Suicide attempt			
Hallucination			
Mental disorder			
Renal and urinary disorders			
Intercapillary glomerulosclerosis			
Ketonuria			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
Microalbuminuria			
Pelvi-ureteric obstruction			
Hepatobiliary disorders			
Biliary dyskinesia			
Biloma			
Cholecystitis acute			
Hepatosplenomegaly			
Investigations			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Magnetic resonance imaging brain abnormal			
Eye disorders			
Cataract subcapsular			
Corneal erosion			
Skin and subcutaneous tissue disorders			
Rash			
Cardiac disorders			
Acute myocardial infarction			
Cardio-respiratory arrest			
Ventricular tachycardia			
Ear and labyrinth disorders			
Deadness neurosensory			
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Metastatic malignant melanoma			
Pregnancy, puerperium and perinatal conditions			
Complication of pregnancy			
Vascular disorder			
Subclavian vein thrombosis			
Based on Table 8 of the response to clarification questions ¹⁵			
^a Subjects who had more than one AE or SAE for a treatment were counted once.			

SOC PT	Teplizumab N=791 ^b n (%)	Control N=245 n (%)	Total N=1,018 n (%)
^b Delay subjects initially randomised to the control arm, who were later also eligible for the open-label course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of subject count. SOCs and PTs are based on MedDRA version 23.0 AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SOC = Systems Organ Class; TESA = treatment-emergent serious adverse event			

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable (see Section 3.4).

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS (Section B.2.9) states that: *‘Teplizumab is a first-in-class treatment, representing the only therapy approved worldwide to delay the onset of Stage 3 T1D in adults and children 8 years of age and older with Stage 2 T1D. The only comparator described in the final NICE scope is established clinical management without teplizumab (e.g., monitoring blood glucose, psychosocial support, education). Therefore, indirect comparisons are not possible or relevant in this context.’*⁹

EAG comment: The EAG considers that, currently in England, most people with Stage 2 T1D are not being identified in the NHS and hence are not receiving any management (see Section 2.3), i.e., the appropriate comparator is ‘no intervention’; in this case, the company’s statement that *‘indirect comparisons are not possible or relevant’* would be appropriate. However, if the comparator is considered to be ‘established clinical management’ including monitoring of blood glucose, psychosocial support and education, an SLR to identify any studies of the outcomes associated with this type of management and consideration of the potential for an indirect comparison would be both possible and relevant.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS, Appendices and response to clarification^{9, 15, 19, 21} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the clinical efficacy and safety of treatments for the delay of Stage 3 T1D in children (≥ 8 years old) and adults at risk (e.g., familial risk) of developing T1D, and the delay of Stage 3 T1D in those people with Stage 2 T1D. Searches were conducted in May 2023 and updated in June 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Whilst the SLR may have benefitted from separate adverse events searches, overall, the EAG has no major concerns about the literature searches conducted.

Although the population included in the teplizumab TN-10 trial, the only trial included in the clinical effectiveness section (B.2) of the CS, was broadly consistent with that specified in the decision problem,

all participants in TN-10 were relatives of people with Stage 3 T1D¹² and were participants in a research study (TrialNet natural History Study, TN-01).¹³ There were no UK participants in TN-10; participants in TN-10 may not be representative of people with Stage 2 T1D who would be identified in clinical practice in England.

Evidence from TN-10 indicates that treatment with teplizumab significantly increased the median time from randomisation to onset of Stage 3 T1D; the primary endpoint of TN-10, was 49.5 months in the teplizumab group and 24.9 months in the placebo group, with a difference of 24.6 months. Onset of Stage 3 T1D occurred in 45% (20/44) of the individuals treated with teplizumab and in 72% (23/32) of the individuals treated with placebo as of the data cut-off date of 30 November 2018.⁹ This effect was maintained in the extended follow-up analysis; where the median time to onset of Stage 3 T1D was 5.0 years in the teplizumab group and 2.3 years in the placebo group (difference: 2.7 years, $p=0.01$).⁹ At a median follow-up time of 745 days (range: 74, 2,683), treatment with teplizumab resulted in a statistically significant delay in the progression to Stage 3 T1D (HR: 0.41; 95% CI: 0.22 to 0.78; $p=0.0066$ by adjusted Cox PH model).⁹

With respect to safety, AEs occurred more frequently in the teplizumab group versus the placebo group (112 versus 23 AEs, respectively).⁹ The summary of TN-10 safety analysis (Section B.2.12.1.2 of the CS) states that: *'The incidence of infections was similar between treatment groups.'*⁹ and that: *'Results from the primary analysis of TN-10 determined that AEs associated with teplizumab were similar to those reported in previous clinical trials of teplizumab in Stage 3 T1D.'*⁹ However, in the additional data from the larger integrated safety analysis population treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular ≥ 3 neutropenia.

4. ■ Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains to the review of cost-effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness (CE) presented in the CS. Therefore, the following section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for CE Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and resource use identification presented in the CS.^{9, 19} The CADTH evidence-based checklist for the PRESS, was used to inform this critique.²⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendices G, H and I of the CS provide details of SLRs conducted to identify evidence to understand the economic burden of T1D in children (≥ 8 years old) and adults.¹⁹ Searches were conducted in May 2023 and updated in June 2024. ■ **EAG comment:** A single set of searches was undertaken to identify relevant studies on the economic evidence and health care resource use in the treatment of the following two populations of interest: individuals at risk of developing T1D or those diagnosed with Stage 2 T1D, and their caregivers. Of secondary interest were individuals with Stage 3 T1D and their caregivers. An additional set of searches was conducted to identify relevant the humanistic burden of T1D in children (≥ 8 years old) and adults.

- The CS, Appendices G, H and I and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{9, 15, 19, 21}
- The following databases were searched for the economic evidence and healthcare resource use on 2 May 2023: Embase, MEDLINE and EconLit (using the Ovid platform). Update searches were conducted on 27 June 2024.
- The same grey literature searches reported in the clinical effectiveness SLR were also used to inform the economics section. These searches included seven key conference proceedings which were manually searched where not available on Embase. Both ClinicalTrials.gov and the WHO ICTRP and five HTA sources were also searched. These searches were limited from 2021 onwards.
- The EAG noted that the strategies reported in Appendix G also contained a utilities facet and queried if these searches were also used to inform the HRQoL section. The company confirmed this stating that *"Any literature that was identified was considered when it was relevant for any of the other SLR workstreams. Therefore, any articles on utilities that were identified through the economic search strategies would have fed into the humanistic SLR as being brought in via an outside source."*¹⁵
- Further to the utilities facet included in the strategies in Appendix G, Appendix H also contained searches to identify evidence to understand the humanistic burden of T1D in children (≥ 8 years old) and adults. These searches were conducted in May 2023 and updated in June 2024 and conducted across the Embase, MEDLINE and MEDLINE In-Process databases via the Ovid search interface. Searches were limited from 2018 onwards and utilised the Scottish Intercollegiate Guidelines Network search filter for observational studies, alongside facets for diabetes and HRQoL/patient-reported outcome studies.

- The EAG noted that the costs searches reported in Appendix G contained the same case studies limit which included the terms *male and female* as in Appendix D which the EAG had concerns may be overly restrictive.
- All searches were well structured, transparent and reproducible. Searches contained a good range of search terms, synonyms and subject headings. Strategies utilised appropriate study design filters where appropriate.
- The EAG's main area of concern regarding the costs searches (Appendix G) was the inclusion of frequency operator on the Costs/Resource use facet. The company justified its inclusion by stating that *"The frequency operators are to remove those articles that include words that are economic in nature but that are not used to indicate the focus of the research that was discussed (the assumption being that an article that actually reported or considered economic outcomes would use related words more than once)."*¹⁵ At the EAG's request the company reran the Embase search without the frequency operator retrieving 5,156 results. The EAG had acknowledged at the time of the request that the results without the frequency operator were likely to be high and suggested the use of a shorter date limit, a suggestion not taken up by the company. Instead, the results were provided as a ris. file but not screened. Unfortunately, the EAG was unable to review the results within the single technology appraisal (STA) timeline, as this would be outside of the EAG remit. Therefore, it remains possible that relevant references may have been missed.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, utilities and costs and resource use are presented by the company in Appendix G, H and I of the CS.¹⁹ The EAG agrees in general that the in- and exclusion- criteria are suitable to fulfil the company's objective to identify relevant CE studies. However, it is unclear whether individuals at risk of developing (Stage 3) T1D are effectively the same as those diagnosed with Stage 2 T1D. The latter group, since it consists of diagnosed people, would receive treatment (defined as ECM), whereas the former group is likely to be untreated.

4.1.3 Conclusions of the CE review

- 4.2 The CS, Appendices and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant evidence to understand the economic burden of T1D in children (≥ 8 years old) and adults.^{9, 15, 19, 21} Searches were conducted May 2023 and updated in June 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, conference proceedings and HTA resources were searched. Whilst the EAG was concerned about the low number of relevant papers retrieved by the Costs/Resource use facet and the decision to include a frequency operator in the search strategy due to its potential to miss relevant papers, overall, the EAG found the searches were sufficient. Since no economic models to address the current decision problem were identified by the company, a de novo model was built, which is discussed in the remainder of this**

section. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

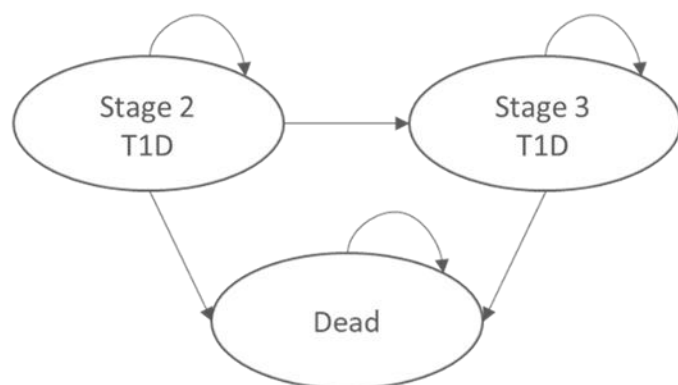
Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	As per the reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	As per the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	As per the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
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	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case
CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQoL-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

The company developed a de novo CE model in Microsoft Excel® to assess the CE of teplizumab compared to ECM for treating people 8 years and over with Stage 2 T1D.

The model adopts a cohort (Markov) approach consisting of three mutually exclusive health states; namely Stage 2 T1D, Stage 3 T1D, and death. Individuals can occupy one state at the time and death is an absorbing state. The company chose this model structure to focus on the outcomes from individuals with Stage 2 T1D, since teplizumab's key benefit consists on delaying progression to Stage 3 T1D. The company assumed that after onset of Stage 3 T1D, patients progress at the same rate for a given age of onset, regardless of whether they had previously received teplizumab or ECM. Thus, Stage 3 T1D-related outcomes were modelled in an aggregated manner (instead of modelling diabetes-related complications using risk equations). Figure 4.1 shows the schematic model structure.

Figure 4.1: Model structure



Based on Figure 5 of the CS⁹

CS = company submission; T1D = type 1 diabetes

Individuals were assumed to enter the model in the Stage 2 T1D health state and receive either teplizumab or ECM. While individuals are in the Stage 2 T1D health state, only general population mortality is assumed to apply. When individuals transition to the Stage 3 T1D health state, they cannot return to Stage 2, and the mortality rate in the Stage 3 T1D health state is assumed to be higher than in Stage 2 (general population only). The excess mortality is assumed to be dependent on the age of onset of Stage 3 T1D, as explained in Section 4.2.6.4.

Teplizumab acquisition and administration costs were accrued at the first model cycle as one-off costs. Disease management costs and utilities were assumed to be dependent on the time since onset of Stage 3 T1D. Costs and utilities were then applied to each health state to calculate total costs and quality-adjusted life years (QALYs) per model cycle, which was set at six months, reflecting the data collection in the TN-10 trial which was at 6-month intervals.²³ A half-cycle correction was implemented to account for events happening at any time during the cycle. The time horizon was assumed to be lifetime, where individuals were simulated to a maximum age of 100 years. An annual discount rate of 3.5% was applied to both costs and health benefits, as per the NICE reference case. The input values of the model and their underlying assumptions are further elaborated in the remainder of Section 4 of the EAG report. **EAG comment:** The company's modelling approach considers *aggregated* Stage 3 T1D-related complications. Commonly, T1D models are focused on Stage 3 and capturing the frequency of the long-term diabetes-related complications. Since the benefit of teplizumab (compared with established clinical management) consists of delaying progression to Stage 3, the EAG considers the modelling approach followed by the company appropriate for the decision problem at hand.

4.2.3 Population

The CS defines the population in the economic analyses as individuals 8 years and over with Stage 2 T1D, defined as those with two or more islet autoantibodies and dysglycaemia, who are at risk of progression to Stage 3 T1D. This patient population is in line with the anticipated licensed indication,²⁹ the final NICE scope,¹⁰ and is consistent with the population included in the TN-10 study.²³ The key baseline characteristics in the economic model are listed in Table 4.2.

Table 4.2: Key baseline patient characteristics used in the economic model

Parameter	Mean	Source
Percentage female	44.68	Herold et al. 2019 ²³
Starting age, years	13.58	
Based on Table 23 of the CS ⁹ CS = company submission		

EAG comment: As explained in Section 2.1 of this report, the EAG is concerned about the definition of the population included in the economic analyses, since the EAG considers that this is dependent on whether the intervention does include a method (i.e., testing) of identifying the specified asymptomatic population or not. The EAG questions whether the intervention is, in fact, teplizumab plus screening/testing in an *asymptomatic population*, in which case the comparator would be placebo/no treatment plus no screening/testing. On the other hand, if the intervention does not include a method of identifying the specified asymptomatic population (screening/testing) and the costs of screening/testing are not included in the economic analyses, the EAG considers that definition of the population should be '*people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected*', in which case the intervention would be teplizumab and the comparator ECM.

In response to clarification question B2,¹⁵ the company indicated that the age range of the TN-10 trial population (≥ 8 years) is representative of individuals with T1D in the UK, noting that the peak age of T1D diagnosis in England and Wales is 12 years.^{23, 30}

Furthermore, the company explained that the results of the TN-10 trial are expected to be generalisable to UK clinical practice since the risk of progression from presymptomatic to symptomatic Stage 3 T1D is expected to be similar between those people who have and who do not have a first-degree relative with Stage 3 T1D.²⁷ Also, the company expects that response to teplizumab is not dependent on geographic location based on evidence from people from North America and Europe (including the UK) with new-onset Stage 3 T1D.³¹

4.2.4 Interventions and comparator

The intervention considered in the economic analyses was teplizumab, which is delivered as a 2 mg per 2 ml clear colourless solution for injection in a single-dose vial, available as a single-vial pack. The dosing regimen is in line with the recommended administration of the commercial product, as described in the Summary of Product Characteristics (SmPC).²⁹ It consists of a 14-day course where, in each day, the total daily infusion dose is calculated on the basis of BSA, as described in Section 4.2.8.2 of this report. The comparator included in the economic analyses was ECM (defined as routine monitoring of blood glucose, psychosocial support and education on the management of T1D), since there are currently no interventional comparators of teplizumab for the treatment of Stage 2 T1D.

EAG comment: As discussed in the previous section of this report, the EAG questions whether there are in fact two populations who are relevant to this appraisal: 1) an asymptomatic population, and 2) a population of incidentally detected patients.

For the asymptomatic population, teplizumab plus screening/testing should be the intervention and placebo/no treatment plus no screening/no testing should be the comparator. For this population, estimates of the number of individuals needed to be tested to detect one case, and the screening/testing costs need to be included in the economic analyses. The company's view is that the inclusion of a screening/testing programme for asymptomatic individuals is outside of the scope of this appraisal (e.g., clarification Questions A6 and B17).¹⁵ Therefore, the company did not provide an estimate of the number of individuals that would be screened/tested to find one individual eligible for treatment with teplizumab or ECM. Furthermore, the company argued that the inclusion of screening/testing would have a neutral effect on the CEA, as it would introduce equivalent costs to both arms of the CE model. The EAG does not agree with this statement since it is considered that in the context of screening, the appropriate comparator should be no screening and no treatment (i.e., the comparator arm would consist of undiagnosed patients). In conclusion, an economic evaluation of teplizumab + screening versus placebo/no treatment + no screening in the asymptomatic population cannot be conducted with the current evidence.

For the population of incidentally detected patients, which is the one currently included in the economic model, the intervention should be teplizumab and the comparator ECM. The EAG, however, has concerns regarding the generalisability to UK clinical practice of the results observed in the comparator arm of the TN-10 trial. The comparator in the TN-10 trial was placebo (saline) administered via IV infusion for 14-days in the outpatient setting, which is different from ECM (defined as routine monitoring of blood glucose, psychosocial support and education on the management of T1D). In response to follow-up clarification Question 3,¹⁵ the company further explained that in fact individuals in TN-10 received *close monitoring for Stage 3 T1D development* in addition to teplizumab or placebo. The company indicated that “*close monitoring in TN-10 consisted of metabolic monitoring with a scheduled oral glucose tolerance test (OGTT) every 6 months and an additional random glucose measurement scheduled every 3 months with a reflex to OGTT should the glucose level be abnormal. Participants were educated about the symptoms associated with Stage 3 T1D at each visit and via routine contact in between visits*”.³² The company concluded that ECM as described in the CS and included in the economic model (routine monitoring of blood glucose, psychosocial support and education on the management of T1D) can be considered comparable to close monitoring in TN-10. The EAG is uncertain about this since Herold et al. 2019 does not seem to report anything on psychosocial support or education on the management of T1D.²³ Hence, it is uncertain whether the estimates of ECM treatment effect observed in TN-10 are the same as those that would be observed when psychosocial support and/or education on the management of T1D would be included as part of ECM. If psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of teplizumab included in the model would be overestimated if these ECM components are effective.

4.2.5 Perspective, time horizon and discounting

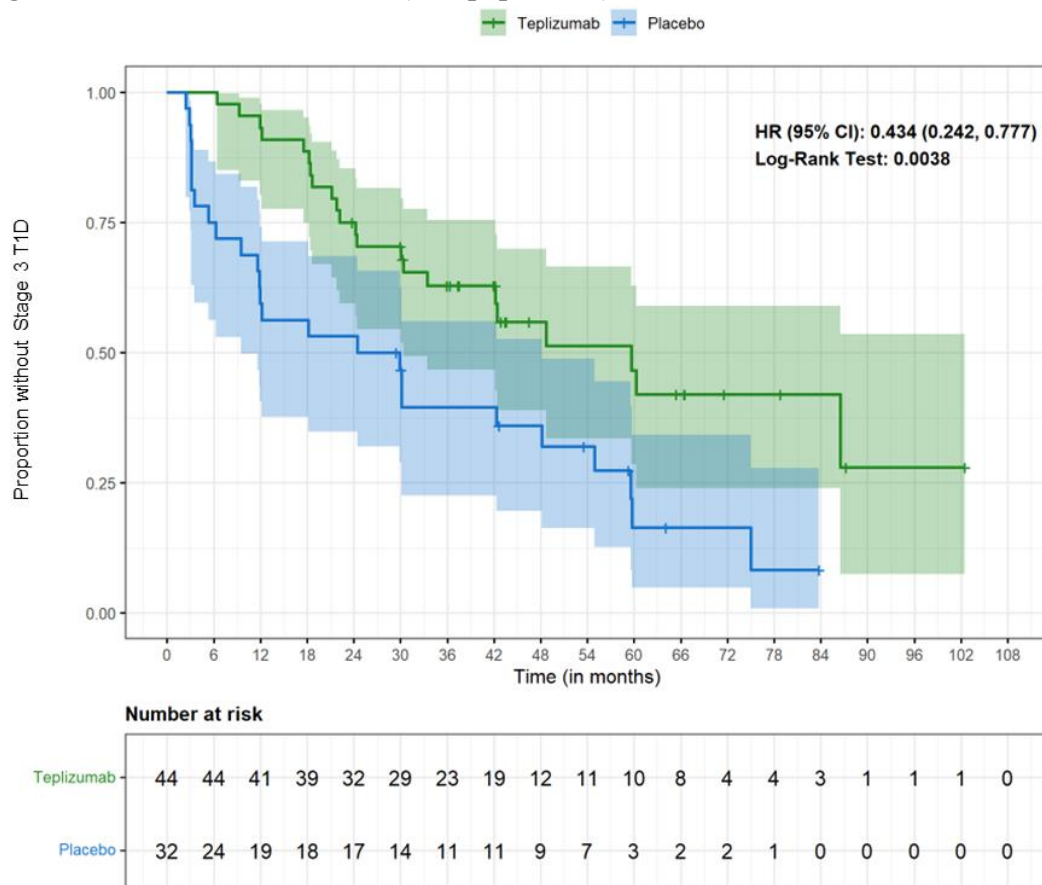
The economic analysis is conducted from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is six months with a lifetime time horizon (92 years) and a half-cycle correction applied.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Time to onset of Stage 3 T1D

Transition probabilities from Stage 2 to Stage 3 T1D were derived from the individual-level data reported by Sims et al. 2021, where the outcomes of the TN-10 trial with an extended follow-up period (median 923 days) were available.²⁴ The KM curves for the ITT population, and both teplizumab and placebo, are shown in Figure 4.2. These data were extrapolated using parametric distributions, following the recommendations in NICE Decision Support Unit (DSU) Report 14.³³

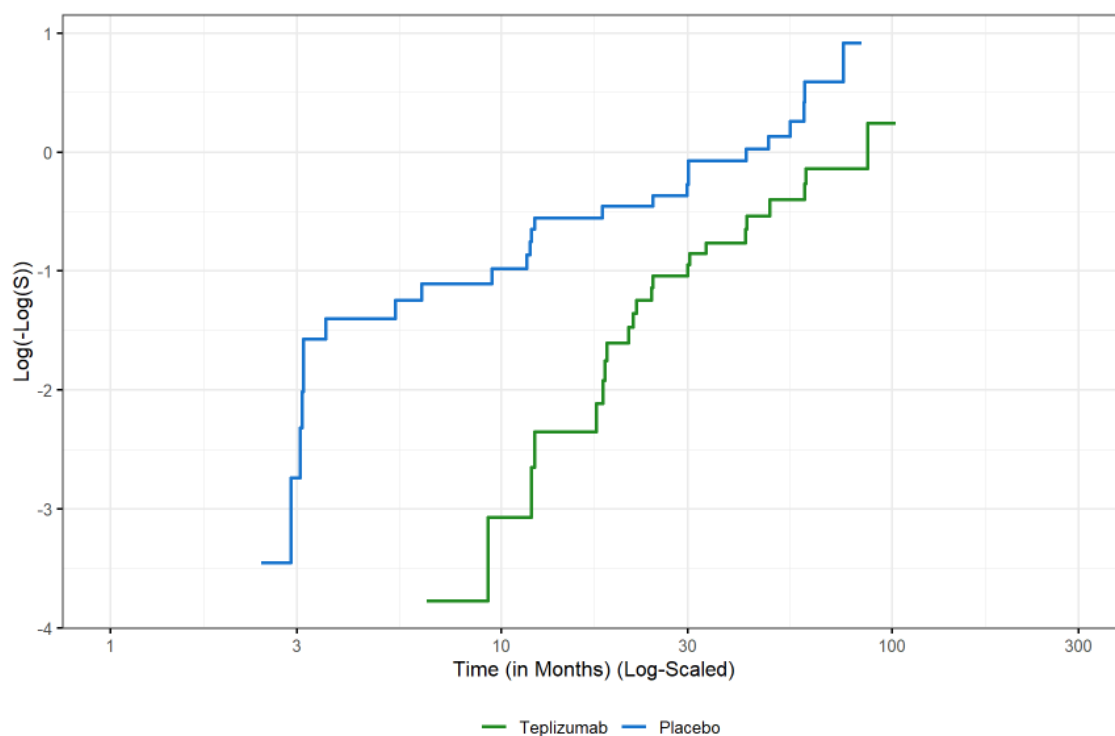
Figure 4.2: Observed KM curves (ITT population)



Based on Figure 6 of the CS⁹

CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

First, the company assessed whether the proportional hazards assumption would be reasonable. For this, the company examined the log-cumulative hazard plots shown in Figure 4.3 and the Schoenfeld residuals shown in Figure 4.4. Based on this assessment the company concluded that the proportional hazards (PH) assumption may not be reasonable since the log-cumulative hazard curves were not parallel and the line fitted to the Schoenfeld residuals was not horizontal. Thus, independent parametric fits were preferred for the base-case analysis.

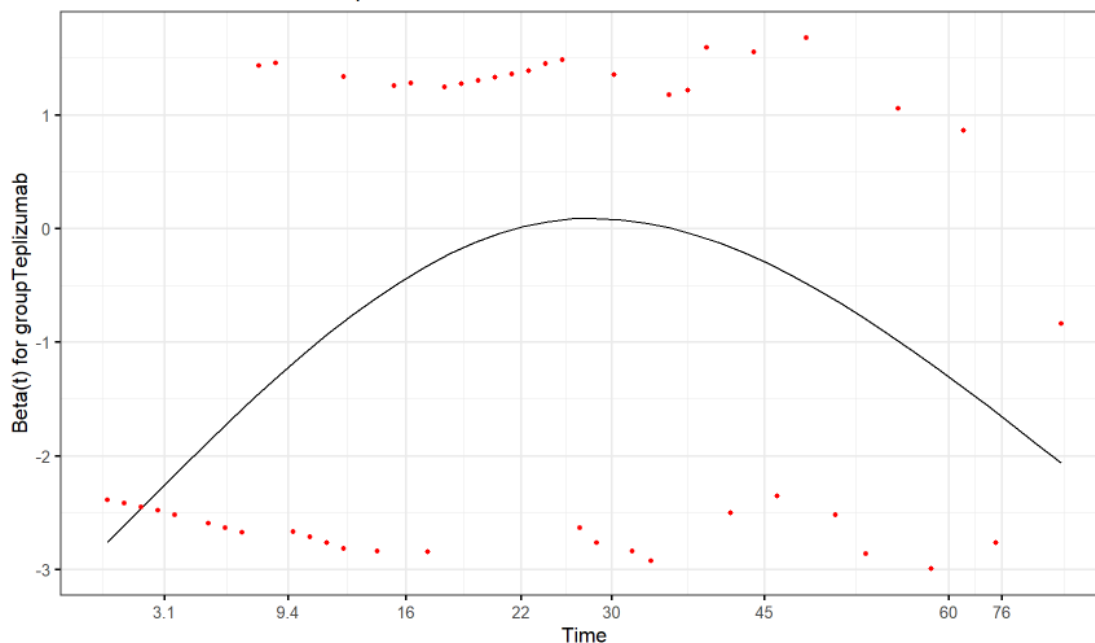
Figure 4.3: Log-cumulative hazard plot (ITT population)

Based on Figure 7 of the CS⁹

CS = company submission; ITT = intention-to-treat

Figure 4.4: Schoenfeld residuals plot (ITT population)

Schoenfeld Individual Test p: 0.1954



Based on Figure 8 of the CS⁹

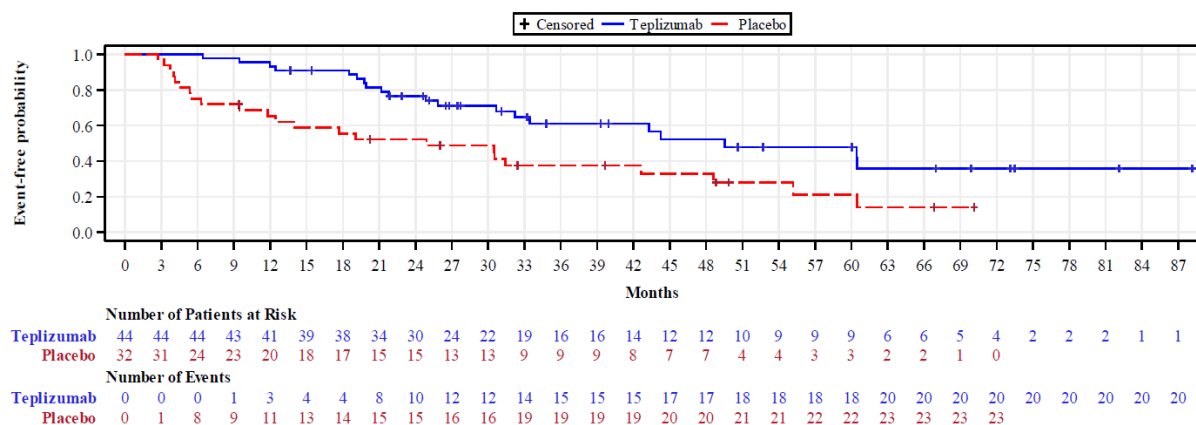
CS = company submission; ITT = intention-to-treat

EAG comment: In response to clarification Question B4,¹⁵ the company explained that the high rate of progression (to Stage 3 T1D) in the placebo arm shortly after randomisation observed in Figure 4.2 is consistent with what is reported in the literature, and referred to the study by Krischer 2013 showing

that the progression rate within the first year is higher than in subsequent years, with more than 40% of relatives of individuals with Stage 3 T1D progressing to onset of Stage 3 T1D after one year and approximately 60% progressing after two years.³⁴ The company presented this question to an external clinical expert, Prof. Colin Dayan, who indicated that the progression rate in the placebo arm is as expected.³⁵ Prof. Dayan further explained that as individuals were recruited from TN-01 into TN-10, a proportion of them would have been in Stage 2 T1D for a longer period of time and that it is likely that these participants were the first to progress to Stage 3 T1D following randomisation.³⁵ People were excluded from the TN-10 trial if they progressed to Stage 3 T1D before the trial began or if they were borderline Stage 3 T1D.^{23, 35}

In Section B.2.6.1 of the CS, the company reported results of the TN-10 trial primary analysis.⁹ These were based on the results in Herold et al. 2019 and the CSR.^{12, 23} The KM curves based on this data set can be seen in Figure 4.5. For the model, the company used data from Figure 4.2, which were sourced from Sims et al. 2021.²⁴ The EAG noticed that these curves were different from those in the CSR (Figure 4.5). When asked about this discrepancy in clarification Question B4,¹⁵ the company explained that both Figure 4.2 and 4.5 were based on individual patient data from TN-10, but derived from different data cuts. The data shown in Figure 4.2 was chosen to inform the economic model given the longer follow-up. The EAG considers it unclear why a difference in event rates over the first six months between the data cuts is observed, when the number of events and censored observations seem to be the same in both figures for the first six months. Using data from Figure 4.2 over Figure 4.5 would favour teplizumab given the faster progression to Stage 3 T1D for the placebo group. As a consequence, it is also unclear whether the parametric fitting and extrapolation described in the sections below was performed with the appropriate data.

Figure 4.5: KM curve for proportion of participants without Stage 3 T1D over time (TN-10; ITT population; primary analysis)



Based on Figure 4 of the CS⁹

CS = company submission; ITT = intention-to-treat; KM = Kaplan-Meier; T1D = type 1 diabetes

Regarding the assessment of the proportional hazards, the EAG agrees with the company that the PH assumption does not seem to hold. However, it should be noted that this is likely due to the high failure rate shortly after randomisation observed in the placebo arm.

4.2.6.1.1 Parametric fitting using individual curves

To select the most appropriate extrapolation option for the time to onset of Stage 3 T1D for both teplizumab and placebo, the company used goodness-of-fit statistics, visual inspection, and clinical

expert opinion regarding the plausibility of the long-term predictions of the alternative parametric survival models. Goodness-of-fit statistics were based on modified Burnham/Anderson Akaike information criterion (AIC),³⁶⁻³⁸ and Kass/Raftery criteria for Bayesian information criterion (BIC).^{39, 40} These statistics are summarised in Table 4.3.

Table 4.3: AIC and BIC statistics for time to onset of Stage 3 T1D using individual curves (ITT population)

Distribution	Teplizumab		Placebo	
	AIC	BIC	AIC	BIC
Exponential	239.6	241.4	232.5	234.0
Weibull	239.0	242.6	234.0	237.0
Gompertz	241.0	244.6	234.2	237.2
Log-logistic	237.3	240.9	234.2	237.1
Log-normal	236.0	239.5	232.3	235.2
Gamma	238.2	241.8	234.2	237.1
Generalised gamma	237.1	242.5	233.9	238.3
Based on Table 24 of the CS ⁹ AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; ITT = intention to treat; T1D = type 1 diabetes				

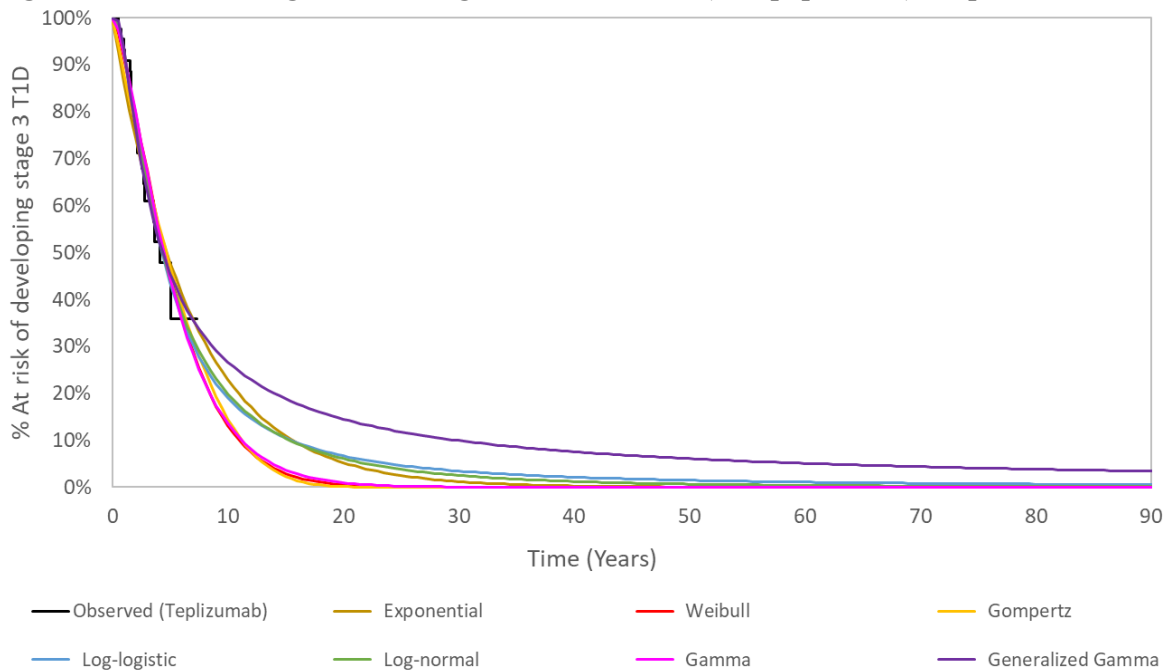
For teplizumab, the log-normal distribution resulted in the best statistical fit having the lowest AIC and BIC estimates. The company indicated that the other distributions produced a good relative fit based on AIC (<4-point difference with respect to the log-normal distribution),³⁶⁻³⁸ and either good or reasonable (<2-point difference or 2-6-point difference with respect to the log-normal distribution) based on BIC.^{39, 40} For placebo, the log-normal and exponential distributions resulted in the best statistical fit in terms of AIC and BIC, respectively. The other distributions resulted in a good relative fit based on AIC (<4-point difference) and a good or reasonable fit (<2-point difference or 2-6-point difference) based on BIC. The criteria to select the distributions with the best fit to the data are summarised in Table 4.4.

Table 4.4: AIC and BIC goodness-of-fit criteria using individual curves (ITT population)

Distribution	Diff. from lowest AIC	AIC relative GoF classification ³⁶⁻³⁸	Diff. from lowest BIC	BIC relative GoF classification ^{39, 40}
Teplizumab				
Exponential	3.6	Good (0-4 difference)	1.9	Good (0-2 difference)
Weibull	3	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Gompertz	5	Reasonable (4-7 difference)	5.1	Reasonable (2-6 difference)
Log-logistic	1.3	Good (0-4 difference)	1.4	Good (0-2 difference)
Log-normal	Lowest AIC	Reference	Lowest BIC	Reference
Gamma	2.2	Good (0-4 difference)	2.3	Reasonable (2-6 difference)
Generalised gamma	1.1	Good (0-4 difference)	3	Reasonable (2-6 difference)

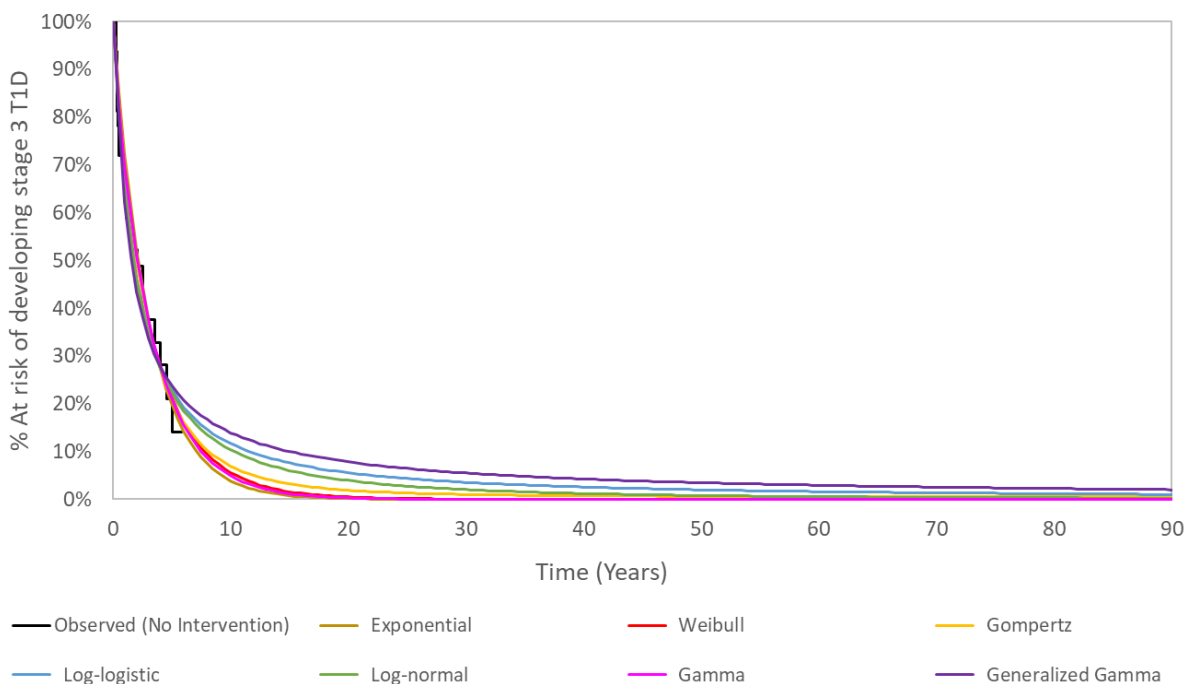
Distribution	Diff. from lowest AIC	AIC relative GoF classification ³⁶⁻³⁸	Diff. from lowest BIC	BIC relative GoF classification ^{39, 40}
Placebo				
Exponential	0.2	Good (0-4 difference)	Lowest BIC	Reference
Weibull	1.7	Good (0-4 difference)	3.0	Reasonable (2-6 difference)
Gompertz	1.9	Good (0-4 difference)	3.2	Reasonable (2-6 difference)
Log-logistic	1.9	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Log-normal	Lowest AIC	Reference	1.2	Good (0-2 difference)
Gamma	1.9	Good (0-4 difference)	3.1	Reasonable (2-6 difference)
Generalised gamma	1.6	Good (0-4 difference)	4.3	Reasonable (2-6 difference)
Based on Table 25 of the CS ⁹ AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; GoF = goodness-of-fit; ITT = intention-to-treat				

In addition, the company presented an overlay of the parametric curves on the teplizumab KM data for the ITT population, as shown in Figure 4.6. Based on this, the company concluded that all distributions had similar visual fits to the observed data up to the tail of the KM curve. Regarding the long-term extrapolations, the company only indicated that the clinical plausibility of generalised gamma extrapolation may be challenged due to the plateau observed at the tail of the curve. A similar plot for the placebo arm is shown in Figure 4.7. The company also concluded here that all distributions had reasonable visual fits, noting that the generalised gamma model also seemed to overpredict the probability at the tail of the curve.

Figure 4.6: Time to Stage 3 T1D using individual curves (ITT population) – teplizumab arm

Based on Figure 9 of the CS⁹

CS = company submission; ITT = intention-to-treat; T1D = type 1 diabetes

Figure 4.7: Time to Stage 3 T1D using individual curves (ITT population) – placebo arm

Based on Figure 10 of the CS⁹

CS = company submission; ITT = intention-to-treat; T1D = type 1 diabetes

Based on the presented evidence, the company considered that for teplizumab, the log-normal distribution was the most appropriate candidate due to the best visual and statistical fit to the KM data. For the placebo arm, however, the company indicated that the log-normal distribution lacked clinical validity, resulting in unrealistically high estimates of the proportion of individuals who will not have progressed to Stage 3 T1D in the long term. These estimates are presented in Table 4.5. For this reason,

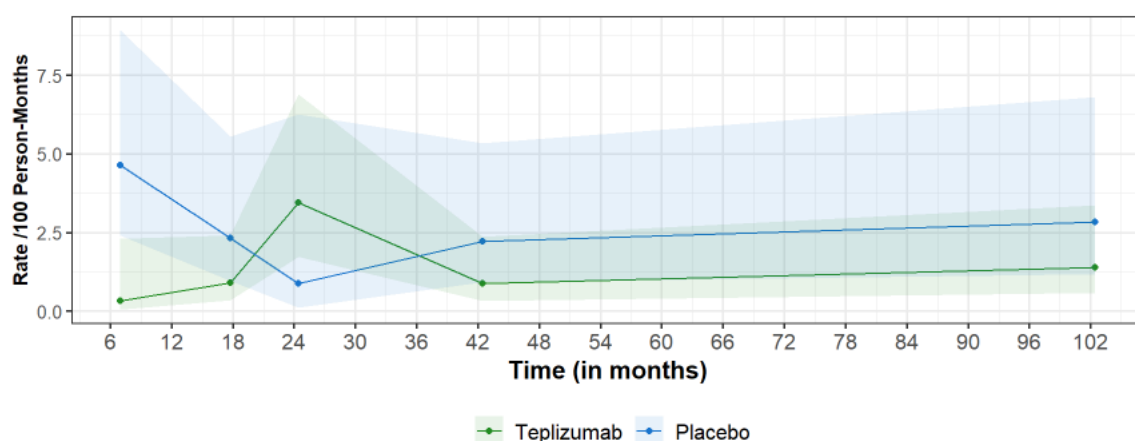
the company selected the exponential distribution to model the placebo arm in the base-case (it provided the best overall visual fit to the observed KM curve – according to the company and had the second lowest AIC and lowest BIC).

Table 4.5: Proportion of individuals in Stage 2 T1D by parametric fitting in placebo arm

Time (years)	Exponential ^a	Log-normal	Gamma	Weibull	Gompertz	Log-logistic	Gen-gamma
0							
5							
10							
15							
Based on Table 26 of the CS and Table 10 of the response to the request for clarification ^{9, 15}							
^a Selected for individuals receiving established clinical management in the base-case							
CS = company submission; T1D = type 1 diabetes							

EAG comment: Based on the evidence presented in this section, the company considered that the log-normal and the exponential distributions were the most appropriate candidates to extrapolate the observed KM data, for teplizumab and placebo, respectively. However, NICE DSU Report 14 recommends that “*if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type*”.³³ The EAG asked the company to clarify the choice of different types of parametric models in clarification Question B5, but no answer was provided.^{9, 15}

In the same clarification question, the EAG asked the company to provide for both teplizumab and ECM a plot of the observed hazard functions over time. This could be used to support the choice of parametric distributions (for example, when an exponential distribution is selected, a constant hazard function over time should apply). These can be seen in Figure 4.8. It can be seen that the plot does not start at Time = 0, which is unfortunate, since this could have potentially used to validate the rapid decline in survival observed in Figure 4.2 in the placebo arm (i.e., a rapid progression in placebo should come with increasing hazards at the beginning). It can be seen nevertheless that the hazard functions are not constant over time, implying that these do not correspond with an exponential distribution. Also, the hazards functions only seem to be parallel after 42 months (even though there is a gap in observation before that where the previous observation point was at 24 months), which also supports the choice of non-proportional hazards model, as the company already explained.

Figure 4.8: Observed hazard functions over time

Based on Figure 4 of the response to the request for clarification^{9, 15}

ITT = intention-to-treat; T1D = type 1 diabetes

The company assessed the face validity of the exponential and log-normal curves for the placebo arm with an external clinical expert, Prof. Colin Dayan.³⁵ Prof. Dayan agreed with the proposed approach of selecting the exponential distribution since this is in line with the curve of individuals progressing from Stage 2 to Stage 3 T1D from the Diabetes Prevention Trial–Type 1 (DPT-1) study.^{35, 41} Prof. Dayan also cited evidence which has found that there are very few participants across multiple cohorts of autoantibody-positive populations who do not progress to Stage 3 T1D within 10 years.^{35, 42, 43} However, no range of estimates was provided in order to assess whether other distributions could be considered to provide reasonable predictions. For example, the company indicated that the log-normal distribution produced clinically unrealistic estimates of the proportion of individuals who will not have progressed to Stage 3 T1D in the long term. However, no justification was further provided that can be used to explain why this was the case and to what extent progression was underestimated by the log-normal distribution. The company discussed the validity of the generalised-gamma distribution with Prof. Dayan who indicating that predicting 10% of individuals remaining in Stage 2 T1D at 15 years could be considered unrealistic.

In response to clarification Question B6,^{9, 15} the company also presented of estimates of the proportion of individuals in Stage 2 T1D over time by parametric fitting in the teplizumab arm. These are shown in Table 4.6. However, the company did not provide any further discussion that could be used to assess whether other distributions could be considered to provide reasonable predictions.

Table 4.6: Proportion of individuals in Stage 2 T1D by parametric fitting in teplizumab arm

Time (years)	Log-normal ^a	Exponential	Gamma	Weibull	Gompertz	Log-logistic	Gen-gamma
0	██████	██████	██████	██████	██████	██████	██████
5	██████	██████	██████	██████	██████	██████	██████
10	██████	██████	██████	██████	██████	██████	██████
15	██████	██████	██████	██████	██████	██████	██████

Based on Table 11 of the response to the request for clarification^{9, 15}

^a Selected for individuals receiving teplizumab in the base-case

T1D = type 1 diabetes

In summary, the EAG asked the company to revise the selection of parametric distributions for their base-case analysis based on the evidence presented in the CS, response to clarification and NICE DSU TSD 14 recommendations.^{9, 15, 33} The company maintained their initial choice and prefer a log-normal distribution for teplizumab and an exponential distribution for ECM. The EAG, on the other hand, considers that there are a number of issues related to this choice that have not been resolved by the company. These are summarised below:

- Using different types of parametric distributions across treatment arms is uncommon and usually not recommended by NICE DSU TSD 14.³³ The EAG prefers using the same type of parametric distribution for both arms.
- The exponential distribution hazard function is constant over time which does not match with observed hazard functions in Figure 4.8. The EAG prefers using a parametric distribution with non-constant hazard function.
- Face validity by the clinical expert was focused on assessing the validity of the exponential distribution for the placebo arm only. However, no range of possible long-term values was provided. These were relatively similar for the gamma or Weibull distributions (as can be seen in Table 4.5), which also show a good fit to the data (Table 4.4). Furthermore, assuming an exponential distribution to extrapolate the placebo arm is the most favourable choice for teplizumab. The EAG prefers using a gamma or Weibull distribution for the placebo arm.
- The log-normal extrapolation is one of the most favourable for the teplizumab arm. Given that at this moment there is uncertainty regarding the long-term extrapolations (e.g., after 4 years the number of individuals at risk is low in Figure 4.2), the EAG prefers a more conservative approach.
- The Weibull and gamma distributions also showed a good fit to teplizumab data in Table 4.4.

For the reasons summarised above, the EAG prefers using a Weibull or a gamma distribution for both arms in the revised EAG base-case (see Section 6).

4.2.6.1.2 Parametric fitting using a joint distribution

The same analyses were presented by the company when a joint distribution for both teplizumab and placebo arms was assumed, even though the company indicated that the PH assumption would not be appropriate. Goodness-of-fit statistics and criteria are summarised in Table 4.7 and 4.8, and an overlay of the parametric curves on the teplizumab and placebo KM data for the ITT population are shown in Figure 4.9 and 4.10.

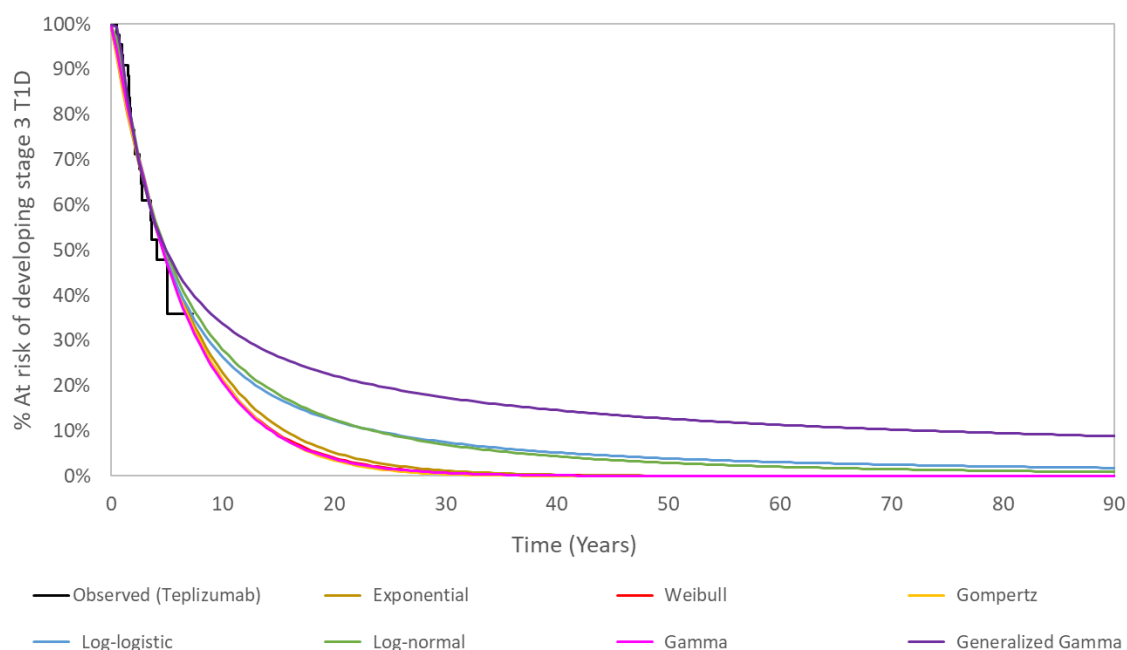
Table 4.7: AIC and BIC statistics for time to onset of Stage 3 T1D using joint curves (ITT population)

Distribution	AIC	BIC
Exponential	472.2	476.8
Weibull	474.0	481.0
Gompertz	474.1	481.1
Log-logistic	472.0	479.0
Log-normal	468.6	475.6
Gamma	473.7	480.7
Generalised gamma	467.8	477.1
Based on Table 27 of the CS9 AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; ITT = intention to treat; T1D = type 1 diabetes		

Table 4.8: AIC and BIC goodness-of-fit criteria using a joint model (ITT population)

Distribution	Diff. from lowest AIC	AIC relative GoF classification ³⁶⁻³⁸	Diff. from lowest BIC	BIC relative GoF classification ^{39, 40}
Exponential	4.4	Reasonable (4-7 difference)	1.2	Good (0-2 difference)
Weibull	6.2	Reasonable (4-7 difference)	5.4	Reasonable (2-6 difference)
Gompertz	6.3	Reasonable (4-7 difference)	5.5	Reasonable (2-6 difference)
Log-logistic	4.2	Reasonable (4-7 difference)	3.4	Reasonable (2-6 difference)
Log-normal	0.8	Good (0-4 difference)	Lowest BIC	Reference
Gamma	5.9	Reasonable (4-7 difference)	5.1	Reasonable (2-6 difference)
Generalised gamma	Lowest AIC	Reference	1.5	Good (0-2 difference)

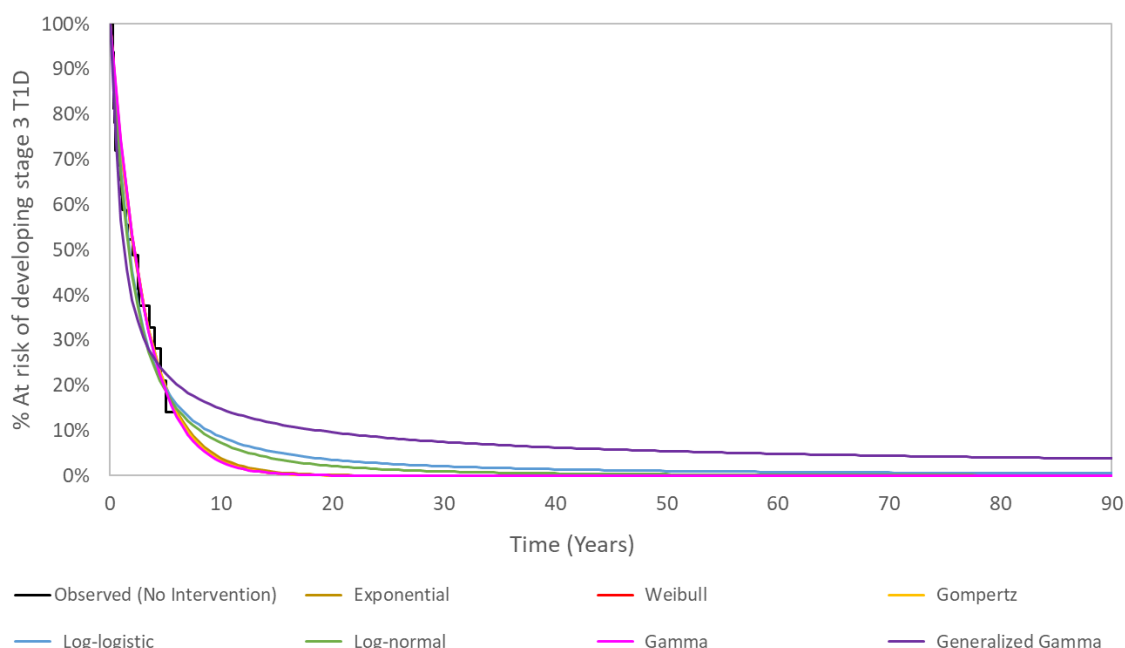
Based on Table 28 of the CS⁹
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; GoF = goodness-of-fit; ITT = intention to treat

Figure 4.9: Time to Stage 3 T1D parametric fits for individuals on teplizumab using a joint parametric distribution (ITT population)

Based on Figure 11 of the CS⁹

CS = company submission; ITT = intention-to-treat; T1D = type 1 diabetes

Figure 4.10: Time to Stage 3 T1D parametric fits for individuals on placebo using a joint parametric distribution (ITT population)



Based on Figure 12 of the CS⁹

CS = company submission; ITT = intention-to-treat; T1D = type 1 diabetes

Based on the presented evidence, the company concluded that if adopting a joint modelling approach would be considered appropriate, the log-normal distribution should be chosen for the base-case, as it generated the best visual fit to the KM curve (according to the company) and the best statistical fit (i.e., lowest BIC and second lowest AIC). The company also indicated that the generalised gamma model clearly overpredicted the KM curve from year 5 onward, while other distributions produced reasonable fits to the observed data up to the tail of the KM curves.

4.2.6.2 Risk of developing DKA at onset of Stage 3 T1D

Once individuals move to the Stage 3 T1D health state, they are assumed to be at risk of experiencing DKA events. The company assumed the same risk of DKA events in both treatment arms.

The company referred to Besser et al. 2022 to indicate that in the UK, approximately 25% of individuals with Stage 3 T1D experience DKA events, but that identifying and monitoring individuals with Stage 2 T1D is assumed to reduce the risk of DKA by 90%.⁴⁴ Therefore, in the model, the company assumed that 2.5% of patients at onset of Stage 3 T1D would experience DKA events regardless the treatment arm.

EAG comment:

In clarification Question B7,¹⁵ the EAG asked the company to provide a comparison with other studies such as NICE TA943 or Roze et al. 2021, which are also cited in the CS.^{45, 46} The company indicated that both NICE TA943 and Roze et al. 2021 used the CORE diabetes model and that the information about the data used in the model is limited.

The company referred to another publication reporting on the validation of the CORE diabetes model,⁴⁷ using data from the Diabetes Control and Complications Trial (DCCT; US data) to inform the risk of

DKA giving a range of 1.8%-2% of individuals experiencing DKA events, which according to the company is close to the value from the Besser et al. 2022.

4.2.6.3 Mortality for Stage 2 T1D

In the absence of published data indicating that individuals with Stage 2 T1D have an increased risk of death compared with the general population, the mortality risk for this health state was derived from the UK general population life tables.⁴⁸ The company used in the base-case the UK general population life tables based on 2020-2022 data. However, since this time period was concurrent with the COVID-19 pandemic, life tables based on an earlier time period (2017-2018) were used in scenario analyses.

EAG comment: For the same reason described by the company, the EAG prefers using life tables before the COVID-19 pandemic (2017-2018) in the EAG revised base-case.

4.2.6.4 Mortality for Stage 3 T1D

An increased risk of death compared to the general population was implemented in the economic model as a function of the age of Stage 3 T1D onset. The underlying assumption was that delaying the onset of Stage 3 T1D would lead to developing T1D later in life and, therefore, to an increase in total life years. The company considered two approaches, which are described in the remainder of this section.

4.2.6.4.1 Base-case analysis: excess mortality by age bracket

The excess mortality (compared to the general population) associated with Stage 3 was modelled by applying an age-dependent HR. Two HR's (one for children and one for adults – cut-off age 18 years at onset of Stage 3 T1D) were applied to the UK general population life tables, which can be seen in Table 4.9.

The HR for children (<18 years) was sourced from Samuelsson et al. 2024, where an analysis of the Swedish National Diabetes Register, including data for 15,188 individuals with Stage 3 T1D and 74,210 controls from between 2000 and 2019, was conducted.⁴⁹ The company selected this source for their base-case as it was the most recent publication identified and indicated that it is expected to reflect the most accurate representation of the current standard of care in the absence of recent UK-specific data. However, Samuelsson et al. 2024 did not provide a mortality HR for adults.

Another publication, Lung et al. 2014, providing pooled mortality estimates for adults and children with Stage 3 T1D based on meta-analyses, was identified by the company.⁵⁰ The company considered these data outdated and therefore were not used for their base-case. However, the relationship between the mortality estimates for adults and children in Lung et al. 2014 was used to define the HR for adults in the base-case as follows. In Lung et al. 2014, the mortality for adults (age of diagnosis >18 years) was reported to be approximately half of the mortality for individuals diagnosed before 18 years (2.41 versus 4.93, respectively).⁵⁰ Thus, the company assumed that the mortality for adults with Stage 3 T1D in the base-case was 50% of the mortality estimate for children with Stage 3 T1D. The company concluded that this assumption was made based on published evidence showing excess mortality among individuals with Stage 3 T1D relative to the general population in Sweden.⁵¹

Table 4.9: HRs stratified by age at onset of Stage 3 T1D

Age at Onset of Stage 3 T1D	HR (95% CI)	Source
Before 18 years	1.57 (1.16, 2.12)	Swedish registry ⁴⁹

Age at Onset of Stage 3 T1D	HR (95% CI)	Source
After 18 years	1.285 (NA)	Assumption (50% of the mortality estimate for children) ⁵⁰
Based on Table 29 of the CS ⁹ CI = confidence interval; CS = company submission; HR = hazard ratio; NA = not applicable; T1D = type 1 diabetes		

4.2.6.4.2 Scenario analysis: meta-regression of excess mortality

Another study based on the Swedish National Diabetes Registry was considered by the company in scenario analyses. The study by Rawshani et al. 2018 reported excess risk of all-cause mortality based on an analysis of 27,195 individuals with Stage 3 T1D and 135,178 matched control individuals from the general population (1998 to 2012).⁵¹ The study reports that Stage 3 T1D is associated with an increased risk of mortality compared to the general population, and that this excess risk of mortality decreases with age. Since Rawshani et al. 2018 findings are based on older data compared to Samuelsson et al. 2024 (1998-2012 versus 2000-2019, respectively), the company preferred using the latter for their base-case analysis. The approach based on Rawshani et al. 2018 was included in the model as a scenario analysis since the HRs are reported for several age categories and not only for children and adults, as can be seen in Table 4.10.

Table 4.10: Adjusted HRs for all-cause mortality stratified by age at onset of Stage 3 T1D

Age	HR (95% CI)
0 to 10 years	4.11 (3.24, 5.22)
11 to 15 years	3.21 (2.58, 4.00)
16 to 20 years	3.02 (2.44, 3.73)
21 to 25 years	2.90 (2.41, 3.50)
26 to 30 years	2.83 (2.38, 3.37)
Based on Table 30 of the CS ⁹ CI = confidence interval; CS = company submission; HR = hazard ratio; T1D = type 1 diabetes	

A meta-regression was further conducted on the data points reported in Rawshani et al. 2018, using the following equation:

$$\text{Log}(\text{HR}) = \text{Intercept} + B1 \times \log(\text{age}),$$

where HR is the excess mortality ratio compared to the general population, age is the age of onset of Stage 3 T1D, and B1 is the coefficient of the Log(age) covariate. The intercept and coefficient estimates are presented in Table 4.11.

Table 4.11: Meta-regression model for excess mortality

Input	Estimate (95% CI)	SE
Intercept	1.74 (1.28 to 2.21)	0.24
B1	-0.22 (-0.38 to -0.06)	0.08
Based on Table 31 of the CS ⁹ CI = confidence interval; CS = company submission; SE = standard error		

EAG comment: The EAG asked the company to justify why the Swedish studies by Samuelsson et al. 2024 and Rawshani et al. 2018 were selected to estimate the excess mortality due to Stage 3 T1D in

clarification Question B8.¹⁵ In their response, the company explained that these studies were selected because of their robust designs, both using large datasets from the Swedish National Diabetes Registry, but the generalisability to the UK setting was not discussed. The generalisability of Swedish mortality data from Rawshani et al. 2018 was discussed at the company's advisory board meeting.^{17, 52} Clinical experts indicated that mortality rates in the UK were similar to that in Sweden, and hence Swedish data (Rawshani et al. 2018) would be favoured over the meta-analysis by Lung et al. 2014.⁵⁰

In the same clarification question, the EAG asked the company to provide a comparison of (similar) approaches with other studies such as NICE TA943 or Roze et al. 2021. The company noted that both Roze 2021 and the EAG model for NICE TA943 were based on the CORE diabetes model and that in this model the risk of death is based on the specific diabetes-related events (e.g., stroke, hypoglycaemia). For this reason, the company considered that methods in this submission and these studies are not directly comparable, indicating furthermore that both the EAG report for NICE TA943 and the publication by Roze et al. 2021 provided limited information on the mortality data used as input parameters for these models.

4.2.6.5 Adverse events

The company identified AEs based on Herold et al. 2023, which listed AEs with an incidence rate of $\geq 10\%$ in individuals treated with teplizumab.²⁸ The company selected for inclusion in the economic model the five most common AEs for which the incidence rate was higher in those allocated to teplizumab versus the comparator group. The AEs included were: lymphopenia, leukopenia, neutropenia, decreased blood bicarbonate and rash. Most AEs were grade 1 or 2 in severity and the majority were resolved without intervention. As a result, the company assumed an AE duration of seven days for these. However, lymphopenia was assumed to last 45 days, based on the TN-10 trial.²³ The company only presented the excess proportion of these events in the teplizumab versus placebo group and not absolute numbers (Table 4.12).

Table 4.12: AEs (and excess proportion) included in the economic model

AE	Excess proportion (%) (versus placebo)
Lymphopenia	63.2%
Leukopenia	36.8%
Neutropenia	18.0%
Blood bicarbonate decreased	11.0%
Rash	24.3%
Based on Table 37 of the CS ⁹ AE = adverse event; CS = company submission	

4.2.7 Health-related quality of life data identified in the review

The company performed a SLR in order to find studies assessing HRQoL and/or utilities in T1D (see also Section 4.1 and Appendix H of the CS).¹⁹ Based on that review no relevant studies were identified to estimate the required utility input parameters of the model. Hence, the company performed targeted searches in order to find relevant papers. The EAG questions whether the publication year limit of the SLR was not overly strict (2018), given that the papers that the company have now used to estimate input data were all published before 2018. The EAG also finds it worrisome that no details were provided about the targeted search, as it is now unclear if no other relevant studies exist that could have been used to estimate model inputs.

4.2.7.1 Health state utility values

4.2.7.1.1 Utility estimates for Stage 2 T1D

The company assumed that individuals with Stage 2 T1D have the same quality of life (QoL) as the UK general population because they do not present symptoms.⁵³⁻⁵⁵ This was supported by expert advice from UK diabetes clinicians, who indicated that no substantive decrement in utility is observed in individuals with presymptomatic T1D (Stage 1 or Stage 2 T1D) compared with the general population.⁵⁶ For the age-specific utilities of the UK general population (see Table 4.13), a regression model was used from the 2022 NICE DSU report that fitted an adjusted limited dependent variable mixture model to the most recent available Health Survey for England data set (2014) for EuroQoL-5Dimensions-3 Levels (EQ-5D-3L).⁵⁷

Table 4.13: EQ-5D-3L utilities for the UK general population

Age Bracket (years)	Utilities		Utilities Weighted (by sex)
	Female	Male	
0 – 9	NR	NR	0.994 ^a
10 – 19	0.9103	0.9446	0.929
20 – 29	0.9101	0.9332	0.923
30 – 39	0.8981	0.9158	0.908
40 – 49	0.8764	0.8943	0.886
50 – 59	0.8464	0.8684	0.859
60 – 69	0.8082	0.8379	0.825
70 – 79	0.7613	0.8027	0.784
80 – 89	0.7045	0.7634	0.737
90 – 100	0.6376	0.7208	0.684
Based on Table 32 of the CS, values based on Hernández-Alava 2022. ^{9, 57}			
^a Utility for the 0 to 9 years age bracket was estimated using a linear regression based on the utilities for the other age brackets.			
CS = company submission; EQ-5D-3L = EuroQoL-5 Dimensions-3 Levels; NR = not reported, UK = United Kingdom			

To these utilities, a disutility was applied for individuals receiving teplizumab, to account for the burden of receiving IV infusions for 14 days. For the value of the disutility, the UK study by Matza et al. 2013 was used, which reported the disutility of IV infusion to treat the effect of bone metastases compared to no treatment as -0.023.⁵⁸ The vignette presented to the respondents, 121 participants from the general UK population, described that this IV infusion would be given once every four weeks, for a period of two years. The disutility, adjusted for the 14 days that infusions are received, is accounted for in the first model cycle.

4.2.7.1.2 Utility estimates for Stage 3 T1D

The company modelled QoL in Stage 3 T1D by applying several disutilities to the utility estimates of the general population after onset of Stage 3 T1D. Three types of disutility were applied:

1. A disutility during the cycle of onset of Stage 3 T1D to reflect the adjustment of the patient to the next stage of the disease.

2. A disutility during all cycles in Stage 3 T1D to reflect the impact of having symptomatic T1D compared to the general population and patients in Stage 2 T1D.
3. A disutility that increases (becomes more negative) with time spent in Stage 3 T1D to reflect the accumulation of diabetes-related complications over time and their impact of HRQoL.

For the first disutility, that is applied at the moment a patient transitions from Stage 2 to Stage 3, the Swedish study by Sparring et al. 2013 was used.⁵⁹ That study analysed HRQoL (measured with the EQ-5D) in registered individuals from the Diabetes Incidence Study in Sweden with onset of Stage 3 T1D at the age of 15 to 34 years, and with a disease duration of 1, 8, 15 and 24 years, compared with control individuals from the general population matched for age, sex and county of residence. The company considered this study the most appropriate available input source because HRQoL for Swedish individuals with Stage 3 T1D was reported based on disease duration, which aligned with the needs for the model. The study presents the results of a linear regression (Table 4.14), aimed at predicting EQ-5D utility values based on, for example, time since onset of Stage 3 T1D and sex. One of the explanatory variables is having diabetes (compared to no diabetes), and the company have applied its coefficient of -0.025 as the disutility applied during the cycle when Stage 3 of the T1D starts.

Table 4.14: Multiple regression analysis on EQ-5D_{index} from Sparring et al. 2013

Independent variable	Coefficient	p-value
Intercept	0.93	<0.001
Women (vs. men)	-0.024	0.005
Patients with diabetes (vs. control)	-0.025	0.007
Diabetes duration 8 years (vs. 1 year)	-0.023	0.099
Diabetes duration 15 years (vs. 1 year)	-0.055	<0.001
Diabetes duration 24 years (vs. 1 year)	-0.074	<0.001
Education primary school or lower (vs. secondary school or higher)	-0.095	<0.001
Not married or cohabiting (vs. married or cohabiting)	-0.046	<0.001
R-square	0.058	
Adjusted R-square	0.056	
Number of observations	2384	
Based on Table 3 publication Sparring et al. 2013. ⁵⁹ EQ-5D = EuroQoL-5 Dimensions		

For the second type of disutility, the company used Sullivan et al. 2011, in which an UK-based catalogue of EQ-5D index scores was presented.⁶⁰ This catalogue includes estimates of a disutility for having diabetes *without complications* in the UK of -0.0621 compared to the general population. The company applied this disutility in the model to all patients in Stage 3 T1D, for each cycle until death.

Finally, the disutilities for Stage 3 T1D disease duration were also obtained from Sparring et al. 2013.⁵⁹ The study used the one year outcomes as a point of reference in the linear regression analysis (see Table 4.14), so that the coefficients for the explanatory variables 8, 15, or 24 years of disease duration reflect the additional loss of HRQoL due to T1D-related complications that have developed over time.

All disutilities included in the model are summarised in Table 4.15.

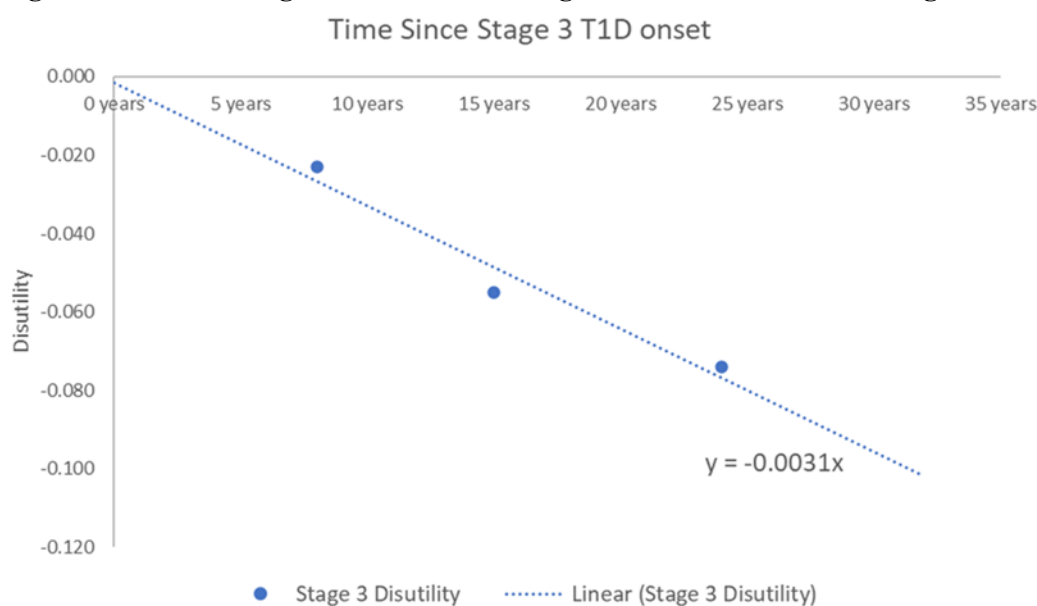
Table 4.15: Disutility values for people with Stage 3 T1D based on time since onset of Stage 3

Type of disutility	Disutility
Onset Stage 3 T1D ⁵⁹	-0.025
Stage 3 T1D (no complications) vs. general population ⁶⁰	-0.0621
Time from onset of Stage 3 T1D 8 years ⁵⁹	-0.023
Time from onset of Stage 3 T1D 15 years ⁵⁹	-0.055
Time from onset of Stage 3 T1D 24 years ⁵⁹	-0.074
Based on Table 34 and 35 of the CS ⁹ CS = company submission; T1D = type 1 diabetes	

The last three disutility values in Table 4.15, i.e., those that depend on time from Stage 3 T1D onset, were used to fit a linear regression model (without intercept) in order to estimate disutilities depending on time since onset of Stage 3 for all model cycles. The regression equation was as follows:

$$\text{Disutility after } x \text{ years from onset Stage 3 T1D} = -0.00314 * x \text{ years from onset Stage 3 T1D}$$

Figure 4.11 shows the three observed disutilities and the linear function that was fitted to them (as implemented in the model).

Figure 4.11: Linear regression model for Stage 3 T1D disutilities according to time from onset

T1D = type 1 diabetes

Based on economic model

4.2.7.1.3 Carer/parent utility for Stage 3 T1D

The company included a disutility in the model to account for carer/parental burden resulting from caring for a child with Stage 3 T1D, such as constant worry, social isolation, disruption to family life and routines and psychosocial maladjustment (see CS Section B.1.3.3.2).^{61, 62} Carers/parent disutilities were only applied for individuals younger than 18 years old in the Stage 3 T1D health state. The carer/parent disutility was estimated to be -0.040 based on López-Bastida et al. 2019, who studied carers' self-reported HRQoL for children with Stage 3 T1D receiving outpatient care at paediatric endocrinology specialised centres in Spain.⁶³ The study reported a carer EQ-5D-5L score of 0.92 which was subtracted from the general population mean utility of 0.96 to obtain the disutility of -0.040. The

company considered this study the most appropriate available input source because UK data were not identified from published literature from the past 10 years.

The company assumed that each child has on average 1.76 carers/parents who take care after onset of Stage 3 T1D until the child reaches adulthood. The number of carers was estimated as a weighted average of the number of carers/parents in families with dependent children using 2023 data on families and children in the UK by family type from the Office for National Statistics (ONS).⁶⁴ Details are provided in Table 4.16.

Table 4.16: Number of carers/parents in families with dependent children in the UK

	Number of families with children (thousands)	Source	Proportion out of total number of families with children	Number of parents with children	Weighted average
Couple family ^a	6,278	ONS ⁶⁴	76%	2	1.76
Lone parent family ^b	2,024		24%	1	
Total	8,302		100%	-	
Based on Table 36 of the CS ⁹					
^a Includes couple families with parents who were married, civil partners, opposite-sex cohabiting, or same-sex cohabiting; assumes 2 parents per family					
^b Assumes 1 parent per family					
CS = company submission; ONS = Office for National Statistics; UK = United Kingdom					

EAG comment: The EAG identified one major concern in the company's approach to estimating HRQoL utilities for the model, one smaller concern regarding the caregiver disutility, and two minor discussion points. These are described below.

To calculate QALYs in Stage 3 T1D, the company applied a disutility dependent on time since the onset of Stage 3 T1D, based on observed relationship in the study by Sparring et al. 2013.⁵⁹ This disutility, which becomes more negative as time since onset increases, is subtracted from the age-dependent utility of the general population, which decreases with age. However, when we consider the regression equation estimated by Sparring et al. 2013 (Table 4.14), we observe that only time since onset of Stage 3 T1D was an explanatory variable, but not age. Thus, the EAG considers that the impact of age may have already been incorporated in the coefficients for 8, 15 and 24 years since onset Stage 3 T1D. To correct for this potential double-counting of the impact of age on the utilities, we can compare the slope of a linear model through the general population utilities and the slope of the line through the disutilities at 8, 15 and 24 months in Sparring et al. 2013.⁵⁹ For the former, we have used the utilities for the general population as presented in Table 4.13 and assumed these apply to the mid-point of each 10-year age bracket. Thus, we find:

$$Utility = -0.00309 * age$$

hence, for each extra year in the model, the utility decreases by 0.00309. From the Sparring study we found:

$$Disutility\ after\ \# \ years\ from\ onset\ Stage\ 3\ T1D = -0.00314 * \# \ years\ from\ onset\ Stage\ 3\ T1D$$

hence, for each extra year in the model, the utility decrease by 0.00314. Therefore, in order to include the impact on HRQoL of having lived with Stage 3 T1D longer without double counting the general impact of age on HRQoL, we can simply subtract the slopes of the two equations, and regard that as the excess utility decline with age due to diabetes-related complications. This would yield an extra 0.00005 decrease in utility per year since the onset of Stage 3 T1D, which is almost negligible.

A smaller concern relates to the disutility that is included in the model in the cycle that a patient progresses to Stage 3 T1D. This disutility was also taken from Sparring et al. 2013 and is the coefficient for the explanatory variable ‘patient with diabetes’ (as compared with the matched non-diabetic individuals).⁵⁹ However, the EAG could not find anything in the paper, either the narrative or in the way the results are presented, that suggests that this coefficient only applies at the moment (year) of onset of Stage 3 diabetes. On the contrary, this disutility appears to have the same role as the disutility that is applied in the model during all cycles in Stage 3 T1D to reflect the impact of having symptomatic T1D compared to a general population and patients in Stage 2 T1D. It should be noted that this disutility estimated by Sparring et al. 2013 (-0.025) is much smaller than the disutility provided by Sullivan et al. 2011 (-0.0621) which is implemented in the model.^{59, 60}

Based on the above, the EAG will adapt the company model (see Section 6) to ensure that no double counting of age-related decline in HRQoL occurs. Given the almost negligible excess utility decline, the EAG will simply forgo the extra utility decline as a function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point. In addition, the EAG will remove the one-off disutility for progressing to Stage 3 T1D.

An issue that will be addressed through EAG explorative scenario analyses regards the carer disutility that was applied in the model. In the clarification letter (Question B9) the EAG asked the company about the carer disutility derived from López-Bastida et al. 2019, which included children aged 2-17 and their carers.¹⁵ The study reported a carer EQ-5D-5L score of 0.92 which was subtracted from the general population mean utility of 0.96. Given that the model population is 13.58 years at the start, the EAG assumes that for the model population the carer utility would likely be higher than 0.92, as the caregiving burden is higher in younger patients. The company indicated in their response that no data were available to adjust for the age in the model population. Additionally, the EAG is not sure if it is reasonable to assume that the caregiver disutility should be applied to both persons in a couple family as it is likely that the total care giving burden is similar to that in a lone family, but now divided between the couple. Thus, the EAG will explore in Section 6 two scenarios where 1) the number of caregivers is limited to one, and 2) the caregiving disutility is halved to correct for the higher average age of the model population.

Finally, the EAG identified two minor issues that have a negligible impact on the incremental cost-effectiveness ratio (ICER):

- The company assumed that the utility in Stage 2 T1D is the same as for the general population. Whilst this does not seem unreasonable, the EAG does wonder if the knowledge that the patient has Stage 2 T1D would not impact HRQoL compared to general population. Some similar remarks were made by experts in the Advisory Board: “...

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■⁵⁶ Given that such decline in HRQoL would likely be transient, the impact of including this in the model would be minimal.

- Also related to Stage 2 T1D, the EAG thinks that the disutility for IV infusion may be slightly low, as it assumes one infusion per four weeks, whereas teplizumab is given for 14 subsequent days, which may increase the burden to patients. However, due to the short period compared to the time horizon of the model, the impact of increasing the disutility on the ICER is negligible.

Due to the minor impact on the model results, the EAG has not implemented any changes in the model regarding the last two points described above.

4.2.7.2 Disutility values adverse events

Section 4.2.7 discussed the AEs that are included in the model. The company used disutility values for these AEs as published by Sullivan et al. 2011 (CS Table 37),⁹ who reported nationally representative preference-based HRQoL scores for the relevant AEs in the UK, based on the EQ-5D.⁶⁰ For rash this disutility is -0.0006, and for the other AEs -0.0722. A weighted average disutility was calculated and applied as a one-off in the first model cycle, accounting for the specified duration of the AE (45 days for lymphopenia and seven days for all other AEs, see also Table 37 in the CS).⁹

4.2.8 Resources and costs

The healthcare cost categories included in the model were treatment acquisition and administration, teplizumab-related resource use (test to confirm eligibility, monitoring tests, pre-medications), Stage 2 and Stage 3 T1D, and adverse events. Costs were inflated to 2023 prices using the NHS Cost Inflation Index (NHSCII) pay and price indices.⁶⁵

4.2.8.1 Resource use and costs data identified in the review

The company conducted a systematic review on the economic burden of T1D in children and adults. No papers were identified providing evidence on costs in Stage 2 T1D. Twenty-one publications were identified for Stage 3 T1D which are reported in Appendix G and I of the CS¹⁹

4.2.8.2 Treatment and acquisition costs (with patient access scheme, PAS)

Total treatment costs for teplizumab include costs from acquisition and administration, concomitant medicines, tests for treatment eligibility, monitoring tests, and pre-treatment medicines. The company does not model the direct costs of ECM since it applies to both arms. In the response to the clarification letter the company describes the comparator ECM as comprising routine monitoring of blood glucose, psychosocial support and education on the management of T1D (Question B3a).¹⁵ Full intervention costs are incurred for each patient with no account made for non-adherence.

4.2.8.2.1 Acquisition and administration

Teplizumab is administered with daily IV infusions using a BSA-based dosing scheme. The company assumes a 14-day course of treatment using single vial packs and the following dosing scheme:

- Day 1: 65 mcg/m²
- Day 2: 125 mcg/ m²
- Day 3: 250 mcg/ m²
- Day 4: 500 mcg/ m²
- Days 5-14: 1,030 mcg/ m²

The company states that the total drug acquisition costs for a standard 14-day treatment course of teplizumab is £[REDACTED]. A PAS with a simple discount of [REDACTED] has been provided by the company leading to a total cost of [REDACTED].

The company included additional costs related to the administration of teplizumab depending on whether the patient is always treated in a hospital setting or also in a closer-to-home setting (see Table 4.17). It is assumed that the first five administrations take place in the hospital setting for all patients, and that for 10% of the patients the remaining administrations also take place in the hospital setting, and for 90% in a closer-to-home setting. For administration in a hospital setting a post-infusion observation period of one hour by an IV infusion nurse is assumed. In the closer-to-home setting a 45-minute observation period by a district nurse is assumed. Finally, costs are incurred in infusion preparation which is assumed to take 15 minutes for a high specialised pharmacist for each infusion. Costs are drawn from standard NHS sources.

Table 4.17: Costs of administering teplizumab

Details of administration	Cost	Source
Closer-to-home administration (30-minute IV infusion, 45 minutes post-infusion observation, 75 minutes total of nurse time)	£139.55	NHS Reference costs (N20AF) ⁶⁶
Hospital administration (30 to 60-minute IV infusion, 30-minute nurse time)	£217.20	NHS Reference Costs (SB12Z) ⁶⁶
Hospital post-infusion observation (IV infusion nurse; 1 hour)	£22.40	GOV.UK ⁶⁷
Infusion preparation (highly specialised pharmacist; 15 minutes)	£29.60	NHS Jobs ⁶⁸
Based on Tables 39 and 43 of the CS ⁹ CS = company submission; IV = intravenous; NHS = National Health Service		

EAG comment: Although requested in the clarification letter,¹⁵ the company have not provided information on the unit price of the teplizumab, or the assumptions made around patient weight. It is therefore not possible for the EAG to validate the estimate of total drug acquisition costs.

4.2.8.2.2 Concomitant medications and tests

Additional medication costs are incurred when administering teplizumab following recommendations from the Pediatric Endocrine Society to pre-medicate individuals prior to teplizumab infusion with (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) consider use of an antiemetic, to mitigate cytokine release syndrome (CRS).⁶⁶ While the recommendations state that this must be done for a minimum of five days, the company elected to include these costs for all 14 days of treatment. Assumptions around administrations, dosing and pack size are listed in Table 4.18. Prices are list prices from the British National Formulary (BNF).⁶⁹

Table 4.18: Use and costs of pre-infusion medications

Drug type	Drug details	Frequency	Cost per tablet	Source	Total cost
NSAID or acetaminophen	Ibuprofen 400 mg tablet; one tablet three	14	£0.10	Draft SmPC ²⁹ NICE BNF ⁷⁰	£1.34

Drug type	Drug details	Frequency	Cost per tablet	Source	Total cost
	times a day when required				
Antihistamine	Cetirizine hydrochloride, 10 mg tablet; once daily	14	£0.02	Draft SmPC ²⁹ NICE BNF ⁶⁹	£0.34
Anti-emetics	Ondansetron, 4 mg tablet; once daily	14	£0.95	Draft SmPC ²⁹ NICE BNF ⁷¹	£13.30
Based on Table 41 of the CS ⁹ Drug use assumptions based on Mehta et al. 2024. ⁶⁶ BNF = British National Formulary; CS = company submission; mg = milligram; NICE = National Institute for Health and Care Excellence; NSAID = nonsteroidal anti-inflammatory drug; SmPC = Summary of Product Characteristics					

According to the SmPC for teplizumab, individuals should undergo complete blood count and liver enzyme tests prior to initiating teplizumab and be monitored for CRS and lymphopenia during treatment. The company assumed both a complete blood count and liver enzyme test takes place on each day of treatment. The unit costs come from a 2014 single-centre UK study on avoiding unnecessary tests. No reasons are provided for why this source was selected. See Table 4.19 for further information.

Table 4.19: Costs of laboratory tests related to teplizumab treatment

Test	Frequency	Unit cost	Source
Complete blood count	14	£2.65	Draft SmPC ²⁹ Akhtar 2014 ⁷²
Liver enzyme test	14	£2.78	Draft SmPC ²⁹ Akhtar 2014 ⁷²
Based on Table 42 of the CS ⁹ CS = company submission; SmPC = Summary of Product Characteristics			

4.2.8.2.3 Tests for eligibility

The company includes some additional costs related to using teplizumab arising from confirmatory tests for Stage 2 T1D. Confirmation requires the presence of at least two positive pancreatic islet cell autoantibodies and dysglycaemia without overt hyperglycaemia. Costs for these tests are derived from different NHS sources and summarised in Table 4.20.

Table 4.20: Costs of confirmatory tests prior to teplizumab treatment

Test	Frequency	Unit cost	Source	Total cost
Autoantibody tests (anti-GAD, anti-ZnT8 and anti-IA2)	1	£29.04	Exeter Clinical Laboratory International ⁷³	£29.04
OGTT – glucose solution	1	£3.98	NICE BNF ⁷⁴	£3.98

Test	Frequency	Unit cost	Source	Total cost
OGTT – blood glucose tests	5	£7.85	National Schedule of NHS Costs ⁷⁵	£39.25
Based on Table 40 of the CS ⁹ anti-GAD = antibodies to glutamic acid decarboxylase; BNF = British National Formulary; CS = company submission; IA2 = tyrosine phosphatase islet antigen-2; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OGTT = oral glucose tolerance test; ZnT8 = zinc transporter protein 8				

EAG comment: It should be noted that the costs of confirmatory tests prior to teplizumab treatment do not capture the full costs of screening for Stage 2 T1D individuals.

4.2.8.3 Health state costs: Stage 2 T1D

Monthly costs for Stage 2 T1D are stratified by age (8-18, 19+ years) and time before onset of Stage 3 T1D (0-6 months, 6-12 months, 12-24 months, and >24 months). The costs are assumed to be independent of treatment.

Assumptions for resource use were based on international monitoring guidelines and advice the company received from UK diabetes clinicians. The company assumes glycaemic monitoring and education/psychological support consultations every six months for adults and every three months for children. Glycaemic monitoring involved continuous glucose monitoring (CGM) and HbA1c testing. Support consultations were assumed to be either multidisciplinary team (MDT) consultations (defined as a patient consultation involving a team of multiple health care professionals with at least two consultants from different national main specialities) or telephone consultations by a diabetologist consultant. Costs are derived from different national sources or previous NICE guidance (Table 4.21).

Table 4.21: Annual healthcare resource use and costs for Stage 2 T1D

Resource	Frequency		Unit cost (assumptions)	Annual cost		Source
	Paediatrics	Adults		Paediatrics	Adults	
CGM	4	2	£43.00 (based on cost of FreeStyle Libre 3 sensor)	£172.0	£86.0	NICE TA943 committee papers ⁷⁶
HbA1c testing	4	2	£14.00 (based on cost of single HbA1c test)	£56.0	£28.0	NIHR ⁷⁷
Paediatric MDT	2	-	£242.00 (WF02B – Treatment code 263)	£484.0	£0.0	NHS England ⁷⁸
Adult MDT	-	2	£133.00 (WF02B – Treatment code 307)	£0.0	£266.0	
Telephone consultation (diabetologist)	5	3	£31.60 (based on annual salary)	£158.0	£94.8	

Resource	Frequency		Unit cost (assumptions)	Annual cost		Source
	Paediatrics	Adults		Paediatrics	Adults	
consultant, 30 minutes)						
Based on Table 44 of the CS ⁹ CGM = continuous glucose monitoring; CS = company submission; HbA1c = glycosylated haemoglobin; MDT = multidisciplinary team; NICE = National Institute for Health and Care Excellence; NIHR = National Institute for Health and Care Research; NHS = National Health Service; T1D = type 1 diabetes; TA = technology appraisal; WF02B = first attendance – multi-professional						

Finally, Table 4.22 presents total monthly costs for Stage 2 T1D stratified by age based on the resource use described in Table 4.21. Note that while the CS says costs are also stratified by time before onset of Stage 3 T1D, no differences in costs are included in the company's base-case analysis.

Table 4.22: Monthly costs for Stage 2 T1D

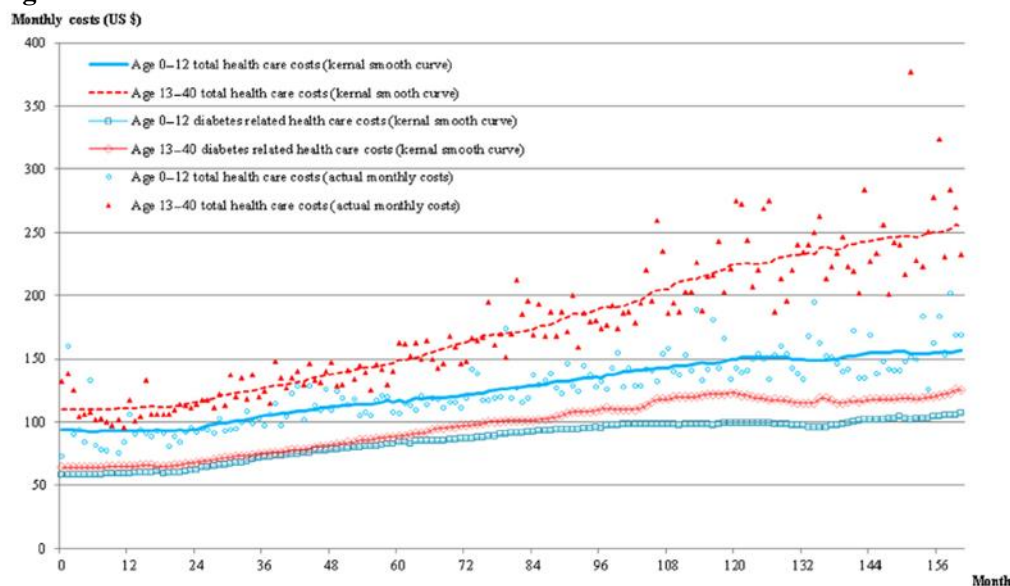
Age	Monthly cost
8-18 years	£72.50
≥19 years	£39.60
Based on Table 45 of the CS ⁹ CS = company submission; T1D = type 1 diabetes	

4.2.8.4 Health state costs: Stage 3 T1D

Monthly costs for those in Stage 3 T1D depend on age at onset of Stage 3 T1D (0-12, 12+ years) and time since onset of Stage 3 T1D (0-8, 9+ years).

Monthly costs were estimated by combining data from Hex et al. 2024 and Ou et al. 2016.^{1,2} Hex et al. 2024 presented top-down estimates of the direct healthcare costs of diabetes in the UK.¹ Total direct healthcare costs were made up of costs related to diagnosis, ongoing management, acute event complications, microvascular and macrovascular complications, and pregnancy related complications, and totalled £1,630,362,000. The prevalence of Stage 3 T1D was estimated to be 327,209 based on audit data from England and population-level data for Scotland. From this, annual and monthly costs of £4,982.63 and £415.22 per-person were estimated, respectively.

The company assumed these costs will increase over time as patients remain in Stage 3 T1D for longer. To model the trajectory of costs over time, the company combined the initial cost estimate presented above with data from Ou et al. 2016.² Ou et al. 2016 reported trends in total and disease-related costs for people with newly diagnosed T1D, stratified by age at diagnosis (0-12, 13-40 years), based on data from Taiwan's National Health Insurance Research Database covering the period 1999 to 2012.² Figure 4.12 presents the data from Ou et al. 2016. The company argued that no relevant data were available from the UK based on their SLR and therefore used these data to estimate total healthcare costs rather than diabetes-related health care costs.

Figure 4.12: Trends in healthcare costs over time from Ou et al 2016.²

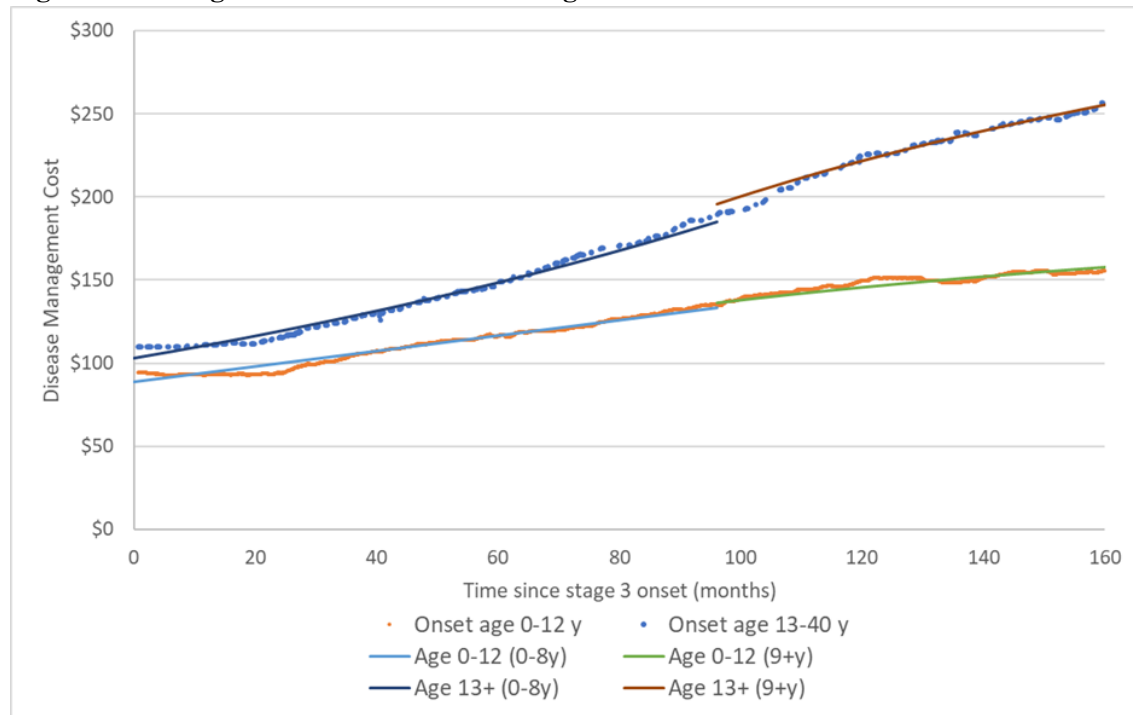
Based on Figure 2 from Ou et al. 2016²

Based on visual inspection of the data for total healthcare costs, the company identified an inflection point at around 8 to 10 years after T1D diagnosis. The company then used a piece-wise regression approach to fit four models to the data based on age of disease onset and time since onset. Different models were fitted to each group and models were scaled such that the costs at time 0 (i.e., intercept) were equal to the monthly cost estimate derived from Hex et al. 2024.¹ The regression models are presented in Table 4.23.

Table 4.23: Regression models for Stage 3 T1D healthcare costs

	Age 0-12 years		Age ≥13 years	
	0-8 years since onset	9+ years since onset	0-8 years since onset	9+ years since onset
Regression parameters (raw data)				
Model type	Linear	Logistic	Exponential	Logistic
Intercept	\$88.4 ^a	-\$53.7 ^a	\$103.2 ^a	-\$338.4 ^a
Slope/rate	\$0.47 ^a	\$41.5 ^a	\$0.006 ^a	\$116.9 ^a
R ²	0.98	0.94	0.99	0.98
Regression parameters (scaled)				
Intercept	£415.22	-£252.29	£415.22	-£1,362.06
Slope/rate	£2.18	£195.64	£0.006	£470.77
Based on Table 46 of the CS ⁹				
^a Costs are in 2012 US dollars.				
CS = company submission; T1D = type 1 diabetes				

In addition, Figure 4.13 shows the different fits of the regression models against the observed (digitised) data.

Figure 4.13: Stage 3 T1D healthcare costs regression models versus observed data

T1D = type 1 diabetes

Based on economic model

EAG comment: The company used the average monthly cost per person from Hex et al. 2024 as the initial cost for individuals transitioning to Stage 3 T1D.¹ However, the costs in Hex et al. 2024 are based on the prevalent and not the incident population, therefore, including patients who may have developed Stage 3 T1D long ago instead of newly diagnosed cases only. The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data,² is incorrect and substantially overestimates healthcare costs for Stage 3 T1D. Average annual costs for individuals in Stage 3 T1D over 60 years [REDACTED] from the company's approach are [REDACTED]. This is more than [REDACTED] higher than the costs of stage 3 T1D in prevalent population from Hex et al. 2024 of £4,982. This concern was raised by the EAG in the clarification letter (Question B15),¹⁵ but the company did not provide sufficient justification for their approach.

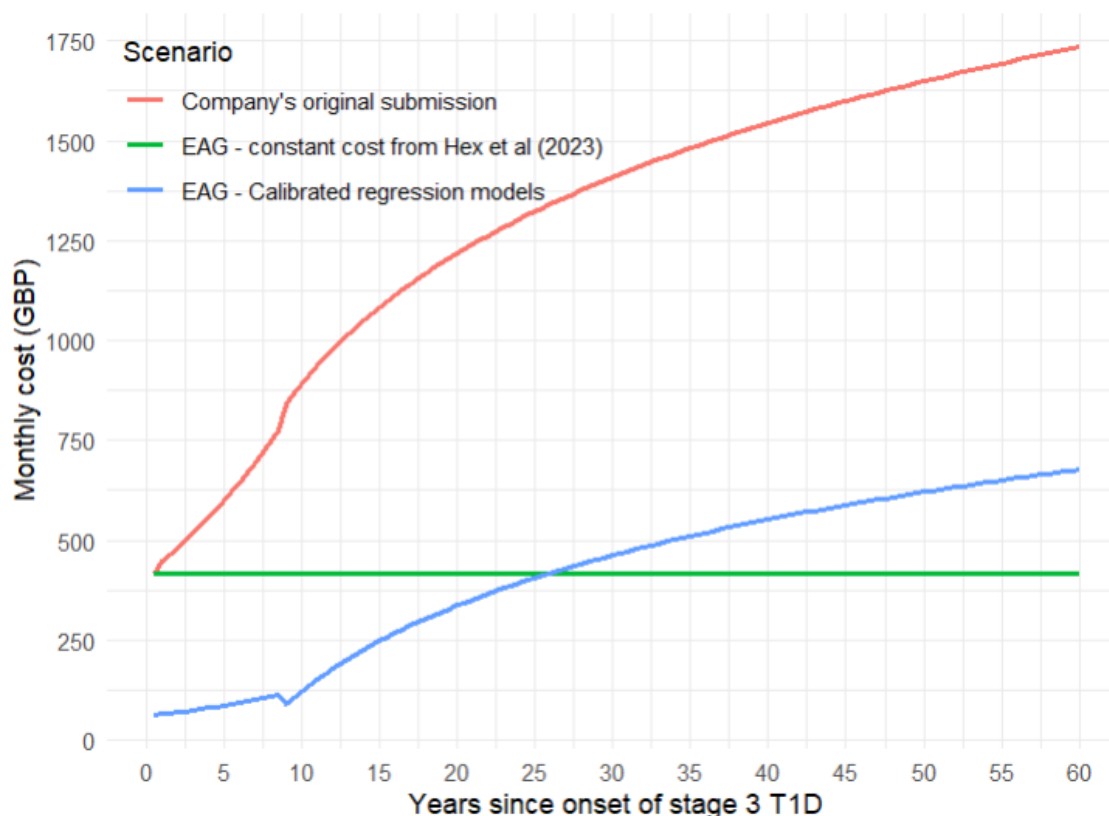
The EAG contends that the *average* monthly costs of Stage 3 T1D should be equal to the estimate from Hex et al. 2024 of £415.22. The EAG considered two main approaches to achieve this. The first is to simply apply the cost of £415.22 irrespective of the time in the Stage 3 health state. This is the simplest approach but will tend to overestimate costs for newly diagnosed individuals and underestimate costs in later periods. The second is to calibrate the regression models such that the average monthly cost over 60 years is equal to £415.22. A period of 60 years was chosen since this was the average time spent in Stage 3 T1D for patients in the ECM arm. This retains the trend of increasing costs the longer the person is in the Stage 3 T1D, but the initial cost estimates are hard to validate. Table 4.24 shows the original regression parameters provided by the company with the calibrated parameters obtained by the EAG.

Table 4.24: Original regression models and EAG calibrated regression models for trend in Stage 3 T1D costs over time

	0-8 years since onset		9+ years since onset	
	Original (CS)	Calibrated (EAG)	Original (CS)	Calibrated (EAG)
	Exponential	Exponential	Logistic	Logistic
Intercept	£415.22	£60	-£1,362.06	-£1,362.06
Slope/rate	£0.006	£0.006	£470.77	£310

CS = company submission; EAG = External Assessment Group; T1D = type 1 diabetes

Figure 4.14 presents the estimated monthly Stage 3 T1D costs over a period of 60 years from Stage 3 T1D onset under the EAG alternative scenarios and the company's base-case approach. It is clear from the figure that the company's approach leads to a substantial overestimation of Stage 3 T1D costs over time compared to the EAG approaches. The revised EAG base-case (Section 6) will apply the average monthly cost from Hex et al. 2024 as a fixed health state cost due to its simplicity and the impossibility to validate the values obtained with the EAG calibrated regression models.

Figure 4.14: Estimates of Stage 3 T1D healthcare costs from the company versus EAG estimates

EAG = External Assessment Group; T1D = type 1 diabetes

Based on economic model

Furthermore, the company used data from Ou et al. 2016 on total healthcare costs rather than diabetes-related healthcare costs.² Using estimates for total healthcare costs would include future unrelated healthcare costs which should not be included according to the NICE reference case. This would increase health state costs for Stage 3 T1D and unfairly favour teplizumab. In their response to the clarification letter the company suggested that using the diabetes-related costs from Ou et al. 2016 would underestimate the costs of Stage 3 T1D, which include acute metabolic complications and other

complications.¹⁵ However, it is unclear from the Ou et al. 2016 study exactly which costs were included in the estimate of diabetes-related costs since only the following information provided: “*The total health care costs and the costs incurred for diabetes, including treatment, examination, and procedures associated with diabetes, were estimated separately*”.²

The company also considered additional costs related to DKA event management at the onset of Stage 3 T1D. The cost per event was estimated at £1,722.32 based on the weighted average of inpatient costs from the “Non-Elective Admissions” under the code KB02G-K (Diabetes with Hyperglycaemic Disorders) in the National Schedule of NHS Costs.⁷⁹ The probability of a DKA event is estimated to be 2.5% and independent of treatment based on data from Besser et al. 2022.⁴⁴ However, the EAG is uncertain whether these costs are not already included in the estimates from Hex et al. 2024.¹

Finally, in the originally submitted model, the company had not accounted for the correlation between parameters of the models developed from Ou et al. 2016 when Stage 3 T1D costs were implemented in the PSA.² In the response to the clarification letter the company indicated that the uncertainty associated to these models is no longer considered but rather only in the initial costs.¹⁵ It is not clear to the EAG why the company chose this approach, as it leads to an underestimation of the variability in the cost outcome.

4.2.8.5 Adverse event costs

The company used data on AE frequencies from Herold et al. 2023,²⁸ and identified five AEs occurring at a higher frequency in the teplizumab versus the control group, namely lymphopenia, leukopenia, neutropenia, decreased blood bicarbonate and rash. The company used the excess proportion of events and included the costs only in the teplizumab arm. The duration of each event is based on data from previous trials of teplizumab and assumptions based on the integrated safety analysis. Costs of events were taken as the cost of a general practitioner visit (duration 10 minutes) from the National Schedule of NHS Costs. These costs are summarised in Table 4.25.

Table 4.25: Adverse event frequency and management costs

Adverse event	Cost per event	Source	Excess proportion % (vs. Placebo)	Source	Duration (days)	Source
Lymphopenia	£56.00	NHS Reference Costs ⁷⁵	63.2%	Integrated safety analysis ²⁸	45	TN-10 ²³
Leukopenia	£56.00		36.8%		7	Assumption based on integrated safety analysis ²⁸
Neutropenia	£56.00		18.0%		7	
Blood bicarbonate decreased	£56.00		11.0%		7	
Rash	£56.00		24.3%		7	
Based on Table 47 of the CS ⁹ CS = company submission; NHS = National Health Service						

4.2.8.6 Health-related quality of life

No HRQoL data were collected as part of the TN-10 trial, so instead literature and expert opinion were required to estimate utilities per health state.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

5.1.1 Original company's CE results

In Section B.3.10 of the CS, the company presented their CE results using the PAS price for teplizumab.⁹ Disaggregated results were presented in Appendix J.¹⁹

Table 5.1 shows the company's base-case deterministic CE results for teplizumab compared to ECM. All results are discounted. Results indicated that teplizumab was more costly but also more effective than ECM. Incremental QALYs for teplizumab were [REDACTED] and incremental costs were [REDACTED], resulting in an ICER of £29,602 per QALY gained. Disaggregated discounted QALYs and costs are shown in Table 5.2 and Table 5.3, respectively.

Table 5.1: Company base-case deterministic CE results (teplizumab, PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Teplizumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	29,602
ECM	[REDACTED]	[REDACTED]	[REDACTED]				

Based on Table 50 in the CS.⁹
 CE = cost effectiveness; CS = company submission; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 5.2: Disaggregated QALY results (teplizumab, discounted)

Health state	QALY teplizumab	QALY ECM	Increment	Absolute increment	(%) Absolute increment
Stage 2 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stage 3 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Caregiver disutility	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AE disutility	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Based on Table 37 in Appendix J of the CS¹⁹
 AE = adverse event; CS = company submission; ECM = established clinical management; NA = not applicable; QALY = quality-adjusted life year; T1D = type 1 diabetes

Table 5.3: Disaggregated cost results (teplizumab, PAS price, discounted)

Cost item	Cost teplizumab (£)	Cost ECM (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Drug administration	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AE management	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Treatment-related resource use	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stage 2 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Cost item	Cost teplizumab (£)	Cost ECM (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Stage 3 T1D					
Based on Tables 38 and 39 in Appendix J of the CS ¹⁹ AE = adverse event; CS = company submission; ECM = established clinical management; NA = not applicable; PAS = patient access scheme; T1D = type 1 diabetes					

5.1.2 Updated company's CE results

In the original model the company made an error in the implementation of the half-cycle correction. The updated results after addressing this error in response to the clarification letter are presented in Table 5.4. The results remain similar but with a lower ICER. The company did not provide updated disaggregated results.

Table 5.4: Updated company base-case deterministic CE results (teplizumab, PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Teplizumab							27,534
ECM							
Based on Table 1 in Appendix 2 of the company's response to the clarification letter. ¹⁵ CE = cost effectiveness; CS = company submission; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year							

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by:

- Increasing total QALYs by delaying the onset of Stage 3 T1D.
- Slightly improving caregiver quality of life.
- Slightly reducing the QALYs due to experiencing treatment-related AEs.

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Reducing costs due to Stage 3 T1D (by delaying its onset), which is more costly than Stage 2 T1D.
- Increasing costs due to treatment acquisition, administration and testing.
- Slightly increasing costs due to experiencing treatment-related AEs.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 400 iterations. The input parameters can be found in Table 48 of the CS, and the probability distributions used in the PSA in the "PSA Inputs" sheet of the economic model.⁹ In the original model there were some errors in the implementation of PSA, especially concerning Stage 3 T1D costs. In the regression models that determined the trend in costs over time for patients in the model, the company had sampled from each model parameter independently. In the updated model, the company did not correct this by accounting

for the correlation between parameters but rather by ignoring variation in these modelled trends. Variation in Stage 3 T1D costs is generated only through variation in the initial stage costs. The updated average PSA results are summarised in Table 5.5 and are overall in line with the deterministic ones shown in Table 5.4.

Table 5.5: Company base-case probabilistic CE results (teplizumab, PAS price, discounted)

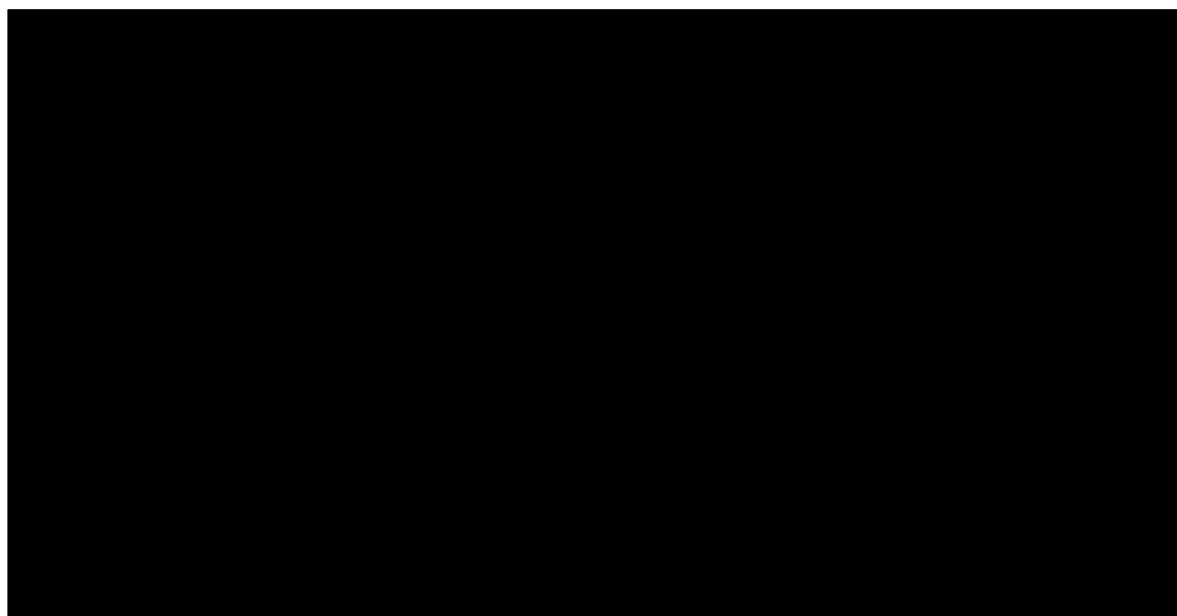
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Teplizumab	██████	██████	██████	██████	██████	██████	29,488
ECM	██████	██████	██████				
Based on Table 1 in Appendix 2 of the company's response to the clarification letter. ¹⁵ CE = cost effectiveness; ECM = Established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = Patient access scheme; QALY = quality-adjusted life year							

The company also plotted the PSA outcomes on a CE-plane. These are shown in Figure 5.1.



████████████████████. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and shown in Figure 5.2. The CEAC plot indicates that at the common threshold of £30,000 per QALY gained, the estimated probability that teplizumab is a cost effective alternative to ECM was ██████.

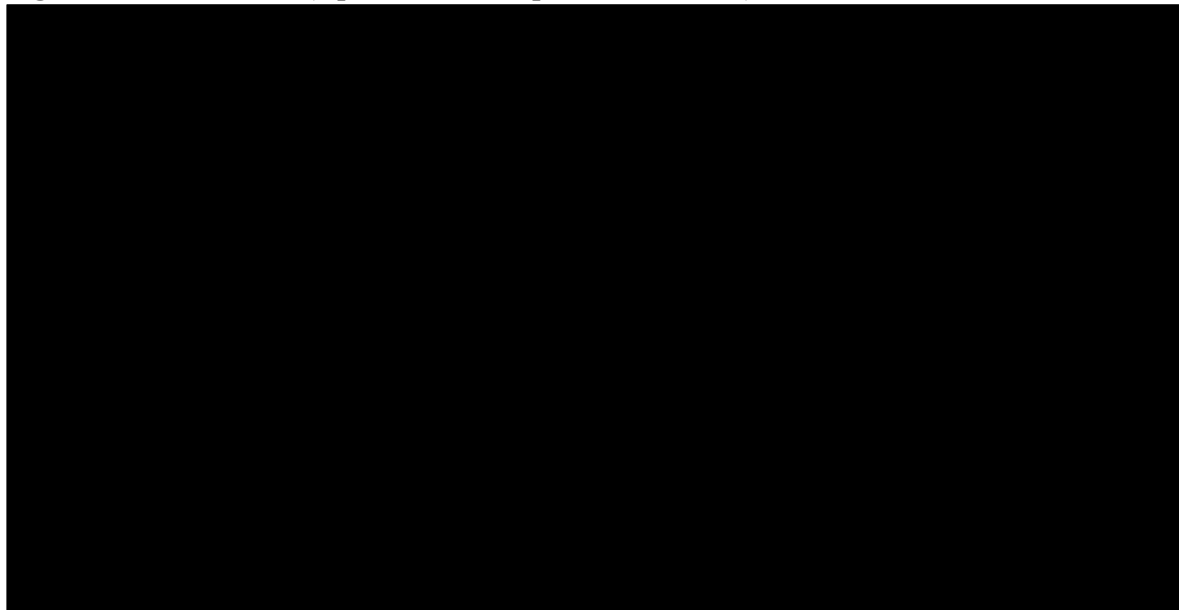
Figure 5.1: PSA CE-plane (teplizumab, PAS price, discounted)



Based on Figure 2 in Appendix 2 of the company's response to the clarification letter.¹⁵

CE = cost effectiveness; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (teplizumab, PAS price, discounted)



Based on Figure 3 in Appendix 2 of the company's response to the clarification letter.¹⁵

CEAC = cost effectiveness acceptability curve; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

EAG comment: The EAG identified several errors in the implementation of PSA in the original model, most notably the failure to account for correlation between parameters in the regression models for Stage 3 T1D costs. In the updated model, the issue was resolved by not incorporating uncertainty in these regression models in the PSA. Variation in Stage 3 T1D costs is generated only through variation in the initial stage costs. Therefore, parameter uncertainty is likely underestimated in the PSA results.

5.2.2 *Deterministic sensitivity analysis*

The company also conducted a deterministic sensitivity analysis (DSA) where all input parameters were varied using the lower and upper bound values of their 95% confidence intervals, if available. Otherwise, parameters were varied by $\pm 20\%$ of their mean value (see tab 'DSA Inputs' of the economic model). Tornado diagrams for incremental costs, incremental QALYs, and the ICER are presented in Figure 5.3, Figure 5.4 and Figure 5.5, respectively. These represent updated results after the correct implementation of the half-cycle correction. Incremental QALYs are most sensitive to

Incremental costs were sensitive to . The ICER was most impacted by the .

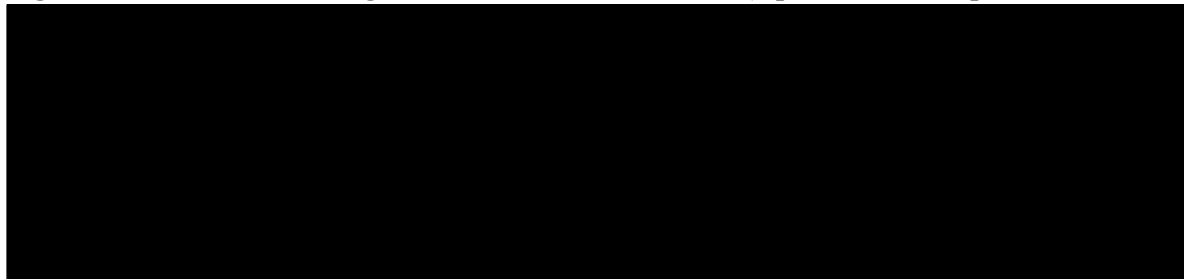
Figure 5.3: DSA tornado diagram for incremental costs (teplizumab, PAS price, discounted)



Based on Figure 4 in Appendix 2 of the company response to the clarification letter.¹⁵

AE = adverse event; DKA = diabetic ketoacidosis; DSA = deterministic sensitivity analysis; PAS = Patient Access Scheme; T1D = type1 diabetes

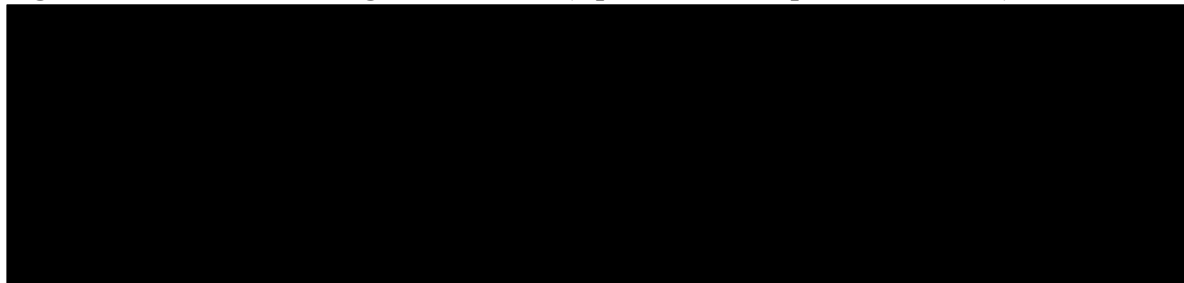
Figure 5.4: DSA tornado diagram for incremental QALYs (teplizumab, PAS price, discounted)



Based on Figure 5 in Appendix 2 of the company response to the clarification letter.¹⁵

AE = adverse event; DSA = deterministic sensitivity analysis; PAS = patient access scheme; QALY = quality-adjusted life-year; T1D = type 1 diabetes

Figure 5.5: DSA tornado diagram for ICER (teplizumab, PAS price, discounted)



Based on Figure 6 in Appendix 2 of the company response to the clarification letter.¹⁵

DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; PAS = patient access scheme; T1D = type 1 diabetes

5.2.3 Scenario analysis

The company presented the results of eight scenario analyses to assess the robustness of the model results to changes in some modelling assumptions. A summary of the results of these scenarios is provided in Table 5.6. These represent the results after correcting the implementation of the half-cycle correction. Note also that scenario 8 (disutilities for Stage 3 T1D based on a multiplicative approach) was included in response to the clarification letter.¹⁵ The scenarios included exploring setting for administrative of IV infusions, risk of death in Stage 3 T1D, general population mortality, time to Stage 3 T1D onset, and discount rates. Most scenario analyses had negligible impact on incremental

QALYs, costs, or the ICER. Using lower discount rates of 1.5% for both costs and health benefits, the company found teplizumab to be dominant versus ECM.

EAG comment: In general, the scenarios explored by the company did not change the main conclusions from their base-case. However, the number of scenarios explored was insufficient to assess the impact of remaining uncertainties on the model results. For example, the company did not explore scenarios choosing different extrapolation options for time to progression to Stage 3 T1D. These scenarios are crucial in order to properly assess the uncertainties in the model and will be explored by the EAG in Section 6 of this report.

Table 5.6: Company scenario analysis results (teplizumab, PAS price, discounted)

Scenario number	Scenario description	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base-case
0	Base-case	██████	██████	27,534	NA
1	30% of individuals receive treatment at a hospital (increased from 10% in base-case)	██████	██████	29,783	1.0%
2	No closer-to-home administration (assumes 100% of individuals receive all 14 days of treatment in hospital). In practice (and in the base-case), a proportion of individuals were expected to use the closer-to-home option.	██████	██████	30,813	4.5%
3	Stage 3 T1D excess risk of death informed by Rawshani et al. 2018. ⁵¹	██████	██████	30,405	3.1%
4	UK life tables from pre-COVID years (2017-2018)	██████	██████	29,307	-0.6%
5	Maximum time to Stage 3 T1D onset for ECM set to 10 years (maximum number of years not set in base-case)	██████	██████	25,422	-13.8%
6	Maximum time to Stage 3 T1D onset for ECM set to 15 years (maximum number of years not set in base-case)	██████	██████	28,607	-3.0%
7	1.5% discount rates for cost and health benefits	██████	██████	401	-98.6%
8	Disutilities associated with Stage 3 T1D based on multiplicative approach	██████	██████	30,023	1.8%
Based on Table 2 in Appendix 2 of the company response to the clarification letter.¹⁵ COVID-19 = coronavirus disease 2019; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; NA = not applicable; PAS = patient access scheme; QALY = quality adjusted life year, T1D = type 1 diabetes					

5.3 Model validation and face validity check

A summary of the validation efforts conducted on the economic model was discussed in the validation Section of the CS (B.3.14).⁹ Other validation aspects, such as the validation of some input parameters are scattered over Document B of the CS.⁹ In addition, more details about model validation were provided by the company in response to some clarification questions.¹⁵ In the remainder of this section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.⁸⁰

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

The company indicated that the model structure and key assumptions were reviewed by UK clinical and health economic experts in an Advisory Board in May 2024.⁵⁶ The company considered the structure of the three-state Markov model described in Section 4.2.2 of this report appropriate for modelling the delay of onset of Stage 3 T1D. The experts considered the structure of the three-state Markov model described in Section 4.2.2 of this report appropriate for modelling the delay of onset of Stage 3 T1D. The experts noted a similar approach was taken for the economic evaluation of the DiRECT trial in T2D. The experts indicated that the model outcomes were in line with those expected in an economic evaluation. Also, taking an aggregate approach to modelling all-cause mortality instead of mortality due to diabetes-related complications in Stage 3 T1D was accepted by experts, noting that teplizumab treatment effect is expected to delay rather than prevent onset of Stage 3 T1D.

The company also emphasised that the experts consulted stated that an exponential distribution for extrapolating treatment efficacy data on the comparator arm was considered a reasonable conservative estimate of outcomes in current clinical practice.⁵⁶ The EAG is unable to critique this statement because in the details of the Advisory Board meeting shared by the company it is not explained how the experts came to this conclusion. However, it should be noted that it seems that the question regarding the face validity of the long-term extrapolations was answered by one clinical expert only. Therefore, the EAG suggests interpreting the above-mentioned statement with caution. Other extrapolation options did result in worse progression outcomes for ECM, but these were not discussed in the CS. If the exponential distribution for ECM indeed represents a conservative estimate, it is likely that all other extrapolations would be deemed as implausible, which would suggest that the exponential distribution would be the only logical choice to model progression in the ECM arm. This would be an important limitation and if that were the case the EAG wonders whether other more advanced survival extrapolations could have been explored by the company. Furthermore, as explained in Section 4.2.6, the EAG considers that the face validity exercise conducted by the experts was focused on assessing the validity of the exponential distribution for the placebo arm only. However, no range of possible long-term values was provided. These were relatively similar for the gamma or Weibull distributions (as can be seen in Table 4.6), which also show a good fit to the data (Table 4.5). The validity of these extrapolations could have been discussed with the experts and the conclusions included in the CS.

5.3.1.2 Cross-validity testing (conceptual model)

The company conducted a review of published literature and grey literature sources (including health technology assessment reports) to identify an appropriate modelling approach for the CEA. The company concluded that individual patient simulation and Markov models have been used to model

disease progression in Stage 3 T1D,^{81, 82} including a hybrid decision tree/Markov microsimulation model for Stage 2 T1D.⁸³

The company noted that previous T1D models mostly focused on Stage 3 T1D patients of the disease, where diabetes-related complications are modelled separately, and transition probabilities are based on risk equations that consider the relationship between risk factors (e.g., HbA1c level, age, time since onset of Stage 3 T1D) and disease-related complications.^{81, 82} The company deemed such a model structure unfeasible for the current appraisal given the lack of data on risk factors and complications in the TN-10 trial.

The company also noted that Mital et al. 2020 evaluated subgroups of Stage 2 T1D individuals defined on HLA-DR3, HLA-DR4, and ZnT8 autoantibody status, using data from the TN-10 trial to inform the annual risk of progressing to Stage 3 T1D.⁸³ The company did not consider this approach for the current appraisal given that HLA testing is not currently used in routine clinical practice (confirmatory testing for Stage 2 T1D prior to initiation of teplizumab is based on autoantibody status only).²⁹ Another reason was the small sample sizes of the HLA subgroups in the TN-10 trial, which would have resulted in increased uncertainty of long-term estimates for the subgroups.

Finally, the company highlighted other limitations associated with microsimulation models, such as the reliance on surrogate measures (i.e., HbA1c) to inform risk equations that are used to predict long-term outcomes and mortality associated with T1D. The company referred to Daly et al. 2022 suggesting that the accuracy of HbA1c as a predictor of macrovascular complications (or mortality) is strongly disputed and, therefore, further validation of this surrogate endpoint is required, especially because small changes in risk factors could have a large impact on the model results.⁸² The company concluded then the projection of surrogate outcome measures over the longer term introduces uncertainty that can limit the external validity of the models, especially over a lifetime horizon, and that previous NICE submission diabetes models have been criticised for using risk equations to predict long-term outcomes.⁸²

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

Input parameters were also reviewed by UK clinical and health economic experts in an Advisory Board.⁵⁶ These included survival curves extrapolations for time to progression, modelling mortality for Stage 3 T1D, utility values or assumptions about frequency of resource use.

5.3.2.2 Model fit testing

Model fit testing was discussed in detail for the survival analyses conducted by the company to guide the choice of progression curves (see Section 4.2.6). Where utility and cost parameters were estimated through regression models, goodness-of-fit of these models were not discussed by the company (see Section 4.2.8).

5.3.3 Validation of the computerised model (technical verification)

The company explained that the model underwent two independent technical validation processes, which examined the extent to which the mathematical calculations were correct and consistent with the model's specifications. This led to corrections of identified errors that were incorporated into a revised model, which was checked again. The company also indicated that all input parameters were checked against source documents (e.g., published sources or internal reports) and any inconsistencies were corrected. Specific details are provided below.

5.3.3.1 External review

Technical verification was conducted by a senior modeller who was not involved in the model development. The model formulas were examined to ensure the expected calculations and translation of the model structure correctly. Correct cell references used in all formulas were also confirmed. Formulas and sequence of calculations for input parameters were also checked. All errors identified were corrected. When the verification process led to unclarities about some aspects of the model technical implementation, these were discussed by the project team and the modeller validating the model; changes were made accordingly and the correct implementation was checked again. No details on the outcomes of the validation exercise (e.g., if any specific tool was used to guide the verification exercise, what type of errors were found and how they were corrected) were provided by the company.

A second validation exercise was conducted by the York Health Economics Consortium (YHEC), which provided a critique of the model and assessed whether the modelling approach was robust. The company indicated that YHEC reported that the chosen modelling approach seemed reasonable and appropriate, given the available clinical effectiveness data for teplizumab, and the nature of Stage 3 T1D long-term outcomes. An external validation report provided feedback in relation to a (small) number of limitations associated with the model, in particular regarding some input parameters, which the company indicated were addressed where feasible/possible. YHEC also completed a validation checklist that did not identify major calculation errors. It was also concluded that the outcomes of both DSA and PSA were consistent with the deterministic base-case outcomes. Again, no details on the outcomes of the validation exercise (e.g., the external validation report mentioned by the company) were provided by the company.

Despite the two external validation rounds, the EAG found some errors in the model (e.g., error in half-cycle correction calculation and PSA ignoring correlation for some input parameters) that were assessed during the clarification phase. These errors had a minor impact on the model results.

5.3.3.2 Extreme value testing

The company mentioned that key input parameters were varied to extreme values (e.g., highest and lowest possible values) in order to identify inconsistencies in the model. Testing results were reviewed, corrections identified, until the final model results were consistent with expected the model behaviour.

5.3.3.3 Testing of traces

Markov traces can be found in the “Model Engine” sheets of the model. A plot of the traces to facilitate visual inspection is included in the model (“Results” sheet).

5.3.3.4 Unit testing

This type of validation was not explicitly mentioned in the CS. For example, it is unknown whether the Visual Basic for Applications (VBA) code was also included in the verification exercises.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

Although it is not explicitly mentioned in the CS, the EAG assumed that model results were presented to experts during the Advisory Board who provided some sort of validation.

5.3.4.2 Cross validation testing (model outcomes): comparisons with other technology appraisals and other models (not necessarily technology appraisals)

In Section B.3.14 of the CS, the company conducted three validation exercises comparing the model results with other published studies. Details are provided below.

5.3.4.2.1 Comparison with NICE TA943

NICE TA943 appraised hybrid closed loop (HCL) systems for managing blood glucose levels in T1D.⁴⁶ To make a comparison with the company's results, the age in the teplizumab model was changed to 43.4 years to align with the age considered in the EAG model from TA943. The comparison of results presented by the company can be seen in Table 5.7. The company considered that the ECM arm of their model should be reflective of current standard of care in the UK and, therefore, results should be comparable between models. The company interpreted that QALYs and life years (LYs) were “*relatively consistent*” across the two models but “*slightly*” higher in the ECM arm of their model.⁹ The company considered that the inclusion of individuals with Stage 2 T1D in their model (as opposed to Stage 3 T1D in TA943) may (partially) explain this difference, since individuals in Stage 2 would be expected to accrue more QALYs and LYs than individuals with Stage 3 T1D. The company's results may also imply that lower mortality rates were applied in their model, reflecting (according to the company) more recent data on T1D.

The EAG considered the company's conclusion that QALYs and LYs were relatively consistent across the two models arbitrary since the differences reported, especially in LYs, cannot be deemed as minor. The EAG understands that the company's model includes patients with Stage 2 T1D, whereas the NICE TA943 includes only Stage 3 T1D. Therefore, the EAG considered that “to allow for direct comparison” not only the baseline age should be changed, but also the Stage 2 health state should be “switched off”, with all patients starting in Stage 3 T1D. The rationale for this scenario was that, once patients are in Stage 3, results should be comparable to those in NICE TA943. The EAG asked company to conduct this scenario in clarification Question B22, but this was not addressed by the company in their response.¹⁵ Instead, the company re-emphasised that their model remains the best approach to address the current decision problem and that, overall, the differences between the models may be explained by differences in the starting patient populations (Stage 2 versus Stage 3 T1D) and different approaches to modelling mortality. The EAG also requested a comparison of the cost results, but these were also not provided. Due to time constraints, the EAG was unable to run the scenario where the Stage 2 T1D health state was “switched off”, and therefore cannot make any judgements on the validity of the results compared to TA943.

Table 5.7: Comparison vs. NICE TA943 EAG Stage 3 T1D model

Model	Population	Starting age (years)	Time horizon	QALYs	Undiscounted LYs
Company	At risk of progressing to Stage 3 T1D	43.4	Lifetime	ECM: [REDACTED] Teplizumab: [REDACTED]	ECM: [REDACTED] Teplizumab: [REDACTED]
NICE TA943 (EAG base-case) ⁴⁶	Stage 3 T1D	43.4	Lifetime	CSII: 14.232 PLGS: 14.291 HCL: 14.392	CSII: 32.499 PLGS: 32.685 HCL: 32.957
Based on Table 53 in CS ⁹					

Model	Population	Starting age (years)	Time horizon	QALYs	Undiscounted LYs
CS = company submission; CSII = continuous subcutaneous insulin infusion; EAG = External Assessment Group; ECM = established clinical management; HCL = hybrid closed loop; LYs = life years; NICE = National Institute for Health and Care Excellence; PLGS = predictive low-glucose suspend; QALY = quality-adjusted life year; T1D= type 1 diabetes; TA = technology appraisal					

5.3.4.2.2 Comparison with Roze et al. (2021) model

Roze et al. 2021 studied the cost effectiveness of continuous subcutaneous insulin infusion (CSII) and the MiniMed 670G system in people with diagnosed T1D.⁴⁵ To make a comparison with the company's results, the age in the teplizumab model was changed to 37.8 years to align with the age considered in Roze et al. 2021. The comparison of results presented by the company can be seen in Table 5.8. The company considered that the QALYs in the ECM arm were “considerably” higher in their model.⁹ As with the comparison with the model in TA943, the company explained that this may be due to the lower mortality in their model. Likewise, the EAG considered the company's conclusion arbitrary and asked the company to conduct a scenario where the Stage 2 health state would be “switched off”. As previously mentioned, the EAG asked company to conduct this scenario in clarification Question B22, but this was not addressed by the company in their response.¹⁵

Table 5.8: Comparison vs. Roze et al. 2021⁴⁵ Stage 3 T1D model

Model	Population	Starting age (years)	Time horizon	QALYs	Undiscounted LYs
Company	At risk of progressing to Stage 3 T1D	37.8	Lifetime	ECM: [REDACTED] Teplizumab: [REDACTED]	ECM: [REDACTED] Teplizumab: [REDACTED]
Roze et al. 2021 ⁴⁵	Stage 3 T1D	37.8	Lifetime	CSII: 12.36 MiniMed 670G system*: 14.09	Not reported
Based on Table 54 in CS ⁹ * The MiniMed system consists of sensor-augmented pump therapy + low glucose suspend CS = company submission; CSII = continuous subcutaneous insulin infusion; ECM = established clinical management; LY = life year; QALY = quality-adjusted life year; T1D= type 1 diabetes					

5.3.4.2.3 Comparison with Mital et al. (2020) model

The company compared their model results with the results of the Mital et al. 2020 study, which was also based on data from the TN-10 trial of teplizumab.⁸³ The comparison of results presented by the company can be seen in Table 5.9. The company considered that the QALYs for both ECM and teplizumab arms were larger in their model, but the differences do not appear “substantial”.⁹ Again, the EAG considered the company's conclusion arbitrary, since while this might be true for the incremental QALYs, the total QALYs estimated for each treatment arm do not seem directly equivalent. As with the other two comparisons previously discussed, the EAG asked the company to clarify their view in clarification Question B22 (including a comparison of cost results as well), but this was not addressed by the company in their response.¹⁵

Table 5.9: Comparison vs. Mital et al. 2020⁸³ Stage 3 T1D model

Model	Population	Starting age (years)	Time horizon	QALYs	Undiscounted LYs
Company	At risk of progressing to Stage 3 T1D	13.58	Lifetime	ECM: [REDACTED] Teplizumab: [REDACTED]	ECM: [REDACTED] Teplizumab: [REDACTED]
Mital et al. 2020 ⁸³	At risk of progressing to Stage 3 T1D	8 to 49	Lifetime	ECM: 18.72 Teplizumab: 19.26	Not reported
Based on Table 55 in CS ⁹ CS = company submission; ECM = established clinical management; LY = life year; QALY = quality-adjusted life year; T1D= type 1 diabetes					

5.3.4.3 Validation against outcomes using alternative input data

This type of validation was not explicitly reported by the company unless it was considered part of the scenario analyses.

5.3.4.4 Validation against empirical data**5.3.4.4.1 Comparison with empirical data used to develop the economic model (dependent validation)**

In clarification Question B21,¹⁵ the EAG asked the company to provide a comparison of the model results versus Table 3 and Table 13 in the CS.⁹ The estimated risk of progression to Stage 3 T1D among individuals on ECM can be seen in Table 5.10. The median time to progression, as estimated from the company's base-case extrapolations (log-normal for teplizumab and exponential for ECM) compared to those reported in the primary and follow-up studies, can be seen in Table 5.11. the company however did not discuss the validity of the model estimates.

Table 5.10: Risk of progression to Stage 3 T1D onset in individuals diagnosed with Stage 2 T1D

Study	Population	Risk of progression to onset of Stage 3 T1D at		
		2 years	4 years	5 years
TrialNet Natural History Study ³⁴	First- and second-degree relatives* aged 1 to 45 years	~60%	74%	NR
DPT-1 ⁸⁴	First- and second-degree relatives* aged 3 to 45 years ⁸⁵	NR	65%	~75%
Fr1da ⁸⁶	Children aged 1.75 to 10 years from the general population, including 3.9% with a first-degree relative	58.6%	NR	NR
Company's Model	As per TN-10	[REDACTED]	[REDACTED]	[REDACTED]

Study	Population	Risk of progression to onset of Stage 3 T1D at		
		2 years	4 years	5 years
Based on Table 14 in clarification letter response. ¹⁵ * Of people with Stage 3 T1D DPT-1 = Diabetes Prevention Trial–Type 1; NR = not reported; T1D = type 1 diabetes				

Table 5.11: Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D (primary analysis)

	Teplizumab (n=44)	Placebo (n=32)
Primary analysis		
Median	49.5 months (32.2, NE)	24.9 months (9.5, 48.6)
Median difference	24.6 months (NE, NE)	
HR (95% CI); p value	0.41 (0.22, 0.78); p=0.0066	
Extended follow-up analysis		
Median	59.6 months ██████████	27.1 months ██████████
Median difference	32.5 months ██████████	
HR (95% CI); p value	0.457 (NR); p=0.01	
Company's model (base-case)		
Median	██████████	██████████
Median difference	██████████	
Based on Table 15 in clarification letter response. ¹⁵ CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; T1D = type 1 diabetes		

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

This type of validation was not reported by the company.

6. External Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 *Explanation of the EAG adjustments*

Table 6.1 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al. 2020:⁸⁷

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the sources of uncertainty can help determine whether additional clarifications, evidence and/or analyses might help to resolve the key issue. Table 6.1 also includes suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG exploratory analyses, and if additional evidence or analyses might help to resolve the identified key issues.

The changes made by the EAG (to the model received with the response to the clarification letter) can be subdivided into the following categories (according to Kaltenthaler et al. 2016):⁸⁸

- Fixing errors (FE) (correcting the model where model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were also explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

6.1.2 *EAG base-case*

The adjustments made by the EAG, to define the EAG base-case (using the base-case after clarification as starting point) are listed below.

6.1.2.1 *Fixing errors*

No errors were found by the EAG in the model provided in response to the clarification letter.

6.1.2.2 *Fixing violations*

1. The EAG prefers using a multiplicative approach to the disutilities associated with Stage 3 T1D, to be in line with the NICE reference case. However, as two of the three company defined disutilities for this stage will be set to zero in the EAG base-case, the additive and the multiplicative approach yield the same results.

6.1.2.3 *Matters of judgement*

2. As explained in Section 4.2.6.1, regarding the extrapolation of time to progression from Stage 2 to Stage 3, following the recommendations in NICE DSU Report 14,³³ the EAG prefers using the

same type of parametric distributions for both treatment arms. Since the hazard functions do not seem to be constant over time (Figure 4.8) a parametric distribution with non-constant hazard function is preferred. Given the uncertainty regarding the long-term extrapolations (observed for example in Figure 4.2, where the number of patients at risk at five years is small), the EAG prefers a more conservative approach for teplizumab (the log-normal extrapolation chosen by the company is on the upper side of the long-term extrapolations). Since the gamma distribution also showed a good fit to teplizumab data in Table 4.4, the EAG prefers using this distribution for its base-case.

3. The EAG prefers using life tables from before the COVID-19 pandemic (2017-2018) to estimate mortality in the general population, as explained in Section 4.2.6.3.
4. As discussed in Section 4.2.8.2, to ensure that no double counting of age-related decline in HRQoL occurs, and given the almost negligible excess utility decline per year, the EAG prefers to forgo the extra utility decline as a function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point.
5. The EAG prefers removing the one-off disutility for progressing to Stage 3 T1D, as described in Section 4.2.8.2.
6. As explained in Section 4.2.8.4, to avoid overestimation of Stage 3 T1D costs, the EAG prefers applying the average monthly cost from Hex et al. 2024 as a fixed health state cost due to its simplicity and the impossibility to validate the values obtained with calibrated regression models.¹

6.1.3 EAG exploratory scenario analyses

The EAG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses. While the main focus was on the key issues described in Table 6.1, other uncertainties were also explored by the EAG. A description of scenario analyses conducted by the EAG is provided below.

The EAG explored the impact of using alternative parametric models to fit time to onset of Stage 3 T1D data for both teplizumab and ECM. Alternative extrapolation options included the exponential, Weibull and log-normal distributions. Other distributions were not considered by the EAG due to a poorer fit to the data and/or a lack of face validity. The EAG also explored scenario analyses using joint models even though the PH assumption does not seem to hold. The results of these scenarios should therefore be interpreted with caution.

The EAG run a scenario where an excess disutility dependent on time since Stage 3 T1D onset was included, as per company's base-case, to explore the impact of a potential double counting of age-related decline in HRQoL. The impact on the one-off disutility for progressing to Stage 3 T1D, which was excluded by the EAG, was also explored. Finally, to address the uncertainty around the implementation of the carer disutility two scenarios were considered where the number of caregivers was set to 1 and the caregiving disutility was halved to correct for the higher average age of the model population.

The EAG exploratory analyses regarding resource used and costs focused solely on Stage 3 T1D costs, given the large impact of these costs on the model results. The EAG explored the scenario where costs were estimated using calibrated regression models, as explained in Section 4.2.8.4, and another scenario where initial costs were based on the prevalent population and then increased over time, as in the company's base-case.

The EAG also run a scenario analysis to explore the uncertainty around the definition of ECM. The comparator arm in TN-10 included at least close monitoring for Stage 3 T1D development in addition

to placebo, where “*close monitoring in TN-10 consisted of metabolic monitoring with a scheduled oral glucose tolerance test (OGTT) every 6 months and an additional random glucose measurement scheduled every 3 months with a reflex to OGTT should the glucose level be abnormal. Participants were educated about the symptoms associated with Stage 3 T1D at each visit and via routine contact in between visits*”. The company concluded that ECM as included in the economic model (routine monitoring of blood glucose, psychosocial support and education on the management of T1D) can be considered comparable to close monitoring in TN-10. However, the EAG is uncertain about this since Herold et al. 2019 does not seem to report anything on psychosocial support or education on the management of T1D.²³ Hence, if psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of ECM included in the model would be underestimated if these ECM components are effective. To explore the potential impact of underestimating the treatment effectiveness of ECM, the EAG selected a Gompertz distribution to extrapolate time to progression to Stage 3 T1D for ECM since this distribution predicts a higher probability of staying in Stage 2 T1D compared to the gamma distribution, which was used in the EAG base-case. Other options, such as the log-normal distribution, estimate a long-term probability of staying in Stage 2 T1D for ECM larger than for teplizumab and therefore are deemed implausible by the EAG.

Finally, The EAG considers that exploring the cost effectiveness of teplizumab in an asymptomatic population of individuals with Stage 2 T1D could be of interest for the Appraisal Committee. For this population, teplizumab plus screening/testing should be the intervention and an estimate of the number of individuals needed to be tested to detect one case, and the screening/testing costs need to be included in the economic analyses. Unfortunately, these estimates were not provided by the company. The comparator in the asymptomatic population should be placebo/no treatment plus no screening/no testing. Placebo/no treatment should be different from ECM since these patients are asymptomatic, thus not detected and hence not treated. Since the comparator arm in TN-10 included at least close monitoring for Stage 3 T1D development in addition to placebo (clarification Question B3),¹⁵ it might be expected that the comparator in the model (ECM) is more effective than no treatment. Thus, a scenario analysis exploring the cost effectiveness of teplizumab plus screening versus no treatment and no screening in the asymptomatic population cannot be conducted with the current evidence. However, a scenario where ECM costs are not included in the comparator arm (i.e., no costs in Stage 2 T1D for undetected patients) and where no treatment is modelled by the assuming the parametric curve with lowest efficacy (which is the exponential), could be seen as an estimation of an approximate lower end ICER for the asymptomatic population. This could be seen as a lower end estimate because the costs of testing are not included and by including them the ICER would only increase.

6.1.4 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the CE

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
The EAG disagrees with the company's approach of modelling progression to Stage 3 T1D	4.2.6	Methods Transparency	Using the same type of parametric distributions for both treatment arms. Assuming parametric distributions with non-constant hazard function is preferred. A more conservative approach for long-term extrapolations. Curve selection: gamma distribution.	+	Partial	Additional data to validate long-term projections.
The EAG disagrees with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D	4.2.8	Methods Transparency	Forgoing extra utility decline depending on years since onset of Stage 3 T1D and retaining the decline in utility per year resulting from the general population.	+	Partial	Re-analyse available or new data to ensure that no double counting of age-related decline in HRQoL occurs.
The EAG disagrees with the company's approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs	4.2.8	Methods Bias & Indirectness	Applying the average monthly cost from Hex et al. 2024 as a fixed health state cost. ¹ .	+	Partial	Re-analyse available or new data to ensure that no overestimation of Stage 3 T1D costs occurs.
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; ^b Explored CE = cost effectiveness; EAG = External Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; T1D = type 1 diabetes						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base-case scenario

Table 6.2 shows the results of the EAG's base-case (discounted and assuming teplizumab PAS price). These indicated that teplizumab was more costly and more effective than ECM, accruing [REDACTED] incremental QALYs at [REDACTED] incremental costs. Compared to the company's base-case (Table 5.4), the incremental costs increased by [REDACTED], and the incremental QALYs decreased by [REDACTED]. Disaggregated discounted QALYs and costs are shown in Tables 6.3 and 6.4, respectively. The EAG would like to emphasise that these results deviate greatly from the company's base-case due to the different assumptions in modelling time to progression to Stage 3 T1D, utilities and costs associated to Stage 3 T1D.

Table 6.2: EAG base-case deterministic CE results (teplizumab PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Teplizumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	165,387
ECM	[REDACTED]	[REDACTED]	[REDACTED]				

Based on economic model after clarification.
 CE = cost effectiveness; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 6.3: Disaggregated QALYs results (EAG base-case, discounted)

Health state	QALY teplizumab	QALY ECM	Increment	Absolute increment	(%) Absolute increment
Stage 2 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stage 3 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Caregiver disutility	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AE disutility	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Based on economic model after clarification.
 AE = adverse event; EAG = External Assessment Group; ECM = established clinical management; NA = not applicable; QALY = quality-adjusted life year; T1D = type 1 diabetes

Table 6.4: Disaggregated cost results (EAG base-case, teplizumab PAS price, discounted)

Cost item	Cost teplizumab (£)	Cost ECM (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Drug administration	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AE management	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Treatment-related resource use	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stage 2 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stage 3 T1D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Cost item	Cost teplizumab (£)	Cost ECM (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Based on economic model after clarification. AE = adverse event; EAG = External Assessment Group; ECM = established clinical management; NA = not applicable; PAS = patient access scheme; T1D = type 1 diabetes					

6.2.2 Results of the EAG PSA

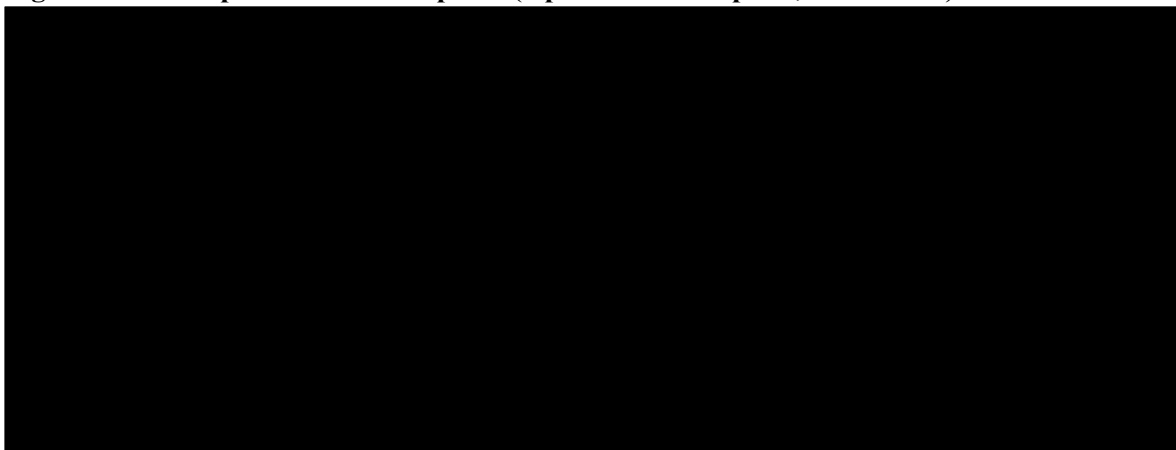
Table 6.5 shows the results of the probabilistic EAG's base-case (discounted, assuming teplizumab PAS price), which are comparable with the EAG base-case results. The CE-plane presented in Figure 6.1 shows that

that [REDACTED]. This indicates that teplizumab is [REDACTED] than ECM. Based on the derived CEAC (Figure 6.2), the probability that teplizumab is cost effective at £20,000 and £30,000 per QALY gained is [REDACTED].

Table 6.5: EAG PSA results (teplizumab PAS price, discounted)

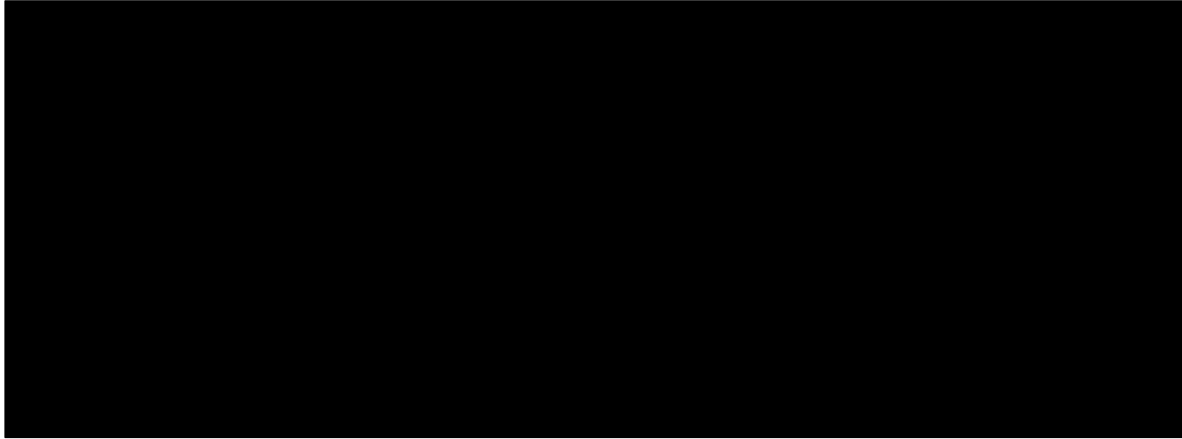
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Teplizumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	171,788
ECM	[REDACTED]	[REDACTED]			
Based on economic model after clarification. EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year					

Figure 6.1: EAG probabilistic CE-plane (teplizumab PAS price, discounted)



Based on electronic model after clarification.

CE = cost effectiveness; EAG = External Assessment Group; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

Figure 6.2: EAG base-case CEAC (teplizumab PAS price, discounted)

Based on electronic model after clarification.

CEAC = cost effectiveness acceptability curve; EAG = External Assessment Group; PAS = patient access scheme; QALY = quality-adjusted life year

6.2.3 Results of the EAG additional exploratory scenario analyses

The results of the scenario analyses are provided in Table 6.6. These results are all conditional on the EAG base-case settings. The scenario analyses conducted by the EAG indicated that the results were (to some extent) sensitive to all changes explored by the EAG, with the exception of including/excluding Stage 3 T1D one-off disutility at onset (which is expected given that it only affects one model cycle). However, it should be noted that the range of ICERs obtained (including the EAG base-case ICER) were all well above the usual CE thresholds used by NICE.

Table 6.6: Results of exploratory scenario analyses by the EAG (teplizumab PAS price, discounted)

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base-case			██████	██████	165,387
Time to Stage 3 T1D onset – individual fitting	Gamma (both arms)	Exponential (both arms)	██████	██████	129,385
		Weibull (both arms)	██████	██████	168,466
		Log-normal (both arms)	██████	██████	151,500
		Log-normal (teplizumab) Exponential (ECM)*	██████	██████	127,392
Time to Stage 3 T1D onset – joint fitting*	Gamma (both arms – individual fitting)	Gamma	██████	██████	136,068
		Exponential	██████	██████	129,385
		Weibull	██████	██████	136,405
		Log-normal	██████	██████	83,170
HRQoL disutility dependent on time since Stage 3 T1D onset	No excess disutility	Excess disutility (company base-case)	██████	██████	105,358
Stage 3 T1D QoL one-off disutility at onset	No disutility	Disutility (company base-case)	██████	██████	164,814
Caregiver disutility	Number of caregivers = 1.76	Number of caregivers = 1	██████	██████	189,851
	Disutility = -0.04	Disutility = -0.02	██████	██████	194,391
Stage 3 T1D costs	Constant state cost	Calibrated regression	██████	██████	173,024
		Initial costs from prevalent population increased over time (company base-case)	██████	██████	97,118
Hypothetical effect of missing ECM components (ECM curve with highest efficacy)*	Time to Stage 3 T1D onset – Gamma individual fitting in both arms	Gamma (teplizumab) Gompertz (ECM)	██████	██████	180,524

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Asymptomatic population (lower end)*	Not considered	Exclude costs of T21D in ECM Exponential for time to Stage 3 T1D onset	██████	██████	172,780
Based on economic model after clarification. * The EAG considers these scenarios may not conform to best practices methodologically and, therefore, they should be interpreted with caution. EAG = External Assessment Group; ECM = established clinical management; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; Inc. = incremental; PAS = Patient Access Scheme; QALY = quality-adjusted life year; QoL = quality of life; T1D = type 1 diabetes					

6.3 EAG's preferred assumptions

The step-by-step changes made by the EAG to derive its base-case, using the CS base-case and the model submitted after clarification as starting point, can be seen in Table 6.7. The change with the largest impact on the results was applying the average monthly cost from Hex et al. 2024 as a fixed health state cost.¹ Assuming a gamma distribution (individual fitting) for both treatment arms to model time to Stage 3 T1D onset, and forgoing extra utility decline depending on years since onset of Stage 3 T1D also had a major impact on the model results. The other two changes included in the EAG base-case (using 2017-2018 life tables and removing the one-off disutility for progressing to Stage 3 T1D) had an almost negligible impact on the results.

Table 6.7: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Teplizumab	██████	██████	██████	██████	27,534
ECM	██████	██████			
Time to Stage 3 T1D onset – individual fitting Gamma (both arms)					
Teplizumab	██████	██████	██████	██████	61,078
ECM	██████	██████			
Life tables 2017-2018					
Teplizumab	██████	██████	██████	██████	27,368
ECM	██████	██████			
Extra utility decline depending on years since onset of Stage 3 T1D forgone					
Teplizumab	██████	██████	██████	██████	46,208
ECM	██████	██████			
One-off disutility for progressing to Stage 3 T1D removed					
Teplizumab	██████	██████	██████	██████	27,601
ECM	██████	██████			
Average monthly cost from Hex et al. 2024 for Stage 3 T1D					
Teplizumab	██████	██████	██████	██████	75,114
ECM	██████	██████			
EAG's base-case					
Teplizumab	██████	██████	██████	██████	165,387
ECM	██████	██████			
Based on the model submitted following the clarification phase. CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

6.4 Conclusions of the CE section

The CS, Appendices and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant evidence to understand the economic burden of T1D in children (≥ 8 years old) and adults.^{9, 15, 19, 21} Searches were conducted in May 2023 and updated

in June 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, conference proceedings and HTA resources were searched. Whilst the EAG was concerned about the low number of relevant papers retrieved by the Costs/Resource use facet and the decision to include a frequency operator in the search strategy due to its potential to miss relevant papers, overall, the EAG found the searches were sufficient. Since no economic models to address the current decision problem were identified by the company, a de novo model was built, which in general complied with the NICE reference case.

The CE key issues highlighted by the EAG throughout this report (and summarised in Table 6.1) were the following:

- 1) The EAG disagrees with the company's approach of modelling progression to Stage 3 T1D.
- 2) The EAG disagrees with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D.
- 3) The EAG disagrees with the company's approach of using prevalent population costs to estimate initial Stage 3 T1D costs which are then increased over time.

The first concern of the EAG in this submission regarding the CE evidence was related to the definition of the population included in the economic analyses, i.e., whether the intervention should include testing/screening to identify the specified asymptomatic population or not. And, related to this, whether the intervention should be teplizumab plus screening/testing in an asymptomatic population, in which case the comparator would be placebo/no treatment plus no screening/testing; or if the intervention does not include screening/testing, the intervention should be teplizumab and the comparator ECM. Related to this, there is also a concern whether the definition of ECM in the CE analyses (defined as routine monitoring of blood glucose, psychosocial support and education on the management of T1D) can be considered comparable to close monitoring in TN-10. The EAG is uncertain about this since Herold et al. 2019 does not seem to report anything on psychosocial support or education on the management of T1D.²³ If psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of teplizumab included in the model would be overestimated if these ECM components are effective. These concerns were discussed in detail in the clinical effectiveness sections of this report, but they are also relevant for the CE.

As mentioned above, one of the EAG main concerns (identified as a key issue) is related to the implementation of time to progression to Stage 3 T1D in the economic model. The main points of concern are summarised below:

- Using different types of parametric distributions across treatment arms is uncommon and usually not recommended by NICE DSU TSD 14.³³
- The exponential distribution hazard function is constant over time which does not match with observed hazard functions.
- Face validity by clinical experts seemed to be focused on assessing the validity of the exponential distribution for the placebo arm only. However, no range of possible long-term values was provided. These were relatively similar for the gamma or Weibull distributions, which also show a good fit to the data. Furthermore, assuming an exponential distribution to extrapolate the placebo arm is the most favourable choice for teplizumab.
- The log-normal extrapolation is one of the most favourable for the teplizumab arm. Given the uncertainty regarding the long-term extrapolations, a more conservative approach would be preferred.

For the reasons summarised above, the EAG selected a gamma distribution for both arms (which also showed a good fit to the data) in its revised base-case, which had a major impact on the model results.

It should be noted though that the key issue described above refers to the selection of extrapolation method for time to progression to Stage 3 T1D data only, but the EAG also identified a potential issue with the data source, which was discussed in detail in the clinical effectiveness sections of this report, but that is also relevant for the CE. In Section B.2.6.1 of the CS, the company reported results of the TN-10 trial primary analysis.⁹ These were based on the results in Herold et al. 2019 and the CSR.^{12, 23} For the model, however, the company used data from Sims et al. 2021.²⁴ The EAG noticed that these KM curves were different in these two studies. When asked about this discrepancy in clarification Question B4,¹⁵ the company explained that both were based on individual patient data from TN-10, but derived from different data cuts and that the data chosen to inform the economic model used a longer follow-up. The EAG considered it unclear why a difference in event rates over the first six months between the data cuts was observed, when the number of events and censored observations seemed to be the same in both figures for the first six months. Using data from Sims et al. 2021 would favour teplizumab given the faster progression to Stage 3 T1D for the placebo group. As a consequence, it is also unclear whether the parametric fitting and extrapolation described in the sections below was performed with the appropriate data.

Regarding the risk of developing DKA and mortality, the EAG considers that the company have not sufficiently justified the selection of studies used to inform the related input parameters. However, the impact of these parameters on the model results is minor and so is the EAG concern around this potential issue

In terms of HRQoL, the EAG disagreed with the approach taken by the company to model health state disutilities for Stage 3 T1D. This also had a major impact on the model results and, therefore, was identified as a key issue by the EAG. To calculate QALYs in Stage 3 T1D, the company applied a disutility dependent on time since the onset of Stage 3 T1D, based on observed relationship in the study by Sparring et al. 2013.⁵⁹ This disutility, which becomes more negative as time since onset increases, is subtracted from the age-dependent utility of the general population, which decreases with age. However, when we consider the regression equation estimated by Sparring et al. 2013 (Table 4.14), we observe that only time since onset of Stage 3 T1D was an explanatory variable, but not age. Thus, the EAG considers that the impact of age may have already been incorporated in the coefficients for 8, 15 and 24 years since onset Stage 3 T1D. Based on this, the EAG adapted the company model (see Section 6) to ensure that no double counting of age-related decline in HRQoL occurs, which increased the ICER greatly. Other smaller concerns related to the disutility included in the model in the cycle that a patient progresses to Stage 3 T1D, the assumption that the utility in Stage 2 T1D is the same as for the general population and that the disutility for IV infusion may be slightly low. For pragmatic reasons, only the first was addressed in the EAG base-case, since the other two would have a negligible effect on the model results. The impact of this change was minor in any case. Finally, issues regarding the carer disutility that was applied in the model that were addressed by the EAG through explorative analyses. In the clarification letter (Question B9) the EAG asked the company about the carer disutility derived from López-Bastida et al. 2019, which included children aged 2-17 and their carers.¹⁵ The study reported a carer EQ-5D-5L score of 0.92 which was subtracted from the general population mean utility of 0.96. Given that the model population is 13.58 years at the start, the EAG assumes that for the model population the carer utility would likely be higher than 0.92, as the caregiving burden is higher in younger patients. The company indicated in their response that no data were available to adjust for the age in the model population. Additionally, the EAG is not sure if it is reasonable to assume that the caregiver disutility should be applied to both persons in a couple family as it is likely that the total care giving burden is similar to that in a lone family, but now divided between the couple. Thus, the EAG explored in Section 6 two scenarios where 1) the number of caregivers was limited to one, and 2) the

caregiving disutility was halved to correct for the higher average age of the model population. The results of these scenarios indicated that the model is also sensitive to changes in these parameters.

The EAG also disagreed with the company in the approach taken to model Stage 3 T1D costs, which also had a major impact on the model results and, therefore, was identified as its final key issue by the EAG. The company used the average monthly cost per person from Hex et al. 2024 as the initial cost for individuals transitioning to Stage 3 T1D.¹ However, the costs in Hex et al. 2024 are based on the prevalent and not the incident population, therefore, including patients who may have developed Stage 3 T1D long ago instead of new cases only. The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data,² is incorrect and substantially overestimates healthcare costs for Stage 3 T1D. This concern was raised by the EAG in the clarification letter (Question B15),¹⁵ but the company did not provide justification for their approach. The EAG contends that the *average* monthly costs of Stage 3 T1D should be equal to the estimate from Hex et al. 2024. The EAG considered two main approaches to achieve this but selected a pragmatic approach of applying the average monthly cost from Hex et al. 2024 as a fixed health state cost due to its simplicity and the impossibility to validate the values obtained with a more elaborated regression model. In addition, the company used data from Ou et al. 2016 on total healthcare costs rather than diabetes related healthcare costs.² Using estimates for total healthcare costs would include future unrelated healthcare costs which should not be included according to the NICE reference case. This would increase health state costs for Stage 3 T1D and unfairly favour teplizumab. In their response to the clarification letter the company suggested that using the diabetes-related costs from Ou et al. 2016 would underestimate the costs of Stage 3 T1D, which include acute metabolic complications and other complications.¹⁵ However, it is unclear from the Ou et al. 2016 study exactly which costs were included in the estimate of diabetes-related costs since only the following information provided: *“The total health care costs and the costs incurred for diabetes, including treatment, examination, and procedures associated with diabetes, were estimated separately”*.²

The company’s base-case deterministic CE (discounted) results for teplizumab compared to ECM indicated that that teplizumab was more costly but also more effective than ECM. Incremental QALYs for teplizumab were [REDACTED] and incremental costs were [REDACTED], resulting in an ICER of £27,534 per QALY gained. These results were obtained after the company corrected the implementation of the half-cycle correction in the original model. The average PSA results were in line with the deterministic ones, but resulted in a slightly higher ICER. The company also plotted the PSA outcomes on a CE-plane.

[REDACTED]. From the PSA results, a CEAC was also calculated and indicated that at the common threshold of £30,000 per QALY gained, the estimated probability that teplizumab is a cost effective alternative to ECM was [REDACTED]. The company’s DSAs and scenario analyses showed that most assumptions on input parameters had a minor impact on the model results, except for the costs and disutilities applied to the Stage 3 T1D health state, which in turn were identified by the EAG as key issues. However, the EAG considered that the number of scenarios explored by the company was insufficient to assess the impact of remaining uncertainties on the model results. For example, the company did not explore scenarios choosing different extrapolation options for time to progression to Stage 3 T1D. These scenarios are crucial in order to properly assess the uncertainties in the model and were explored by the EAG in Section 6 of this report.

The EAG defined a new preferred base-case by:

1. Using a multiplicative approach to the disutilities associated with Stage 3 T1D, to be in line with the NICE reference case. However, as two of the three company defined disutilities for this stage were set to zero in the EAG base-case, the additive and the multiplicative approach yielded the same results.
2. Assuming a gamma distribution for both arms to model time to progression to Stage 3 T1D.
3. Using life tables from before the COVID-19 pandemic (2017-2018) to estimate mortality in the general population.
4. Forgoing the extra utility decline as function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point, as the rate of utility decline for years since onset Stage 3 T1D was almost the same as the rate of decline in the general population.
5. Removing the one-off disutility for progressing to Stage 3 T1D.
6. Applying the average monthly cost from Hex et al. 2024 as a fixed Stage 3 T1D health state cost.¹

The results of the EAG's base-case analysis indicated that teplizumab was more costly and more effective than ECM, accruing [REDACTED] incremental QALYs at [REDACTED] incremental costs. Compared to the company's base-case, the incremental costs increased by [REDACTED], and the incremental QALYs decreased by [REDACTED]. The EAG results deviated greatly from the company's base-case due to the different assumptions in modelling time to progression to Stage 3 T1D, utilities and costs associated to Stage 3 T1D. The EAG's average PSA results were comparable with the EAG base-case results. The CE-plane presented showed that

[REDACTED], indicating that teplizumab was [REDACTED] than ECM. Based on the derived CEAC, the probability that teplizumab is cost effective at £20,000 and £30,000 per QALY gained was [REDACTED]. The scenario analyses conducted by the EAG indicated that the results were (to some extent) sensitive to all changes explored by the EAG, with the exception of including/excluding Stage 3 T1D one-off disutility at onset (which is expected given that it only affects one model cycle). However, the range of ICERs obtained (including the EAG base-case ICER) were all well above the usual CE thresholds used by NICE.

7. References

- [1] Hex N, MacDonald R, Pocock J, Uzdzińska B, Taylor M, Atkin M, et al. Estimation of the direct health and indirect societal costs of diabetes in the UK using a cost of illness model. *Diabet Med* 2024; 41(9):e15326
- [2] Ou HT, Yang CY, Wang JD, Hwang JS, Wu JS. Life expectancy and lifetime health care expenditures for type 1 diabetes: a nationwide longitudinal cohort of incident cases followed for 14 years. *Value Health* 2016; 19(8):976-984
- [3] Besser REJ, Griffin KJ. Transitioning to stage 3 type 1 diabetes: when to start insulin. *Lancet Diabetes Endocrinol* 2024; 12(10):692-694
- [4] Shubrook JH, Brannan GD, Wapner A, Klein G, Schwartz FL. Time needed for diabetes self-care: Nationwide survey of certified diabetes educators. *Diabetes Spectr* 2018; 31(3):267-271
- [5] French R, Kneale D, Warner JT, Robinson H, Rafferty J, Sayers A, et al. Educational attainment and childhood-onset type 1 diabetes. *Diabetes Care* 2022; 45(12):2852-2861
- [6] Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012; 29(7):855-62
- [7] Hakkarainen P, Moilanen L, Hänninen V, Heikkinen J, Räsänen K. Work-related diabetes distress among Finnish workers with type 1 diabetes: a national cross-sectional survey. *J Occup Med Toxicol* 2016; 11(1)
- [8] Azimi T, Johnson J, Campbell SM, Montesanti S. Caregiver burden among parents of children with type 1 diabetes: a qualitative scoping review. *Heliyon* 2024; 10(6):e27539
- [9] Sanofi. *Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*, 2024 [accessed 27.11.24]
- [10] National Institute for H, Care E. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]. Final scope*, 2024 Available from: <https://www.nice.org.uk/guidance/gid-ta10981/documents/final-scope>
- [11] National Institute for Health and Care Excellence. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]: NHS organisation submission (ICBs and NHS England)*. London: NICE, 2024 [accessed 2.12.24]
- [12] Provention Bio I. *TN-10 clinical study report addendum: anti-CD3 MAP (Teplizumab) for prevention of diabetes in relatives at risk for type 1 diabetes mellitus. Final version 1.0 [PDF provided by the company]*, 2020
- [13] University of South Florida. TrialNet pathway to prevention of T1D. NCT00097292. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2023. Available from: <https://clinicaltrials.gov/study/NCT00097292>
- [14] National Institute for Health and Care Excellence. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]: Clarification questions*. London: NICE, 2024

- [15] National Institute for Health and Care Excellence. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]: Response to request for clarification from the EAG*, 2025 [accessed 20.1.25]
- [16] Swaby R, Randell T, Martin R, Shetty A, Millar S, Sachdev P, et al. How many children are out there? A BSPED survey of children and young people with early-stage type 1 diabetes. Presented at 51st Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes (BSPED); 8-10 Oct 2024; Glasgow, UK. *Endocrine Abstracts* 2024; 103
- [17] Sanofi. *Sanofi Pre-symptomatic Type 1 Diabetes Care Pathway July 2024 Advisory Board Meeting Report v1.0 (MAT-XU-2402985)* 2024
- [18] CDER Office of Clinical Pharmacology. *Clinical pharmacology review(s): Application number: 761183Orig1s000 [Internet]*, 2022 [accessed 28.11.24] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000ClinPharmR.pdf
- [19] Sanofi. *Teplizumab for delaying the onset of Stage 3 type 1 diabetes in people 8 years and over with Stage 2 type 1 diabetes [ID6259]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Appendices. Company evidence submission*, 2024 [accessed 27.11.24]
- [20] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline statement. *J Clin Epidemiol* 2016; 75:40-6
- [21] National Institute for Health and Care Excellence. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]: Response to request for clarification from the EAG - Appendix 1* 2025 [accessed 20.1.25]
- [22] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: <http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm>
- [23] Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019; 381(7):603-613
- [24] Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* 2021; 13(583)
- [25] Sims EK, Cuthbertson D, Jacobsen L, Ismail HM, Nathan BM, Herold KC, et al. Comparisons of metabolic measures to predict T1D vs. detect a preventive treatment effect in high-risk individuals. *J Clin Endocrinol Metab* 2024; 109(8):2116-2123
- [26] Sims EK, Geyer SM, Long SA, Herold KC. High proinsulin: C-peptide ratio identifies individuals with stage 2 type 1 diabetes at high risk for progression to clinical diagnosis and responses to teplizumab treatment. *Diabetologia* 2023; 66(12)
- [27] Ziegler AG, Kick K, Bonifacio E, Haupt F, Hippich M, Dunstheimer D, et al. Yield of a public health screening of children for Islet Autoantibodies in Bavaria, Germany. *JAMA* 2020; 323(4):339-351
- [28] Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: a disease-modifying therapy for type 1 diabetes that preserves β -cell function. *Diabetes Care* 2023; 46(10):1848-1856

[29] Sanofi. *Draft Summary of Product Characteristics (Tzield) [PDF provided by the company]*, 2024

[30] NHS Digital. *National Diabetes Audit, 2019-20 Type 1 Diabetes. England and Wales 2021* [accessed 28.11.24] Available from:
<https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FAC%2F6F045A%2FND%25202019-20%2520Type%25201%2520Diabetes%2520Report.pptx&wdOrigin=BROWSELINK>

[31] Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, et al. Teplizumab and β -cell function in newly diagnosed type 1 diabetes. *N Engl J Med* 2023; Epub 2023 Oct 31

[32] National Institute for Health and Care Excellence. *Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]: Clarification questions addendum*. London: NICE, 2025

[33] Latimer N. *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data*. Sheffield: Decision Support Unit, ScHARR, 2011 [updated March 2013]. 52p. Available from:
<http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf>

[34] Krischer JPCPCN. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. *Diabetologia* 2013; 56(9):1919-24

[35] Sanofi. *(Data on file) Clinical Opinion: Professor Colin Dayan. 16 January 2025, 2025*

[36] Burnham KP, Anderson DR, Huyvaert KP. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behav Ecol Sociobiol* 2011; 65(1):23-35

[37] Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociol Methods Res* 2004; 33(2):261-304

[38] Burnham KP, Anderson DR. *Model selection and multimodel inference: a practical information-theoretic approach. 2nd ed*. New York: Springer, 2002.

[39] Raftery AE. Bayesian model selection in social research. *Sociol Methodol* 1995; 25:111-163

[40] Kass RE, Raftery AEC. Bayes Factors. *J Am Stat Assoc* 1995; 90(430):773-795

[41] Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 2015; 38(10):1964-1974

[42] Long AE, Wilson IV, Becker DJ, Libman IM, Arena VC, Wong FS, et al. Characteristics of slow progression to diabetes in multiple islet autoantibody-positive individuals from five longitudinal cohorts: the SNAIL study. *Diabetologia* 2018; 61(6):1484-1490

[43] Hanna SJ, Powell WE, Long AE, Robinson EJS, Davies J, Megson C, et al. Slow progressors to type 1 diabetes lose islet autoantibodies over time, have few islet antigen-specific CD8(+) T cells and exhibit a distinct CD95(hi) B cell phenotype. *Diabetologia* 2020; 63(6):1174-1185

- [44] Besser REJ, Ng SM, Gregory JW, Dayan CM, Randell T, Barrett TC. General population screening for childhood type 1 diabetes: is it time for a UK strategy? *Arch Dis Child* 2022; 107(9):790-795
- [45] Roze S, Buompegniere MI, Ozdemir Z, de Portu S, Cohen O. Cost-effectiveness of a novel hybrid closed-loop system compared with continuous subcutaneous insulin infusion in people with type 1 diabetes in the UK. *J Med Econ* 2021; 24(1):883-890
- [46] National Institute for Health Care Excellence. *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. NICE Technology appraisal guidance TA943 [Internet]*. London: NICE, 2023 Available from: <https://www.nice.org.uk/guidance/ta943/resources/hybrid-closed-loop-systems-for-managing-blood-glucose-levels-in-type-1-diabetes-pdf-82615666856389>
- [47] Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE diabetes model against epidemiological and clinical studies. *Curr Med Res Opin* 2004; 20 (Suppl 1):S27-40
- [48] Office for National Statistics. *National life tables – life expectancy in the UK: 2020 to 2022 [PDF provided by the company]*: ONS, 2024 [accessed 28.11.24]
- [49] Samuelsson J, Bertilsson R, Bülow E, Carlsson S, Åkesson S, Eliasson B, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. *Diabetologia* 2024; 67(4):679-689
- [50] Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PMC. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. *PLoS One* 2014; 9(11):e113635
- [51] Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* 2018; 392(10146):477-486
- [52] Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *N Engl J Med* 2017; 376(15):1407-1418
- [53] Libman I, Haynes A, Lyons S, Pradeep P, Rwagasor E, Tung JY, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes* 2022; 23(8):1160-1174
- [54] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: Standards of care in diabetes-2023. *Diabetes Care* 2023; 46(Suppl 1):S19-40
- [55] Besser REJ, Bell KJ, Couper JJ, Ziegler AG, Wherrett DK, Knip M, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes* 2022; 23(8):1175-1187
- [56] Sanofi. *UK May 2024 Advisory Board for teplizumab in Stage 2 aT1D Final report (MAT-XU-2401585): Summary report [PDF provided by the company]*, 2024
- [57] Hernández-Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by age and sex for the UK (NICE DSU Report)*, 2022

- [58] Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence* 2013; 7:855-65
- [59] Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström KCP. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish population-based study using EQ-5D. *BMC Public Health* 2013; 13:377
- [60] Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011; 31(6):800-4
- [61] Whittemore R, Jaser S, Chao A, Jang M, Grey MCPCN. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ* 2012; 38(4):562-79
- [62] Elhabashy SA, Elhenawy YI, Hassan HA, Abdelmageed RIC. Siblings of children with type 1 diabetes mellitus: psychosocial health, coping. *J Pediatr Nurs* 2023; 73:516-524
- [63] López-Bastida J, López-Siguero JP, Oliva-Moreno J, Vázquez LA, Aranda-Reneo I, Reviriego J, et al. Health-related quality of life in type 1 diabetes mellitus pediatric patients and their caregivers in Spain: an observational cross-sectional study. *Curr Med Res Opin* 2019; 35(9):1589-1595
- [64] Office for National Statistics. *Families and households [Internet]*: ONS, 2024 [accessed 28.11.24] Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/datasets/familiesandhouseholds/familiesandhouseholds/current>
- [65] Jones K, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. *Unit Costs of Health and Social Care 2023 Manual (Table 12.1.1: The NHS Inflation Index [NHSCII])*, 2023. 98p.
- [66] Mehta S, Ryabets-Lienhard A, Patel N, Breidbart E, Libman I, Haller MJ, et al. Pediatric endocrine society statement on considerations for use of teplizumab (tzielid™) in clinical practice. *Horm Res Paediatr* 2024:1-12
- [67] Gov.Uk. Job advert: Sister/Charge Nurse - Infusion Unit | East Sussex Healthcare NHS Trust [Internet]. 2023 [accessed 28.11.24]. Available from: <https://findajob.dwp.gov.uk/details/13603257>
- [68] NHS Jobs. Highly specialised pharmacist - gastroenterology [Internet]. 2023. Available from: <https://beta.jobs.nhs.uk/candidate/jobadvert/C9279-23-5654>
- [69] National Institute for Health Care Excellence. British National Formulary (BNF): cetirizine hydrochloride Medicinal forms [Internet]. London: NICE, 2024 [accessed 1.11.24]. Available from: <https://bnf.nice.org.uk/drugs/cetirizine-hydrochloride/medicinal-forms/#oral-tablet>
- [70] National Institute for H, Care E. British National Formulary (BNF): Ibuprofen Medicinal forms. 2024; 2024
- [71] National Institute for H, Care E. British National Formulary (BNF): Ondansetron Medicinal forms. 2024; 2024
- [72] Akhtar W, Chung YCP. Saving the NHS one blood test at a time. *BMJ Qual Improv Rep* 2014; 2(2)
- [73] Exeter Clinical Laboratory International. *Glutamic acid decarboxylase (GAD) Antibodies [Internet]*. Exeter: Exeter Clinical Laboratory International, 2024 [accessed 28.11.24] Available from: <https://www.exeterlaboratory.com/test/gad-antibodies/>

[74] National Institute for Health Care Excellence. British National Formulary (BNF): Glucose medicinal forms [Internet]. London: NICE, 2024 [accessed 1.11.24]. Available from: <https://bnf.nice.org.uk/drugs/glucose/medicinal-forms/>

[75] NHS England. *National Schedule of NHS Costs 2021/22 (V3, updated 19 May 2023)* [Internet], 2023 Available from: <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>

[76] National Institute for Health Care Excellence. *Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. Final appraisal committee papers* [Internet]. London: NICE, 2023 Available from: <https://www.nice.org.uk/guidance/ta943/evidence/final-appraisal-determination-committee-papers-pdf-13254232142>

[77] National Institute for Health Care Research (NIHR). *Comparing blood tests to detect diabetes during NHS health checks. Detection, screening and diagnosis* [Internet], 2015 Available from: <https://evidence.nihr.ac.uk/alert/comparing-blood-tests-to-detect-diabetes-during-nhs-health-checks/>

[78] NHS England. *NHS Staff Annual Earnings Estimates December 2023: NHS Trusts and other core organisations in England* [Internet], 2023 [accessed 19.5.24] Available from: <https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FF3%2F0C1ABF%2FNHS%2520Staff%2520Annual%2520Earnings%2520Estimates%2520December%25202023%252C%2520NHS%2520Trusts%2520and%2520other%2520core%2520orgs%252C%2520Tables.xlsx&wdOrigin=BROWSELINK>

[79] Department of Health. *NHS reference costs 20??-20??* [Internet]. London: Department of Health, 20?? [accessed ???.??.??] Available from: ????

[80] Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics* 2016; 34(4):349-61

[81] Henriksson M, Jindal R, Sternhufvud C, Bergenheim K, Sörstadius E, Willis M. A systematic review of cost-effectiveness models in type 1 diabetes mellitus. *Pharmacoeconomics* 2016; 34(6):569-85

[82] Daly MJ, Elvidge J, Chantler T, Dawoud DC. A review of economic models submitted to NICE's technology appraisal programme, for treatments of T1DM & T2DM. *Front Pharmacol* 2022; 13:887298

[83] Mital S, Nguyen HV. Cost effectiveness of teplizumab for prevention of type 1 diabetes among different target patient groups. *Pharmacoeconomics* 2020; 38(12):1359-1372

[84] Sosenko JM, Palmer JP, Rafkin-Mervis L, Krischer JP, Cuthbertson D, Mahon J, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. *Diabetes Care* 2009; 32(9):1603-7

[85] Diabetes Prevention Trial - Type 1 Diabetes Study G. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002; 346(22):1685-91

[86] Weiss A, Zapardiel-Gonzalo J, Voss F, Jolink M, Stock J, Haupt F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. *Diabetologia* 2022; 65(12):2121-2131

[87] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessment (TRUST) Tool for assessing uncertainties in health economic decision models. *Pharmacoeconomics* 2020; 38(2):205-216

[88] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016; 20(26):1-48

Single Technology Appraisal

Teplizumab for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes [ID6259]

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 Friday 21 February 2025** 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.

Issue 1 Identification of people with Stage 2 type 1 diabetes (T1D) and definition of the population eligible for treatment with teplizumab (EAG Key Issue 1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The EAG implies that it is unclear how patients are identified in the National Health Service (NHS) due to the lack of a formal screening programme</u> Section 1.3; Pg 13; Table 1.2 Text: “However, given that people with Stage 2 T1D are asymptomatic and that, according to the submission from NHS England, there is currently ‘<i>no commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes,</i>’ it is unclear how people with Stage 2 T1D would be identified such that	The text should be more balanced to recognise that patients are currently being identified in the NHS despite the lack of a commissioned targeted or general population screening programme.	<u>To ensure correct representation of the current clinical landscape:</u> As stated in the clarification response, despite the absence of a screening programme within the NHS, patients are being identified in clinical practice.¹	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
people who could benefit from teplizumab would have equitable access to treatment.”			
This issue also applies to the following text: • Section 2.3; Pg 28: “However, as noted above, it is unclear how people with Stage 2 T1D would be identified for treatment in the NHS in England.” • Section 2; Pg 20; Table 2.1: “The EAG, therefore, considers that it is important to establish how, in practice, individuals eligible for treatment with teplizumab in the NHS in England would be identified.”			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Discussion of a population outside of the scope of this appraisal.</u> Section 1.3; Pg 13; Table 1.2 Text: “The EAG has suggested that either screening/testing should be included in the intervention and the proposed screening/testing process should be included and appropriately costed (i.e. costs for the number of people tested per individual treated) in the economic model or the population should be limited to people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected.”	The text should be revised to bring it in line with the final scope by making it clear that: • The population is not “all those who have been identified by screening” or “those who have been incidentally detected” but is those who have been identified (regardless of mechanism) • The intervention is not “teplizumab plus screening/testing” but is teplizumab alone	<u>To ensure the appraisal is aligned to the final scope.</u>	Not a factual inaccuracy. The EAG appropriately differentiates between two types of the population of those eligible for teplizumab, i.e. those incidentally detected versus those detected by screening, and for which there would be an additional cost of testing a much larger group of asymptomatic individuals.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This issue also applies to the following text: • Section 4.2.4; Pg 68: “In conclusion, an economic evaluation of teplizumab + screening versus placebo/no treatment + no screening in the asymptomatic population cannot be conducted with the current evidence.” • Section 4.2.3; Pg 67: “The EAG questions whether the intervention is, in fact, teplizumab plus screening/testing in an asymptomatic population, in which case the comparator would be placebo/no treatment plus no screening/testing. On the other hand, if the intervention does not include a method of identifying the specified asymptomatic population (screening/testing) and the costs of screening/testing are not included in the economic analyses, the EAG considers that definition of the population should be ‘people aged 8 and over in whom Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) has been incidentally detected’, in which case the intervention would be teplizumab and the comparator ECM.” • Section 2.2; Pg 27-28: “However, the EAG considers that, given that people with Stage 2 T1D are asymptomatic and that there is currently ‘no commissioned targeted or general population screening and monitoring programme to identify individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes,’ if the population is as defined in the decision problem and in Section 2.1 and includes all people aged 8 and over with Stage 2 T1D (2 or more pancreatic islet autoantibodies and dysglycaemia) then it could be argued that the intervention should be defined as teplizumab plus screening” • Section 2.1; Pg 25: “If all patients eligible for teplizumab are to be identified then this raises the question as to whether the population is consistent with an intervention, which is, in fact, teplizumab plus screening/testing.” • Section 2; Pg 22; Table 2.: “Note that if the population is all those who have been identified by screening then the cost of the diagnostic test should be included.”			Not a factual inaccuracy. The EAG appropriately differentiates between two types of the population of those eligible for teplizumab, i.e. those incidentally detected versus those detected by screening, and for which there would be an additional cost of testing a much larger group of asymptomatic individuals.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Requested information is not available</u> Section 2.1; Pg 26-27 Text: “no information has been provided about either the number of people who would be eligible for testing or the proportion of those tested who would be eligible for treatment with teplizumab.”	Add text to clarify that this information is currently not known, as the parameters of a screening programme have not been defined by the National Screening Committee (NSC).	<u>To ensure the appraisal is aligned to the final scope:</u> Information regarding the number of people who would be eligible for testing requires consideration of who should be screened/tested, the frequency of screening/testing, the accuracy of testing itself, and the appropriate healthcare setting which is beyond the scope of this appraisal and within the remit of the NSC.	Not a factual inaccuracy. The EAG appropriately notes that if those eligible for teplizumab are not found incidentally, but instead detected by screening, then there would be an additional cost of testing a much larger group of asymptomatic individuals, which needs to be estimated.

Issue 2 Appropriateness of ‘established clinical management’ as a comparator for treatment with teplizumab (EAG Key Issue 2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>No routine identification does not mean there is no established clinical management.</u>	The text should be revised to present a balanced view of the NHS practice, as the presence of established clinical management is not dependent on routine identification.	<u>To correct a statement that contradicts direct evidence:</u> Lack of routine patient identification does not mean that there cannot be	Not a factual inaccuracy. The EAG appropriately is attempting to differentiate between

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Furthermore, the statement that there is no education or monitoring programmes, provision for self-assessment of blood glucose nor psychosocial assessment/support is factually incorrect and contradicts the evidence from UK clinical experts on the existing early-stage T1D clinics. Section 1.3; Pg 13; Table 1.3 Text: “The EAG considers that if a condition is not routinely identified there cannot be established clinical management for that condition. This is consistent with the submission from NHS England which stated that there are no education or monitoring programmes, no provision for self-assessment of blood glucose and no	Furthermore, the text should be revised to reflect that some individuals have and continue to be identified with early-stage T1D in the UK. These individuals are being managed in pre-symptomatic T1D clinics that provide education, monitoring, self-assessment of blood glucose and psychosocial support as required.	established clinical management for the individuals who are identified. In practice, despite the lack of a formal identification pathway, people with Stage 2 T1D are being diagnosed and managed in pre-symptomatic clinics in the UK, utilising protocols in line with international consensus guidelines.	clinical management and ‘established clinical management’.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
provision for psychosocial assessment/support for people with people with Stage 2 T1D."			
This issue also applies to the following text: - Section 2; Pg 21; Table 2.1: "The EAG notes that, as indicated above, there is currently no routine process to identify eligible patients in the NHS in England, and therefore it would seem that there is currently no established clinical management." - Section 3.4; Pg 61: "The EAG considers that, currently in England, most people with Stage 2 T1D are not being identified in the NHS and hence are not receiving any management..."			
<u>Discussion of a comparator outside of the scope of this appraisal.</u> The text below incorrectly represent the comparator as per the final scope from NICE. Section 1.3; Pg 14; Table 1.3 Text: "What alternative approach has the EAG suggested? The EAG has suggested that the	As per the final scope published by NICE, the text should be revised to make it clear that the comparator in this appraisal is established clinical management.	<u>To ensure the appraisal is aligned to the final scope.</u>	Not a factual inaccuracy. Given that no patients are currently identified by screening then there cannot be any established clinical management of those patients.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
comparator is no screening/ testing and no management and that this means that the cost of Stage 2 T1D in the comparator arm of the economic model should be zero.”			
This issue also applies to the following text: - Section 3.4; Pg 61: “The EAG considers that, currently in England, most people with Stage 2 T1D are not being identified in the NHS and hence are not receiving any management (see Section 2.3), i.e., the appropriate comparator is ‘no intervention’; in this case, the company’s statement that ‘<i>indirect comparisons are not possible or relevant</i>’ would be appropriate.” - Section 4.2.4; Pg 68: “In conclusion, an economic evaluation of teplizumab + screening versus placebo/no treatment + no screening in the asymptomatic population cannot be conducted with the current evidence.”			
<u>It is not known whether the incremental cost-effectiveness ratio (ICER) would increase as a result of the EAG’s proposed alternative comparator approach.</u> Section 1.3; Pg 14; Table 1.3	The text should be revised to indicate that the expected effect on the cost-effectiveness estimates is uncertain.	<u>To ensure speculation is not presented as fact:</u> It is not known whether using the EAG’s alternative comparator approach would increase the ICER, as the modelling approach would need to be changed accordingly.	Not a factual inaccuracy. If the cost of established clinical management is zero then the comparator cost will decrease and so the ICER will increase. The EAG appropriately indicates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: "What is the expected effect on the cost effectiveness estimates? The ICER would probably increase." Section 6.1.3; Pg 113 Text: "This could be seen as a lower end estimate because the costs of testing are not included and by including them the ICER would only increase."		In order to evaluate teplizumab plus screening/testing compared to no treatment plus no screening/testing, as proposed, the model structure would need to be substantially altered to include the parameters of a screening programme, as well as the outcomes for people who have undiagnosed Stage 2 T1D. In line with the NICE reference case, such analysis should not only include costs, but also all benefits of a screening programme, which go beyond the access to treatment with teplizumab. For the no treatment and no screening/testing arm, outcomes for people with undiagnosed Stage 2 T1D would need to be modelled, however, to the company's best knowledge, no such data exists. Furthermore, no	some uncertainty, which might be due to unknown additional changes by using the word 'probably'.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		screening programme has been designed and therefore neither the costs, nor benefits can be quantified. Given these fundamental unknowns, the ICER that would be obtained in an analysis proposed by the EAG and how it would compare to that for the analysis in line with the final scope is unknown.	
<u>The text below incorrectly implies that the company suggested that more than half of all those with early-stage T1D are being identified in the NHS setting.</u> Section 2.3; Pg 28 Text: “The EAG notes that the British Society for Paediatric Endocrinology and Diabetes (BSPED) data do not indicate that more than half of children and young people (CYP) with early-stage T1D are being	The text should be revised to reflect that more than half of individuals who have been identified as having early-stage T1D were identified in an NHS setting, outside of research studies.	<u>To ensure the company’s response to clarification questions is not misrepresented:</u> The company’s comments in the clarification letter response highlighted that individuals are being identified outside of screening programme settings in the UK, based on the BSPED data. It was not intended to be implied that half of <i>all</i> individuals with early-stage T1D are identified in the NHS. Instead, the	Not a factual inaccuracy. This was a quote from the company clarification response.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
identified in the NHS setting, but rather that of a total of 111 CYP with ≥ 1 islet autoantibody who were reported as being managed (across 84 units in the UK) and who were not on insulin (early-stage T1D), 53% (fewer than 60 patients) were identified in an NHS setting (either through targeted screening or clinical symptoms). The EAG therefore retains the view that, currently in England, most people with Stage 2 T1D are not being identified in the NHS and hence are not receiving any management (i.e., the cost of the comparator arm of the economic model should be zero)."		company emphasised that, among the individuals identified as having early-stage T1D in the study, half of those were identified in the NHS.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The text below is not accurate in relation to the potential impact of established clinical management on the cost-effectiveness model.</u> Section 4.2.4; Pg 68 Text: “If psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of teplizumab included in the model would be overestimated if these ECM components are effective.”	The text should be corrected that any difference in close monitoring in TN-10 compared to ECM would have no impact on the treatment effect in the model. Any diagnosis of Stage 3 T1D in TN-10 is confirmed by the presence of hyperglycaemia and not symptoms alone.	<u>To correctly reflect disease progression and how it applies to the cost-effectiveness assessment.</u>	Not a factual inaccuracy. If ECM in the model is not the same as ECM in TN-10 (which is unclear for the EAG), then the treatment effect observed in TN-10 would not be the same as the one implemented in the model.
This issue also applies to the following text: - Section 6.4; Pg 121: “If psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of teplizumab included in the model would be overestimated if these ECM components are effective.” - Section 6.1.3; Pg 113: “Hence, if psychosocial support or education on the management of T1D were not included in TN-10, then the treatment effect of ECM included in the model would be underestimated if these ECM components are effective. To explore the potential impact of underestimating the treatment effectiveness of ECM, the EAG selected a Gompertz distribution to extrapolate time to progression to Stage 3 T1D for ECM since this distribution predicts a			Not a factual inaccuracy. Please refer to the previous response and note that in Table 6.6 of the EAG report we referred to this scenario as “Hypothetical effect of missing ECM components”, so that it

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		higher probability of staying in Stage 2 T1D compared to the gamma distribution, which was used in the EAG base-case.... Since the comparator arm in TN-10 included at least close monitoring for Stage 3 T1D development in addition to placebo (clarification Question 3), it might be expected that the comparator in the model (ECM) is more effective than no treatment.”	should be understood as an exploratory scenario analysis.

Issue 3 The EAG disagrees with the company's approach of modelling progression to Stage 3 T1D (EAG Key Issue 5)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The text below comments on the company assumptions in an unbalanced manner.</u> - Section 1; Pg 16; Table 1.6 Text: "The company assumed: - Different types of parametric distributions for the intervention and comparator arms (log-normal for teplizumab and exponential for established clinical management [ECM]), which in general is not recommended. - An exponential distribution for ECM, where non-constant hazard functions are observed. - An exponential distribution for ECM results in the lowest long-term extrapolations compared to other choices.	Justification for these assumptions were included in the company submission (CS) and should be provided to avoid misleading the reader.	<u>To ensure complete information is presented:</u> Thorough clinical and technical justification for these assumptions was provided by the company in Section B.3.3.2.1 of the CS and Questions B5 and B6 of the clarification letter response.	Not a factual inaccuracy. The points quoted by the company are not subjective interpretations of the data.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• A log-normal distribution for teplizumab results in the long-term extrapolations at the upper end compared to other choices.”			

Issue 4 The EAG disagrees with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D (EAG Key Issue 6)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The EAG approach underestimates the effect on utility associated with Stage 3 T1D duration</u> Section 4.2.7.1.3; Pg 87: Text: "Therefore, in order to include the impact on health-related quality of life (HRQoL) of having lived with Stage 3 T1D longer without double counting the general impact of age on HRQoL, we can simply subtract the slopes of the two equations, and regard that as the excess utility decline with age due to diabetes-related complications. This would yield an extra 0.00005 decrease in utility per year since the onset of Stage 3 T1D, which is almost negligible.... Given the almost negligible excess utility decline, the EAG will simply forgo the extra utility decline as a	The approach implemented by the EAG is contrary to evidence regarding HRQoL in T1D and should be corrected.	<u>Correction of the EAG cost-effectiveness model:</u> The EAG's proposed approach to correct for potential double-counting lacks clinical validity and is therefore incorrect.	This is not a factual error. As explained in the EAG report, the company's approach to estimating a utility decrement to model the decline due to duration of Stage 3 T1D leads to double counting which needs to be corrected for. The company model includes a general utility decline due to age plus an additional time-dependent decline due to the duration of Stage 3 T1D. The former is estimated through Hernández-Alava 2022, whereas the latter is

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point.”			estimated from Sparring 2013. However, the EAG has pointed out in their report that the decline in utility by time since onset of Stage 3 T1D observed in Sparring et al. is also function of general age-related decline of QoL combined with the utility decline specifically due to duration of Stage 3 T1D. Thus, using the regression coefficients for this combined time-effect from Sparring on top of the general age-dependent utilities in the UK leads to double counting. As explained in the report (and cited here by the company), as the decline in utility

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			per year is the same for the Hernández-Alava and the Sparring studies, the conclusion must be that with the Sparring data no time-dependent disutility due to duration of Stage 3 T1D can be estimated.
This issue also applies to the following text: Section 6.1.2.3; Pg 112: “As discussed in Section 4.2.8.2, to ensure that no double counting of age-related decline in HRQoL occurs, and given the almost negligible excess utility decline per year, the EAG prefers to forgo the extra utility decline as a function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using the age-dependent general population utilities as a starting point.”			See above
<u>Clarifying “extra utility decline” for Stage 3 T1D</u> Section 1.1; Pg 12 Text: “Forgoing the extra utility decline as function of years since onset of Stage 3 T1D and only retain the decline in utility per year that results from using	The phrase “extra utility decline” should be substituted with a more appropriate term that represents what this value measures. For example, the term “disutility due to Stage 3 T1D” would be	<u>To ensure correct use of terminology.</u>	The EAG disagrees that the company’s suggested text is more informative and appropriate. The term “disutility due to Stage 3 T1D” is more suitable for the disutility of Stage 3 T1D versus no diabetes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the age-dependent general population utilities as a starting point.”	more appropriate and informative.		More importantly, the EAG is not using the phrase “extra utility decline” but “extra_utility decline as function of years since onset of Stage 3 T1D”, which is both correct and considered informative by the EAG.
This issue also applies to the following text: • Section 1.5, Pg 17, Table 1.7: “For the current data, the EAG preferred forgoing the extra utility decline depending on years since onset of Stage 3 T1D as the rate of decline was almost the same as the rate of decline in the general population.” • Section 1.2; Pg 12: “Forgoing extra utility decline depending on years since onset of Stage 3 T1D and retaining the decline in utility per year resulting from the general population.” • Other instances of “extra utility decline” are mentioned in multiple places in the EAG report, including on Pg 12, 18, 19, 114 and 124			No changes made. The phrase “extra_utility decline depending on years since onset of Stage 3 T1D”, is both correct and considered informative by the EAG.

Issue 5 The EAG disagrees with the company's approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs (Key Issue 7)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG indicated that <u>justification was not provided for the company's Stage 3 T1D cost estimates approach, although it was provided.</u> Section 4.2.8.4; Pg 94 Text: "This concern was raised by the EAG in the clarification letter (Question B15), but the company did not provide justification for their approach."	The text should be revised to reflect that justification for the approach was provided in the responses to clarification question B15.	<u>Factual accuracy:</u> Justification was provided in the response to clarification question B15.	Not a factual inaccuracy. The company response to the clarification letter restated the company approach but did not address the specific concerns identified by the EAG. We do not dispute that Hex et al (2024) is an appropriate source of stage 3 T1D costs. Our concern is with using the estimate from Hex to model initial costs which are then increased over time. The estimate from Hex relates to a prevalent population of people with stage 3 T1D including people who have had stage 3 T1D for decades. It is not an appropriate source for initial costs for

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			people with newly diagnosed stage 3 T1D who have not yet experienced complications of the disease at the same rate as the prevalent population.
This issue also applies to the following text: Section 6.4; Pg 123: “The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data, is incorrect and substantially overestimates healthcare costs for Stage 3 T1D. This concern was raised by the EAG in the clarification letter (Question B15), but the company did not provide justification for their approach.”			Not a factual inaccuracy. See above response. The company responded to the clarification question but only restated the approach. They did not justify why estimates from Hex et al. (2024) based on a prevalent population are an appropriate source for costs in patients with newly diagnosed stage 3 T1D.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The EAG indicated that the company approach is incorrect and substantially overestimates healthcare costs.</u> Section 4.2.8.4; Pg 94 Text: “The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data, is incorrect and substantially overestimates healthcare costs for Stage 3 T1D.”	The wording should be amended to reflect a more balanced perspective, given no validation for this assertion is provided.	<u>Factual accuracy:</u> It is incorrect to state that the company approach is incorrect and substantially overestimates healthcare costs. No validation for this assertion is provided and the publication used to estimate the initial Stage 3 costs² highlights these costs may be underestimated.	Not a factual inaccuracy. We provide clear rationale for why the approach used leads to a substantial overestimation of stage 3 T1D costs. To repeat: The cost estimates from Hex et al. (2024) are based on a prevalent population with stage 3 T1D which includes patients who have had stage 3 T1D for many years. The company uses these costs as initial costs for patients with newly diagnosed stage 3 T1D and then increases them over time according to the data from Ou et al. (2016). This means average stage 3 T1D costs in the model substantially

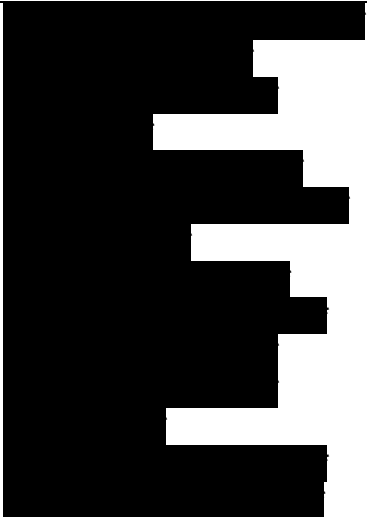
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			overestimate the cost estimate from Hex et al. (2024). Over 60 years in stage 3 T1D [REDACTED] [REDACTED] average annual costs of being in stage 3 T1D are [REDACTED] which is more than [REDACTED] the average annual cost of stage 3 T1D in the UK prevalent population from Hex et al. (2024) of £4,982. This additional explanation has been added to the EAG report.
This issue also applies to the following text: Section 4.2.8.4; Pg 95: “It is clear from the figure that the company’s approach leads to a substantial overestimation of Stage 3 T1D costs over time compared to the EAG approaches.”			Not a factual inaccuracy. See above response.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>The EAG preferred approach uses a fixed cost for Stage 3 T1D.</u> Section 1.5; Pg 18; Table 1.8 Text: “The EAG applied the average monthly cost from Hex et al. 2024 as a fixed health state cost of Stage 3 T1D.”	Revert to company approach, as the approach implemented by the EAG is contrary to evidence regarding T1D progression.	<u>Factual accuracy:</u> A fixed cost approach is not consistent with disease progression and vastly underestimates the impact of disease-related costs increasing over time. It is well established that the cost of treating T1D increases with time due to increased complications, as modelled with the company approach using the best data available.	Not a factual inaccuracy. For the reasons given above and in the EAG report the EAG considers that the approach used in the company’s base-case is inappropriate and biased. As described in the EAG report, the EAG considered two approaches to modelling stage 3 T1D costs: 1) applying the estimate from Hex et al. (2024) across all cycles; 2) calibrating the regression models such that the average cycle cost over patients remaining time in stage 3 T1D equalled the estimate from Hex et al. (2024). Option 2 is consistent with the trend of increasing T1D costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			over time. The two approaches produced similar estimates of cost-effectiveness and for simplicity the EAG adopted option #1. Option #2 could be used instead. Option #1 provides a more favourable cost-effectiveness estimate than option #2. Importantly both options are preferred to the company's base case approach which substantially overestimates stage 3 T1D costs over time.

Issue 6 Responses to additional EAG comments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Selective reporting of content</u> - Section 2.1; Pg 26 Text: “The EAG notes that, in the summary report of the company’s advisory board meeting (provided at the EAG’s request), it is stated that: [REDACTED]	As per the advisory board meeting, the report also states: [REDACTED] This quote should be added to the text.	<u>To ensure information is not presented in a selective manner:</u> Reporting selective content from the advisory board is misleading as it only includes information fitting a narrative of lack of existing pre-symptomatic patient management. Clinicians in the advisory board also noted current and expected guidance to be used in clinical practice for patient referrals and management for people with early-stage T1D, and this provides important context.	Not a factual inaccuracy. The EAG appropriately illustrates the current ad hoc approach and lack of screening to identify patients eligible for teplizumab.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			
<u>The EAG state that the company did not provide information regarding the number of patients in TN-01 who were eligible for TN-10.</u> • Section 3.2.1; Pg 42 Text: “The company’s response did not provide the total number of participants in TN-01 who met the eligibility criteria specified for TN-10, stating only that: ‘A total of 146 individuals who were identified	The text should be amended to reflect the fact that the company provided the information requested.	<u>To avoid misrepresenting the company response:</u> As stated in the response to the clarification questions, 146 individuals were eligible for screening based on the presence of an abnormal oral glucose tolerance test (OGTT)	Not a factual inaccuracy. The EAG acknowledged that one criterion was an abnormal OGTT, but the question is how so few patients were found to be eligible given the much larger number with an abnormal OGTT in TN-01, i.e. which other criteria were applied.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
through the TrialNet Natural History/Pathway to Prevention study and gave informed consent for this study were assessed for eligibility in TN-10”		and providing consent to participate To further clarify, the 146 assessed participants represent the total number of eligible participants from the 16 TN-01 sites selected for recruitment into TN-10.	
<u>The EAG state uncertainty regarding relatives of people with T1D having a different mechanism of disease progression compared to those without relatives with T1D, which is not based on evidence.</u> Section 3.2.3; Pg 46 Text: “The EAG notes that, whilst some evidence has been provided to support the view that having a first degree relative with T1D does not affect risk of progression from pre-symptomatic T1D to Stage 3 T1D, this is not the same as evidence that there is no variation in the mechanism of progression	The text should be revised, as there is no evidence that individuals with or without a first-degree relative would have a different rate of progression or mechanism of disease and therefore would respond differently to teplizumab.	<u>To ensure information is not misrepresented:</u> Information has been provided within Section B.2.5.2 of the CS that shows no impact on prognosis of having a first degree relative or not.³ There is also no biological rationale to suggest this.	Not a factual inaccuracy. The EAG appropriately differentiates between the prognostic effect of the presence or not of family history and its role as a treatment effect modifier.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and that any such variation would not result in variation in the effects of teplizumab.			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Teplizumab referred to having potential immunosuppressive effects</u> Section 1.4; Pg 14-15 Text: “The potential impact of adverse events of special interest (AESIs) is unclear, in relation to the immunosuppressive effects of teplizumab (Table 1.5)”	The text should be replaced to state “immunomodulatory” rather than “immunosuppressive”.	<u>To ensure correct nomenclature is used:</u> Any potential immunosuppressive effects of teplizumab are temporary and resolve within a short time period. Within the TN-10 trial, lymphopenia began to resolve whilst participants were still receiving teplizumab infusions, indicating an immunomodulatory mechanism of action rather than one that promotes broad-spectrum and long-lasting immunosuppression.⁴⁻⁶	Not a factual inaccuracy. The EAG appropriately refers to the potential immunosuppressive effect of teplizumab.
<u>The EAG place particular emphasis on treatment with teplizumab resulting in an increased risk of Grade ≥3 neutropenia</u> Section 1.4; Table 1.5	The text should be revised to delink increased risk of infection and incidence of >Grade 3 neutropenia.	<u>Clarification on teplizumab safety profile:</u> In relation to the integrated safety analysis, a transient decrease in mean	Not a factual inaccuracy. Although in fact there might be a link, this sentence does in fact link

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: "Additional data were provided (see Section 3.2.5) and the EAG notes that treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular severe (≥ 3) neutropenia."		neutrophil count was observed starting on Day 1 and reaching a nadir around Day 8. Mean neutrophil counts resolved by Day 29 for both Course 1 and Course 2 administration. Of all patients with $\geq$ Grade 3 neutropenia, 2 participants had association with $\geq$ Grade 3 infection. One participant had Grade 4 neutropenia on Days 2-8 and Grade 3 pilonidal cyst on Days 625-634. One participant had Grade 3 neutropenia on Days 191-194 and Grade 3 "infection of unknown origin" on Days 189-198. This participant had additional confounders from concomitant	infection with neutropenia.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		medications known to be associated with neutropenia. None of the $\geq$ Grade 3 neutropenia events were associated with sepsis or febrile neutropenia.	
This issue also applies to the following text: - Section 3.2.5.2; Pg 53: “The EAG notes that treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular ≥ 3 neutropenia.” - Section 3.6; Pg 62: “However, in the additional data from the larger integrated safety analysis population treatment with teplizumab appears to be associated with increased risk of infection and of blood and lymphatic system disorders, in particular ≥ 3 neutropenia.”			Not a factual inaccuracy. Although in fact there might be a link, this sentence does in fact link infection with neutropenia.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Assumption of patient population as being out of scope</u> The sentence below assumes that people with symptomatic T1D suggestive of new-onset diabetes could not have early-stage T1D, which is not correct. Section 2.1; Pg 26 Text: “Importantly, the abstract additionally reported the reasons for early identification, which were listed as family screening (42%), clinical symptoms suggestive of new-onset diabetes (37%) and following an autoimmune screen (21%); since symptomatic patients are outside the scope of this assessment, all reported methods of early identification, used in the UK, involved some form of targeted screening.”	It is important to revise the text and clarify that people may present with clinical symptoms suggestive of new-onset diabetes that is not overt hyperglycaemia. These people could have Stage 2 T1D; T1D stage would need to be confirmed by measuring blood glucose levels, which is not reported in the abstract.	<u>Factual accuracy:</u> Assuming that people with clinical symptoms suggestive of new-onset diabetes could not have early-stage T1D and are out of scope is incorrect. The only information that is provided by this abstract is that the included population was not on insulin.	Not a factual inaccuracy. The company seem to be contradicting the description of the population in the scope i.e. stage 2 T1D, presented in their company submission: “Clinical symptoms are not present at Stage 2.” (p. 13).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Statement that details of clinical experts consulted were not provided</u> - Section 3.2.3; Pgs 45-46 Text: “details of the disciplines and experience of the healthcare professionals were not provided.” - Section 3.2.3; Pg 45 Text: “The second source was described as advice from UK clinicians at a Sanofi advisory board who indicated that they did not expect the mechanism of T1D to be dissimilar for those who do and do not have a relative with Stage 3 T1D, however, no source document for this advice was provided with the initial submission”	Details of the clinicians/healthcare professionals providing the opinion at both advisory boards were provided in Appendix M of the CS. The text should be revised to indicate that the summary report of the company’s advisory board meeting was provided.	<u>Factual accuracy.</u>	Corrected.
<u>Rate of progression across first 6 months</u>	It should be clarified that the difference in event rate between the two KM curves is negligible.	<u>To correctly represent the data:</u> The numbers at risk and events up to 6	Not a factual inaccuracy. The EAG would like to thank the company for

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Additional explanation needed to describe the Kaplan-Meier (KM) curves. Section 4.2.6.1; Pg 71 Text: “The EAG considers it unclear why a difference in event rates over the first six months between the data cuts is observed, when the number of events and censored observations seem to be the same in both figures for the first six months”		months are consistent between the KM curve figure from Sims et al. 2021 (Figure 4.2 in the EAG report) and the KM curve figure from the clinical study report (CSR) (Figure 4.5 in the EAG report). The event rates during this period are very similar when the KM curves are superimposed and this difference is negligible. The superimposed KM curves are shown in Figure 1 in the Appendix at the end of this document.	the additional clarification, but this was not available while writing the EAG report and it remains unclear why a difference is observed. The curves look indeed similar but whether the difference is negligible or not is subjective, as it might affect long-term extrapolations.
<u>The EAG suggest no answer was provided for the choice of parametric models when justification was provided in response to the clarification questions.</u>	The text should be revised to reflect that justification was provided.	<u>Factual accuracy:</u> Justification was provided in the response to clarification question B5 and was further elaborated on in the	Not a factual inaccuracy. Response to B5 stated that “the exponential and log-normal curves were reviewed by an external clinical expert, Prof. Colin Dayan. Prof. Dayan

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1.1; Pg 75 Text: “The EAG asked the company to clarify the choice of different types of parametric models in clarification Question B5, but no answer was provided.”		response to clarification question B6.	agreed with the proposed approach of selecting the exponential fit”, which did not clarify the choice of different types of parametric models for the different arms, which is in general not recommended, as mentioned in the clarification question. Response to B6 was referring to B5 and the validity of the exponential distribution but not really explaining why the other extrapolations were valid or not.
<u>The EAG flagged that the hazard function plot does not start at zero, implying that there may be an issue with the plot, but the presentation of this plot does not impact the results.</u>	The text should be revised to correctly reflect the nature of the data presented in the plot.	<u>Factual accuracy:</u> The datapoints on the graph represent the average hazards or rates (events per person-time) for a given period. Therefore,	Not a factual inaccuracy. The EAG flagged that the hazard function plot does not start at zero, because the plot does not start at zero. We did not have the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1.1; Pg 75 Text: “It can be seen that the plot does not start at Time = 0, which is unfortunate, since this could have potentially used to validate the rapid decline in survival observed in Figure 4.2 in the placebo arm (i.e., a rapid progression in placebo should come with increasing hazards at the beginning).”		the datapoint at month 6 represents the average rate from 0 to 6 months, the datapoint at month 18 represents the average rate from 6 to 18 months, etc. As noted in the response to clarification question B5, the average hazards or rates (events per person-time) are calculated based on the quintiles (i.e., 20th, 40th, 60th, 80th percentiles) of times where events were observed across both groups.	intention to imply anything with that, just to point out that it would have helped with the selection of a parametric model knowing if the hazard functions had one or more turning points for example. Furthermore, it is common practice to show the functions starting from zero. We thank the company for the additional clarification.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Face validity assessment by clinical expert</u> Section 4.2.6.1.1; Pg 77 Text: “Face validity by the clinical expert was focused on assessing the validity of the exponential distribution for the placebo arm only”	The text should be revised to clarify that the clinical expert reviewed all of the distributions for the placebo arm.	<u>Factual accuracy:</u> During the meeting with the clinical expert (Prof. C. Dayan) all distributions for the placebo arm were presented and discussed.	Not a factual inaccuracy. Please refer to our response above: Response to B5 stated that “the exponential and log-normal curves were reviewed by an external clinical expert, Prof. Colin Dayan. Prof. Dayan agreed with the proposed approach of selecting the exponential fit”. We do not doubt that all distributions were presented to Prof. Dayan, but in our opinion, this was not reflected in the clarification responses.
<u>Rates of DKA reference</u> Section 4.2.6.2; Pg 79 Text: “The company responded that the publication by Besser at al. reported DKA risk for newly diagnosed individuals in the UK,	The text should be revised to indicate that justification was provided.	<u>Factual accuracy regarding justification provided by the company:</u> This was discussed in the response to clarification question B7.	Corrected as the company suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and reduction in risk if individuals are monitored, but no further justification as to why this was the preferred source to inform the model was provided”			
<u>Mortality for Stage 3 T1D</u> The EAG notes that generalisability of Swedish mortality data to the UK was not discussed, although it was supported by clinical experts • Section 4.2.6.4.2; Pg 82 Text: “The EAG asked the company to justify why the Swedish studies by Samuelsson et al. 2024 and Rawshani et al. 2018 were selected to estimate the excess mortality due to Stage 3 T1D in clarification Question B8. In their response, the company explained that these studies were selected because of their robust designs, both using large datasets from the Swedish National Diabetes	The text should be revised to reflect the full information provided by the company, including the fact that clinical experts indicated that Swedish mortality data is generalisable to the UK.	<u>To avoid selective reporting of information provided by the company:</u> Although not included in the response to clarification question B8, please note that the generalisability of Swedish mortality data from Rawshani et al. 2018⁷ was discussed at an advisory board convened by the company. Clinical experts indicated that the mortality rate in the UK was estimated to be similar to that in Sweden, and hence Swedish data (Rawshani et al. 2018)	Corrected as the company suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Registry, but the generalisability to the UK setting was not discussed."		would be favoured over a 2014 meta-analysis (Lung et al. 2014). ⁸	
<u>The EAG questioned how caregiver disutility was applied and have not sufficiently justified their alternative.</u> Section 4.2.7.1.3; Pg 87 Text: "the EAG is not sure if it is reasonable to assume that the caregiver disutility should be applied to both persons in a couple family as it is likely that the total care giving burden is similar to that in a lone family."	Revert to company approach.	<u>To ensure correct characterisation of the carer impact:</u> In the absence of sufficient justification, it is inaccurate to assume that a lone family therefore means a lone caregiver. It cannot be known if a lone family relies on other individuals to support with caregiving.	Not a factual inaccuracy. Please note that the EAG base-case follows the company's approach. One caregiver only was explored as EAG scenario analysis.
<u>Stage 3 T1D disutility</u> The EAG was unable to find support for the disutility from Sparring et al. 2013 being applied at onset of Stage 3 diabetes. However, the company understands this is supported by the publication.	The text should be revised to indicate that disutility from Sparring et al. 2013 is applied at onset of Stage 3 T1D based on company interpretation of the data being presented at diagnosis of diabetes.	<u>Factual accuracy:</u> The disutility value is based on an EQ-5D index score of -0.025 for 'patients with diabetes' relative to 'controls' as reported in Table 3 of Sparring et al. 2013 under the "Diabetes diagnosis"	This is not a factual error, but a difference in interpretation of the results from the study by Sparring et al. To re-iterate, the EAG interprets the presented regression coefficient as the loss in utility when a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.1.3; Pg 87 Text: “This disutility was also taken from Sparring et al. 2013 and is the coefficient for the explanatory variable ‘patient with diabetes’ (as compared with the matched non-diabetic individuals). However, the EAG could not find anything in the paper, either the narrative or in the way the results are presented, that suggests that this coefficient only applies at the moment (year) of onset of Stage 3 diabetes.”		category.⁹ These were reported separately from EQ-5D index scores based on disease duration. The section of the table where the -0.025 value is reported is labelled ‘<i>Diabetes diagnosis</i>’. Within the manuscript narrative it reads: “<i>The model [referring to the multivariable regression analysis] showed that sex, being diagnosed with diabetes, ..., had significant negative impact on the health outcome measures</i>” (page 7, under subsection titled ‘Variation on health-related quality of life’). Based on this, we interpreted the EQ-5D index score of -0.025 for patients with diabetes to	patient is diagnosed with Stage 3 T1D, not just in the year of diagnose, but all subsequent years. This continuing decrease in utility is in the company model already captured through a disutility of -0.0621 that is based on Sullivan et al. 2011. It should also be noted that removal of the one-off disutility that the company applied increases the ICER by only £67 per QALY gained.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		be applied at diagnosis of diabetes, i.e., onset of Stage 3 T1D.	
<u>The context of the following statement was misinterpreted by the EAG and should be clarified</u> Section 5.3.1.1; Pg 104 Text: “The EAG is also unclear how the exponential extrapolation could be considered <i>conservative</i> when it is the most favourable to teplizumab.”	The text should be revised to clarify that this was with respect to clinical progression from Stage 2 to Stage 3 T1D.	<u>To avoid misrepresenting the company response:</u> “Conservative” was used in this context to describe the rate of clinical progression from Stage 2 to Stage 3 T1D (i.e., the proportion of individuals still in Stage 2), and not in relation to teplizumab.¹⁰	Corrected as the company suggested.

Issue 7 Data, wording and formatting clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Cross-reference</u> Section 1.4; Pg 15; Table 1.5 Text: “Section B.2.10.4 of the CS”	Text should be changed to “B.2.10.1.4 of the CS”	Incorrect section number referenced.	Corrected.

<u>Text error: Reference year</u> • Two instances in Table 1.8 in Section 1.5; Pg 18 • One instance in Table 1.9 in Section 1.6; Pg 19 • Four instances in text in Section 4.2.8.4; Pgs 94-95 • One instance in Figure 4.14 in Section 4.2.8.4; Pg 95 • One instance in Table 6.7 in Section 6.3; Pg 120 • Four instances in text in Section 6.4; Pg 123 Text: “Hex et al. 2023” or “Hex et al. 2016”	Throughout the report, the text should be changed to “Hex et al. 2024”.	The publication year is 2024 rather than 2023 or 2016.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Outcomes</u> Section 2, Table 2.1; Pg 21 Text: “Time to starting insulin treatment”	“Time to starting insulin treatment” was added by EAG as an outcome addressed in the CS; although it was noted in the CS that this is largely the same as time to progression of Stage 3 T1D, technically TN-10 did not measure time to insulin treatment.	TN-10 did not measure time to insulin treatment.	Not a factual inaccuracy: this was in Table 1 of the company submission.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Cross-reference</u> - Section 2.1; Pg 25 Text: “The clinical pathway, proposed in the CS (Figure 2.1), is consistent with this specification and starts with people already diagnosed with Stage 2 T1D” - Section 2.3; Pg 28 Text: “The decision problem addressed in the CS and the clinical pathway illustrated in Figure 2.1 are consistent with this specification”	Cross-references to Figure 2.1 should be changed to Figure 2	Incorrect cross-reference.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Outcomes</u> Section 2.4; Pg 29 Text: “The EAG notes that the CS does not include any assessment of possible long-term effects of teplizumab treatment on symptoms and complications of T1D that might potentially arise from delayed progression from Stage 2 to Stage 3 T1D.”	We would suggest revising the text to avoid implying that such assessment of long-term effects is appropriate or necessary.	It would be inappropriate for the company to speculate on long-term effects of teplizumab treatment that are not yet supported by clinical evidence.	Not a factual inaccuracy: a statement of lack of long term evidence is not a request for speculation.
<u>Text error: SLR updated searches date</u> Section 3.1.1; Pg 30 Text: “27 June September 2024”	“September” should be removed	Incorrect date; updated searches were conducted on 27 June 2024.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Formatting error: SLR quality assessment</u> Section 3.1.5, Table 3.2; Pg 35-36	The font colours of the response options in rows 1.3, 2.1-2.6, 4.1-4.2, and 5.1-5.2 needs to be aligned with that shown in Table 8 in the CS appendices	Incorrect formatting.	Not a factual inaccuracy: Table 8 in the CS appendices was incorrectly formatted.
<u>Missing text: TN-10 inclusion criterion</u> Section 3.2.1; Pg 37 Text: “Included participants were people with Stage 2 T1D (≥8 years old) who were relatives of people with Stage 3 T1D with ≥2 or more diabetes-related autoantibodies detected in two samples obtained within six months before randomisation”	Additional inclusion criterion missing here: “Evidence of dysglycaemia during an OGTT” (see Table 5 in section B.2.2 of the CS as per Herold 2019).	Incomplete information.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Formatting error: Table for summary of TN-10 methodology</u> Section 3.2.1, Table 3.3; Pg 37-38	Table 3.4 is missing bullet formatting as per Table 6 in section B.2.3.1 of the CS.	Clarify presentation of information.	Table 3.3 edited to improve clarity.
<u>Formatting error: Table for TN-10 Eligibility criteria</u> Section 3.2.1, Table 3.4; Pg 39	Table 3.4 is missing bullet formatting as per Table 7 in section B.2.3.3 of the CS.	Clarify presentation of information.	Table 3.4 edited to improve clarity.
<u>Text error: Trial number</u> Section 3.2.1; Pg 40 Text: "TN-0 trial"	Text should be changed to "TN-01 trial".	Incomplete trial number.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference error:</u> <u>Incorrect citation</u> Section 3.2.3; Pg 45 Text: "... with having a first-degree relative.²⁷"	Instead of reference number 27, the following reference should be cited: Ziegler AG, Kick K, Bonifacio E, et al. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. <i>JAMA</i>. Jan 28 2020;323(4):339-351. doi:10.1001/jama.2019.21565	Incorrect reference cited.	Corrected
<u>Reference error:</u> <u>Incorrect citation</u> Section 3.2.3; Pg 45 Text: "familial cases of T1D' (insert cs response).²⁸"	Instead of reference number 28, the following reference should be cited: American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. <i>Diabetes Care</i>. Jan 1 2025;48(Supplement_1):S27-s49. doi:10.2337/dc25-S002 Additionally, the extra text "(insert cs response)" should be removed.	Incorrect reference cited.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Table title</u> Section 3.2.4.4, Table 3.11; Pg 49 Text: “Table 3.11: C-peptide area under the time–concentration curve (AUC) at...”	Text should be revised to “Table 3.11: Insulin interval secretion (2 hours)...” Thus, the AUC abbreviation in the table footnotes can be removed.	Incorrect table title.	Corrected.
<u>Formatting error: Table for Study design of trials included in the integrated safety analysis</u> Section 3.2.5.2, Table 3.13; Pg 50-51	Table 3.13 is missing bullet formatting as per Table 6 in the response to clarification question A25.	Clarify presentation of information.	Bullets unnecessary.
<u>Text error: Table title</u> Section 3.2.5.3, Table 3.17; Pg 54 Text: “Table 3.17: Treatment-emergent SAEs...”	Text should be revised to “Table 3.17: Grade 3 TEAEs...”	Incorrect table title.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Formatting error: Table shading</u> Section 3.2.5.3, Table 3.18; Pg 57	The “Hepatobiliary disorders” row of the table should be formatted as a system organ class with purple shading.	Missing appropriate table row shading.	Corrected.
<u>Text error: Cross-reference</u> Section 3.2.5.3, Table 3.19; Pg 61 Text: “Based on Table 7 of the response...”	The text should be revised to “Based on Table 8 of the response...”	Incorrect table cross-reference.	Corrected.
<u>Text error: Figure source</u> Section 4.2.6.1; Pg 71 Text: “The EAG noticed that these curves were different from those in Herold et al. 2019 (Figure 4.5).”	The figure in Figure 4.5 (Figure 4 in the CS) is from the TN-10 CSR and not from Herold et al. 2019. Therefore, “Herold et al. 2019” should be changed to “the CSR.”	Incorrect text.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text errors: Cross-references</u> - Section 4.2.6.1; Pgs 74-76 and 78-79 Text in table/figure footnotes: - Figure 4.6: “Based on Figure 5...” - Figure 4.7: “Based on Figure 6...” - Table 4.5: “Based on Table 6...” - Figure 4.8: “Based on Figure 8...” - Figure 4.9: “Based on Figure 7...” - Figure 4.10: “Based on Figure 8...”	The cross-references should be revised as follows: - In the Figure 4.6 footnote: “Based on Figure 9...” - In the Figure 4.7 footnote: “Based on Figure 10...” - In the Table 4.5 footnote: “Based on Table 26...” - In the Figure 4.8 footnote: “Based on Figure 4...” - In the Figure 4.9 footnote: “Based on Figure 11...” - In the Figure 4.10 footnote: “Based on Figure 12...”	Incorrect table/figure cross-references.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Incorrect description</u> Section 4.2.6.4.1; Pg 80 Text: “Another Swedish publication, Lung et al. 2014...”	The word “Swedish” should be removed.	The study by Lung et al. was not conducted in Sweden.	Corrected.
<u>Text errors: Cross-references</u> - Section 4.2.6.4; Pg 81 Text in table/ footnotes: - Table 4.9: “Based on Table 12...” - Table 4.10: “Based on Table 30...” - Table 4.11: “Based on Table 31”	The cross-references should be revised as follows: - In the Table 4.9 footnote: “Based on Table 29...” - In the Table 4.10 footnote: “Based on Table 30...” - In the Table 4.11 footnote: “Based on Table 31...”	Incorrect table cross-references.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Table data label</u> Section 4.2.7.1.2, Table 4.14; Pg 84 Text: “Independent variable”	The text should be revised to “Dependent variable.”	The variables are incorrectly described per Table 3 in Sparring et al. (2013).	This is not a factual error. The heading in Table 4.14 covers the list of independent variables below the heading. In contrast, in table 3 of Sparring et al. the heading ‘Dependent variable’ refers to the row listing ‘EQ-5D_{index}’ and ‘EQ VAS score’ as the two dependent variables explored. Thus, the headings in Table 4.14 and Table 3 cannot be compared.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Data error: Incorrect value</u> Section 4.2.7.1.2; Pg 85 Text: “Disutility after x years from onset Stage 3 T1D = -0.00314”	The number 4 should be deleted, making the value “0.0031”.	The value was incorrect as per Section B.3.4.2.3 in the CS.	This is not a factual error, the company’s Excel model uses more decimals than reported in company submission document B.
<u>Text error: Cross-reference</u> Section 4.2.7.1.3; Pg 86 Text: “However, when we consider the regression equation estimated by Sparring et al. 2013 (Table 4.13)...”	Cross-reference to Table 4.1.3 should be changed to Table 4.1.4.	Incorrect table cross-reference.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Comparator definition</u> Section 4.2.8.2; Pg 88 Text: “The company assumed zero direct costs for the comparator, citing the absence of an existing standard of care.”	As stated in B.3.2.3 of the CS and the response to clarification question B3, the comparator was established clinical management.	Incorrect definition of comparator.	Changed to: “The company does not model the direct costs of ECM since it applies to both arms.”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference errors:</u> <u>Incorrect citations</u> Section 4.2.8.2.1, Table 4.17; Pg 89 Text: “NICE BNF⁶⁹” in the “NSAID or acetaminophen” and “Anti-emetics” rows	The correct NICE BNF citation in the “NSAID or acetaminophen” row is: - National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Ibuprofen Medicinal forms. Accessed 1 November, 2024. https://bnf.nice.org.uk/drugs/ibuprofen/medicinal-forms/#oral-tablet The correct NICE BNF citation in the “Anti-emetics” row is: - National Institute for Health and Care Excellence (NICE). British National Formulary (BNF): Ondansetron Medicinal forms. Accessed 1 November, 2024. https://bnf.nice.org.uk/drugs/ondansetron/medicinal-forms/#oral-tablet	Incorrect citations referenced.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference error: Incorrect citation</u> Section 4.2.8.3, Table 4.21; Pgs 91-92 Text: “NHS England⁷⁶” in the “Paediatric MDT,” “Adult MDT” and “Telephone consultation” rows	Reference number 76 is the correct NHS England reference for the “Paediatric MDT” and “Adult MDT” rows, but not for the “Telephone consultation” row, which should be: NHS England. NHS Staff Annual Earnings Estimates December 2023, NHS Trusts and other core orgs 2024.	Incorrect citation referenced.	Corrected.
<u>Data errors: Incorrect values</u> Section 4.2.8.3, Table 4.22; Pg 92 Text: “£2.65” and “£2.78”	“£2.65” should be changed to “£72.50” and “£2.78” should be changed to “£39.60”	Incorrect values presented, as per Table 45 of the CS.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference error: Missing citation</u> Section 4.2.8.4; Pg 96 Text: “The cost per event was estimated at £1,722.32 based on the weighted average of inpatient costs from the “Non-Elective Admissions” under the code KB02G-K (Diabetes with Hyperglycaemic Disorders) in the National Schedule of NHS Costs.”	The following reference should be cited: National Health Services (NHS). National Schedule of NHS Costs 2021/22 (V3, updated 19 May 2023). 2023. https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/	Missing citation from the CS.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference error: Incorrect citation</u> Section 4.2.8.4; Pg 96 Text: “The probability of a DKA event is estimated to be 2.5% and independent of treatment based on data from Besser et al. 2022.⁵⁵”	The following reference should be cited instead of reference number 55: Besser REJ, Ng SM, Gregory JW, Dayan CM, Randell T, Barrett T. General population screening for childhood type 1 diabetes: is it time for a UK strategy? <i>Arch Dis Child</i>. Sep 2022;107(9):790-795. doi:10.1136/archdischild-2021-321864	Incorrect citation referenced (a different article by Besser et al. that was also published in 2022).	Corrected.
<u>Text error: Missing parentheses</u> Section 5.1.2; Pg 98; Table 5.3 Text: “()” in the “Increment (£)” column and “Stage 3 T1D” row	Parentheses should be added around the values. Thus, the text should be changed to “()”	Missing parentheses	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Cross-reference</u> Section 5.1.2; Pg 98; Table 5.4 Footnote Text: “Based on Table 50 in the CS.⁹”	Text should be changed to “Based on Table 1 in Appendix 2 of the company’s response to the clarification letter.¹⁵”	Incorrect document and table referenced.	Corrected.
<u>Formatting error: Figure outlines</u> Section 5.2.2; Pg 101-102; Figures 5.3, 5.4 and 5.5	Formatting of the turquoise figure outlines should be modified so that the legends are visible in each figure.	The outline is obscuring the legend in each figure.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Advisory board</u> Section 5.3.1.1; Pg 104 Text: “The company considered the structure of the three-state Markov model described in Section 4.2.2 of this report appropriate for modelling the delay of onset of Stage 3 T1D. The company noted a similar approach was taken for the economic evaluation of the DiRECT trial in T2D.”	Text should be changed to “The experts considered the structure of the three-state Markov model described in Section 4.2.2 of this report appropriate for modelling the delay of onset of Stage 3 T1D. The experts noted a similar approach was taken for the economic evaluation of the DiRECT trial in T2D.”	As noted in Section B.3.14.1.1 of the CS and the advisory board report, these statements were made by the experts attending the advisory board rather than the company.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reference error: Missing citation</u> Section 6.1.3; Pg 113 Text: "...where "close monitoring in TN-10 consisted of metabolic monitoring with a scheduled oral glucose tolerance test (OGTT) every 6 months and an additional random glucose measurement scheduled every 3 months with a reflex to OGTT should the glucose level be abnormal. Participants were educated about the symptoms associated with Stage 3 T1D at each visit and via routine contact in between visits"."	A citation referencing the company's Clarification Questions Addendum from January 2025 should be added.	Missing source citation.	Added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text error: Incomplete cross-reference</u> Section 6.1.3; Pg 113 Text: “clarification Question 3”	Text should read “clarification Question B3”.	Incomplete cross-reference.	Corrected.
<u>Reference error: Incorrect author</u> Section 7; Pg 126 Text: “[18] Pharmacology COoC. <i>CLINICAL PHARMACOLOGY REVIEW(S) (761183Orig1s000)</i>, 2022...”	Author name should be changed from “Pharmacology COoC” to “CDER Office of Clinical Pharmacology”.	Incorrect author name used.	Corrected.

Issue 8 Errors in the marking of confidential information in the EAG report

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 48	"C-peptide preservation remained significant at 24 months ([REDACTED] overall; [REDACTED] in those progressing to Stage 3 T1D)." Both p-values should be marked as confidential.	"C-peptide preservation remained significant at 24 months ([REDACTED] overall; [REDACTED] in those progressing to Stage 3 T1D)."	Corrected.
Page 87	"Some similar remarks were made by experts in the Advisory Board: [REDACTED]" The quote from the advisory board should be marked as confidential.	"Some similar remarks were made by experts in the Advisory Board: [REDACTED]"	Corrected.
Page 89	"The company states that the total drug acquisition costs for a standard 14-day	"The company states that the total drug acquisition costs for	Corrected.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	treatment course of teplizumab is £[REDACTED].” The cost of teplizumab should be marked as confidential.	a standard 14-day treatment course of teplizumab is [REDACTED].”	
Page 97	“...resulting in an ICER of [REDACTED] per QALY gained.” The ICER from the original company’s CE results does not need to be marked as confidential (and is correspondingly not highlighted in Table 5.1 of the EAG report).	“...resulting in an ICER of £29,602 per QALY gained.”	Corrected.

References

1. Swaby R, Randell T, Martin R, et al. How many children are out there? A BSPED survey of children and young people with early-stage type 1 diabetes. presented at: 51st Annual Meeting of the British Society for Paediatric Endocrinology and Diabetes; 08 Oct 2024 - 10 Oct 2024 2024; Glasgow, UK.
2. Hex N, MacDonald R, Pocock J, et al. Estimation of the direct health and indirect societal costs of diabetes in the UK using a cost of illness model. *Diabet Med*. Sep 2024;41(9):e15326. doi:10.1111/dme.15326
3. Koeger M, Hummel S, Weiss A, et al. *Abstract #413: Use of teplizumab to delay stage 3 type 1 diabetes: generalisability of the TN-10 trial to a European population*. . 2024. *IDS 2024*. 4-8 November.
4. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. Aug 15 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
5. Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β -Cell Function. *Diabetes Care*. 2023;46(10):1848-1856. doi:10.2337/dc23-0675
6. Kokori E, Olatunji G, Ogieuhi IJ, et al. Teplizumab's immunomodulatory effects on pancreatic β -cell function in type 1 diabetes mellitus. *Clin Diabetes Endocrinol*. Aug 10 2024;10(1):23. doi:10.1186/s40842-024-00181-w
7. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. Aug 11 2018;392(10146):477-486. doi:10.1016/s0140-6736(18)31506-x
8. Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PM. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. *PLoS One*. 2014;9(11):e113635. doi:10.1371/journal.pone.0113635
9. Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish population-based study using EQ-5D. *BMC Public Health*. Apr 22 2013;13:377. doi:10.1186/1471-2458-13-377
10. Sanofi (Data on File). *UK May 2024 Advisory Board for teplizumab in Stage 2 aT1D Final report (MAT-XU-2401585)*. 2024. *Summary Report*. Date of preparation: November 2024.

Appendix: Rate of progression in TN-10 placebo arm

Figure 1. TN-10 KM curve from Sims et al. 2021 superimposed over the TN-10 KM curve from the CSR



CSR = clinical study report; KM = Kaplan-Meier