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:

Appraisal Committee Meeting 2:

1. **Comments on the Draft Guidance from Sanofi**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Breakthrough T1D, the type 1 diabetes charity
   b. British Society for Paediatrics Endocrinology and Diabetes
   c. Diabetes UK
   d. NHS England
   e. West Yorkshire Integrated Care Board (ICB) and the West Yorkshire Association of Acute trusts (WYATT)

3. **Comments on the Draft Guidance received through the NICE website**
   a. Comment from Kidney Research UK
   b. Comment from Diabetes clinician/researcher

4. **External Assessment Group critique of company comments on the Draft Guidance**
   a. EAG critique addendum

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Appraisal Committee Meeting 3:

6. **NICE call for evidence**

7. **Company response to the call for evidence**
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8. **External Assessment Group critique of company response to the call for evidence**
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9. **Factual accuracy check of External Assessment Group critique**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 8th September 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sanofi
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Treatment pathway (3.2): Sanofi consider that the language in section 3.2 confuses the infrastructure required for teplizumab infusion with requirements for the wider pre-symptomatic type 1 diabetes pathway.** When considering the treatment pathway for teplizumab in Stage 2 type 1 diabetes, it is important to separate the resources that are required for administering teplizumab from the wider management of pre-symptomatic type 1 (Stage 1 and Stage 2) diabetes (independent of immunotherapy). Sanofi are aware that an end-to-end pathway for pre-symptomatic T1D is in development by a Task and Finish group led by NHS England and experts. Sanofi understand that this will provide a resource for decision makers, based on expert review of the evidence across the pathway. Different elements of the pathway will include identification of presymptomatic T1D for adults and paediatrics, assays for testing and confirmation of staging, data collection, support, management and follow up and funding and commissioning. In one advisory board, the experts informed that "the cost of implementing teplizumab and the infusion service is not significant, but the pathway setup is more complex".[3] The group noted that these are two separate elements regarding funding implications. With regard to "additional infrastructure in the NHS to support any potential recommendation of teplizumab", based on expected patient numbers managed in 8-12 tertiary centres, Sanofi maintains that the 14-day teplizumab administration will create limited additional demand on the NHS. We request that discussion of the treatment pathway by the committee focuses on the pathway associated with teplizumab treatment, rather than being conflated with the wider pre-symptomatic type 1 diabetes pathway. As detailed in the submission, and already captured in the cost-effectiveness model, the only teplizumab-specific infrastructure required is related to the infusion itself. This is expected to include: • 15 min infusion preparation time by a highly specialist pharmacist/day • Hospital administration: 30-60 minutes intravenous infusion with 30mins dedicated nurse time/day, or • Closer-to-home administration: 30 minutes intravenous infusion, with additional 45mins dedicated nurse time/day • Daily pre-medication costs (nonsteroidal anti-inflammatory drug or acetaminophen, antihistamine and anti-emetics) • Daily laboratory evaluation costs (complete blood count and liver enzyme test) Given the infrastructure requirements are routine and utilise standard infusion capabilities within the NHS, and patient numbers are expected to be limited (see comment 3 for rationale), we

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	suggest that the implementation of teplizumab is not expected to place significant additional demand on the NHS.
2	**Identifying the eligible population for teplizumab (3.3): "It [the committee] decided that the potential increase in demand for ad-hoc autoantibody testing and the associated costs, if teplizumab were recommended, should have been captured in the model". Sanofi is concerned that it would be inappropriate to capture these costs in the model.** In line with the Summary of Product Characteristics, the model includes the cost of confirmatory autoantibody testing in the teplizumab arm only. Any additional costs related to patient identification should be considered as occurring prior to, or 'upstream of', the point at which individuals are included in the model, and would therefore apply equally to both the teplizumab arm and the established clinical management arm. In the draft guidance, the committee agrees that the model structure (section 3.8) and established clinical management as the comparator (section 3.4) are both appropriate for decision making in the appraisal of teplizumab. Testing takes place before the decision to treat with teplizumab and/or established clinical management. As stated, it is important to note that there are benefits associated with testing and established clinical management, such as diabetic ketoacidosis prevention and an easier transition into type 1 diabetes,[1] which are not related to teplizumab. Including additional costs of testing or identification only in the teplizumab arm of the cost-effectiveness model mixes different clinical pathways and economic impacts, which would bias the results. If an increase in ad-hoc autoantibody testing costs is to be considered within the appraisal of teplizumab, this could be captured within the budget impact assessment. This ensures the cost-effectiveness evaluation of teplizumab is focused on the direct effects of teplizumab only, and allows any financial and practical implications of increased testing to be considered separately. This will further support implementation and resource impact guidance for integrated care boards.
3	**Identifying the eligible population for teplizumab (3.3): "The committee also decided that the lack of data on the size and composition of the population eligible for teplizumab was a significant uncertainty. It concluded that it needed more information on the number of people in each of the identified populations that might present for autoantibody testing." Sanofi have sought additional clarification:** To inform this, Sanofi sought to expand understanding on the four distinct populations defined in the draft guidance that may be tested and subsequently identified as having Stage 2 type 1 diabetes: • Those identified in research studies • Those tested due to clinical concern about hyperglycaemia • Those who have a first-degree relative with type 1 diabetes • Those requesting testing Sanofi gathered information on how they might present, how they would be managed and any potential change in autoantibody testing practice if teplizumab were recommended. Sanofi conducted two advisory boards (31st July and 19th-21st August 2025) to hear from experts to help inform the population question.[2,3] Participants included a mix of clinical and payer experts from across England, including adult and paediatric secondary care and primary care clinicians;

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trust and integrated care board pharmacists; commissioners and a financial officer. The advisory board reports are supplied as references supplementary to this response.

The advisory boards indicated three key themes:

- Autoantibody testing for type 1 diabetes by a specialist diabetes team in secondary care may increase by a mild to moderate level with the introduction of teplizumab, initially driven by the testing of children and young people with a first-degree relative who has type 1 diabetes. This modest increase would be driven by more clinicians offering to test or more clinicians agreeing to test a first-degree relative upon request.
- Autoantibody testing is unlikely to occur in primary care without a national initiative, due to a lack of guidance and widespread awareness of pre-symptomatic type 1 diabetes by primary care clinicians.
- An end-to-end pathway is critical for management of autoantibody testing in clinical practice, and for any decision to increase autoantibody testing for pre-symptomatic type 1 diabetes within the NHS. Without a funded end-to end pathway in place, clinicians are reluctant to increase autoantibody testing for type 1 diabetes as identified people with type 1 diabetes may not be monitored or managed appropriately. This is a consideration independent of potential reimbursement of teplizumab.

Testing in secondary care

Teplizumab's availability may encourage some specialist diabetes clinicians to increase testing in some patient cohorts, most likely children and young people who are first-degree relatives of those already diagnosed with type 1 diabetes. Experts stated that autoantibody testing would be contingent on motivated clinicians to complete this testing, and not every clinician would action, nor patient accept, this. The number of first-degree relatives tested and any increase in the number of requests because of teplizumab reimbursement, in line with the marketing authorisation, are explored in scenario analysis (Table 3).

Testing in primary care

Ad-hoc autoantibody testing for pre-symptomatic type 1 diabetes is currently extremely limited in primary care due to low general population awareness meaning proactive individual requests for autoantibody testing are rare in the absence of a national screening programme. Other contributing factors are a lack of general practitioner knowledge and complexities in ordering autoantibody tests. General practitioners and primary care nurses are unlikely to pursue testing proactively without a national incentive or guidance in place, and improvements in infrastructure. It was noted that the advisors did not anticipate a sudden uptake in patient testing in the absence of national guidance and in addition, not all patients identified will want treatment with teplizumab.

Number of people in each of the identified populations that might present for autoantibody testing

- **Those identified in research studies:** This predominantly refers to the Early Surveillance for Autoimmune diabetes (ELSA) in paediatrics and Type 1 Diabetes Risk in Adults (T1DRA) in adult studies. To date, these studies have screened over [redacted] people [redacted] and [redacted] people respectively. [redacted]

  Without a comprehensive pathway for the management of pre-symptomatic type 1 diabetes within the NHS, it is expected that a significant proportion of individuals will

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continue to be directed to ELSA and T1DRA for autoantibody testing. It would be reasonable to assume a modest increase in testing in this population.

- **Those tested due to clinical concern about hyperglycaemia:** As these individuals are diagnosed with Stage 2 type 1 diabetes incidentally when tested for a different clinical concern, the availability of teplizumab is not expected to have a direct impact on autoantibody testing in this cohort. These individuals will present independent of teplizumab availability and therefore should not be included in any autoantibody testing attributed to the availability of teplizumab.
- **Those who have a first-degree relative with type 1 diabetes:** A mild to moderate increase in autoantibody testing of first-degree relatives, driven by secondary care, could be expected. This is expected to be due to both clinicians offering autoantibody testing more frequently to this population, and more people within this population proactively asking clinicians for autoantibody testing which is then acted upon. Clinical judgement and integrated care board-governed guidelines will determine whether the requested autoantibody test is proactively/reactively funded when requested. A proportion of these individuals are expected to be tested via ELSA and T1DRA.
- **Those requesting testing:** First-degree relatives are expected to be the population most likely to request autoantibody testing, as these are an engaged community with an existing awareness of the benefits of pre-symptomatic type 1 diabetes testing. Numbers associated with this cohort are captured within the "those who have a first-degree relative with type 1 diabetes" cohort above.

  From a general population perspective, awareness of type 1 diabetes early detection remains limited. Primary care lacks consistent infrastructure for autoantibody testing and healthcare professional training for pre-symptomatic type 1 diabetes management, meaning autoantibody testing is likely to remain in the secondary care setting. Without an established NHS pathway, only individuals with first-degree relatives already in secondary care can access NHS autoantibody testing upon request. Although individuals can request a test, the ability to test at scale would require agreement with the relevant integrated care board, which is not expected in the absence of a national screening programme. Consequently, teplizumab availability is unlikely to significantly impact general population awareness or understanding of autoantibody testing.

<u>Scenario analysis for the potential increase in demand for ad-hoc autoantibody testing and the associated costs</u>

A Collaborative Working project between Sanofi and the University Hospitals of Morecambe Bay NHS Foundation Trust started in Q1 2025 to pilot early detection of pre-symptomatic type 1 diabetes in a clinical setting.[4] Preliminary results from approximately the first three months of this project indicate a [redacted]

To assess a mild to moderate increase in testing of the first-degree relative population, Sanofi have adapted the structure of the NICE Budget Impact Test (BIT) completed for teplizumab (ID6259 Teplizumab BIT to company v4.0 24042025) to estimate the number of incident first-

degree relatives (Table 1) and prevalent first-degree relatives (Table 2) who would be eligible for testing.

Table 1. Calculating the incident first-degree relative population in England

Step	Input	Output	Source/Assumptions
Incidence of type 1 diabetes in England	9,275	-	NHS Digital[5]
Population growth rate	2.06%	9,466	NICE assumption
Proportion of people with stage 3 type 1 diabetes	100%	9,466	NICE assumption due to Stage 2 type 1 diabetes being asymptomatic
Number of familial direct relatives (first-degree relatives)	2	18,932	Assumed 2 first-degree relatives per person with type 1 diabetes
Proportion of people who are aged 8 years and over	91%	17,272	Office of National Statistics
Uptake of testing	-	-	Applied as per Table 3

Table 2. Calculating the prevalent first-degree relative population in England

Step	Input	Output	Source/Assumptions
Prevalent population with type 1 diabetes in England	270,935	-	NHS Digital[5]
Number of familial direct relatives (first-degree relatives)	2	541,870	Assumed 2 first-degree relatives per person with type 1 diabetes
Proportion of people who are aged 8 years and over	91%	494,357	Office of National Statistics
Uptake of testing	-	-	Applied as per Table 3

To estimate number of individuals and associated costs, Sanofi explored the costs in the first year. An assumption was made that both the incident and prevalent first-degree relative populations would be offered autoantibody testing once. For the prevalent population, these figures therefore represent the one-off costs incurred when testing a proportion of this population; these costs would not apply in subsequent years. For the incident population, it is expected that these costs would be incurred annually, as a new first-degree relative incident population are tested each year.

Whilst an increase in testing of first-degree relatives is expected, it is unclear how the availability of teplizumab will affect the uptake. Sanofi have therefore tested several scenarios increasing testing uptake to [redacted] and [redacted] (Table 3), from the current base rate of [redacted]. To estimate associated costs, the number of tests (adjusted for uptake) have then been multiplied by the cost of one panel of autoantibody tests (£29.04 per autoantibody test panel [anti–glutamic acid decarboxylase, anti-zinc transporter 8 and anti–tyrosine phosphatase-like insulinoma antigen 2]).[6]

Even under a [redacted] uptake scenario, incremental testing costs [redacted] remain modest and predictable within the context of NHS spending on type 1 diabetes management. These costs are small when set against the substantial ongoing costs of managing Stage 3 type 1 diabetes, including widespread adoption of hybrid closed-loop systems referred to in the draft guidance (section 3.12). This may also be considered a conservative approach as we have assumed in the analysis two first-degree relatives for every one person with type 1 diabetes, when in reality this may be lower.

Table 3. Scenario analysis regarding patient identification in the first year of teplizumab availability in England

Scenario	Total individuals tested	Incremental tests vs. baseline	Total testing cost	Incremental cost vs. baseline
Current [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident (annual)	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent (one-off)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing	[redacted]	[redacted]	[redacted]	[redacted]
Incident (annual)	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent (one-off)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing	[redacted]	[redacted]	[redacted]	[redacted]
Incident (annual)	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent (one-off)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing	[redacted]	[redacted]	[redacted]	[redacted]
Incident (annual)	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent (one-off)	[redacted]	[redacted]	[redacted]	[redacted]

Summary

The availability of teplizumab may result in a mild to moderate increase in autoantibody testing within secondary care, primarily for children and young people with first-degree relatives having type 1 diabetes. The data suggests that while testing accessibility might improve with teplizumab's availability, current uptake remains modest. Any uplift in testing is expected to integrate smoothly into existing NHS systems for several reasons: the small number of patients requiring treatment, the short 14-day treatment duration, and the use of existing specialist infusion centres within secondary care.

4

Adverse events (3.7): In response to the committee's request that "The costs of cytokine release syndrome should be included in the teplizumab arm of the model, in line with the incidence rate of 5.8% from the integrated safety analysis", this has been considered in the revised cost-effectiveness model.

The 5.8% incidence rate that the committee refers to is the incidence rate of cytokine release syndrome for patients receiving teplizumab in the integrated safety analysis of five clinical trials of teplizumab.[7] In the same integrated safety analysis, cytokine release syndrome was reported in 1.2% of patients receiving control.[7] As the model captures the excess risk of adverse events occurring, 4.6%, rather than 5.8%, has been included for cytokine release syndrome for teplizumab. It should be noted that in the TN-10 study, cytokine release syndrome was reported in 1 patient in the teplizumab arm (2.3%) and no patients in the placebo arm.[8]

Cytokine release syndrome events resolved within 2 to 3 days from onset in the integrated safety analysis; thus, a duration of 2.5 days was used for cytokine release syndrome as an adverse event in the model.

The disutility applied for cytokine release syndrome was informed by a 2023 publication reporting EQ-5D-3L health-related quality of life utilities for the UK.[9] Values of -0.0288 and -0.0267 were

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	reported for males and females, respectively, for disorders involving the immune mechanism.[9] The proportions of patients that were male/female in the TN-10 trial of teplizumab (44.68% female)[10] were then used to estimate a single weighted disutility of -0.028 for cytokine release syndrome in the model. The cost for cytokine release syndrome management was informed by the NHS costing code WJ11Z (disorders of immunity), with a day case cost of £526.65.[11] The impact of zeroing out cytokine release syndrome on the revised base case results is presented in Table 7 (comment 12).
5	**Modelling progression to stage 3 type 1 diabetes (3.9): Sanofi maintain that the log-normal distribution for teplizumab and the gamma distribution for established clinical management remain the most suitable curve fits for modelling progression to Stage 3 type 1 diabetes.** In response to the committee's request "to see further exploration of hazard functions and curve fitting to verify" the company approach, Sanofi has completed additional supportive analysis as detailed below. NICE's Decision Support Unit Technical Support Document 21[12] describes a variety of survival modelling approaches that can be used when hazard functions are complex, e.g., exhibiting several changes over time. One such approach is the use of flexible parametric survival methods incorporating splines or fractional polynomials. Splines were used to fit curves to the data from the TN-10 trial, addressing the committee's concern particularly regarding the use of an exponential model, which assumes a constant hazard, for the projections of the placebo arm. The spline models fitted are based on three possible scales: 1) log cumulative hazards (with 0 knots corresponds to a Weibull distribution, and assumes proportional hazards), 2) log survival odds (with 0 knots corresponds to a log-logistic distribution, and assumes proportional odds); or 3) log-normally distributed event times (with 0 knots corresponds to a log-normal distribution, and expresses the group effect as increase/decrease in the mean log-event time). Models with 1 or more knots can be viewed as more flexible versions of the corresponding parametric model (knots are points where different polynomial segments are joined together to form the curve; hence, increasing the number of knots allows for capturing observed changes in the hazards). Spline models may show a better fit to the data than standard models due to their flexibility, but the performance of the splines over the long term requires face validity checks. Analyses were run based on models fitted with hazard, odds, and normal scales and 0, 1, 2, and 3 knots. Results showing goodness of fit statistics for both teplizumab and placebo are shown in Figure 1 and Figure 2; these include both the standard parametric models used in the initial company submission, as well as the new fits based on flexible parametric models (splines).

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	Figure 1. Goodness of fit statistics for teplizumab using standard and flexible parametric models  AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion *Figure 2. Goodness of fit statistics for placebo using standard and flexible parametric models*

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	 AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion For teplizumab, the log-normal standard parametric projections, that were applied in the Company's original base case submission, still have the best fit based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Based on AIC, only log-normal is the best fit while spline Normal with 1 knot (normal_1 in Figure 1 above) is the second best fit. Based on BIC, only log-normal is the best fit and log-logistic is the second best fit. For placebo, the splines models show a better fit than the standard models (lower overall AIC/BIC). Spline Normal with 3 knots (normal_3 in Figure 2) is ranked as the best fit and Spline Normal with 2 knots (normal_2 in Figure 2) is the second best fit. Based on BIC, only exponential and log-normal are the best fits. Figure 3 shows a comparison between the base case projections and those projections derived from using splines. The figure shows the normal spline with 3 knots for placebo because this was the statistical model with the best fit for the placebo arm. The same flexible statistical model is used for teplizumab. The spline models, as expected, are a better visual fit to the observed data, displaying different sections that follow the observed hazards. The long-term projections are comparable between the flexible and the standard parametric models. Considering all the results for time to event projections based on both standard and flexible parametric models, we concluded we should continue using a log-normal model for teplizumab in the revised base case (in line with the original company submission), given that a log-normal model retained the best goodness-of-fit statistics. For established clinical management, we are using the gamma model in the revised base case, as suggested by the External Assessment Group. Although the gamma model did not exhibit the best goodness of fit statistics, the long-term

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	projections from the gamma model and those projections derived from the best fit model (normal spline with 3 knots) are aligned. Use of these flexible parametric models was explored in scenario analyses. One scenario was conducted using log-normal for teplizumab and the normal spline with 3 knots for established clinical management. Another scenario was conducted using the normal spline with 3 knots for both teplizumab and established clinical management. The results of these scenario analyses are presented in Table 7 (comment 12; scenarios 13 and 14). *Figure 3. Comparison of flexible and standard base case parametric projections*  LogN = log-normal; PBO = placebo; TEP = teplizumab; T1D = type 1 diabetes
6	**Approach to estimating decline in disutility (3.10): In response to the committees request that they "would like to see exploration of the rate of disutility over time in stage 3 type 1 diabetes, and how this interacts with the one-off disutility and constant disutility values applied", Sanofi have explored a new approach to estimate disutility over time in Stage 3 type 1 diabetes.** Sanofi acknowledge the committee's comments that "a time-dependent disutility was appropriate", and that Sparring (2013) is an appropriate data source that is not "double counting age-related effects on utility". Sanofi have therefore retained a time-dependent disutility utilising Sparring (2013), but adapted the rate of decline in response to the committee's comments. In the original economic model, Stage 3 type 1 diabetes disutilities increased linearly with disease duration, reflecting the increased risk for comorbidities in the long-term. The model has now been updated to use a piece-wise linear approach to capture the Stage 3 type 1 diabetes disutilities; disutilities can now change following two different decline rates. To aid the committee, the implementation has been made flexible in the model so that it is possible to define an inflexion point and two different rates of utility decline: a rate of decline that applies from Stage 3 type 1 diabetes onset and up to the inflexion point, and another rate of decline that applies after the inflexion point. For the revised base case, a lower utility decline, -0.0026 (absolute) or -0.28% (relative), is now applied through the initial 10 years of living with Stage 3 type 1 diabetes. After 10 years, the utility decline increases to -0.0028 (absolute) or -0.30% (relative). A baseline utility of 0.93 was used for the estimation of relative decline,[13] in alignment with the original submission.

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	The inflexion point at 10 years and the adjusted rates of decline were informed by additional simulation analysis using the Core Diabetes Model, to reflect the anticipated impact of hybrid closed loop systems on the long-term quality of life trajectory: • For the first 10 years, the Core Diabetes Model simulation was run with a 10-year time horizon. The analysis indicated that mean annual utility was 0.005 higher for patients using hybrid closed loops compared to those without it. • For the period beyond 10 years, the Core Diabetes Model simulation was run with an 80-year time horizon. This suggested a 0.03 higher mean annual utility for hybrid closed loop users. These utility differences were used to inform downward adjustments to the slope of the original linear decline function, reflecting the positive impact of hybrid closed loops on patient quality of life. The 10-year inflexion point was selected in alignment with the committee's statement that "complications associated with stage 3 T1D take 10 years to manifest." An exploratory scenario is also provided where the same inflexion point is used (10 years), but the utility declines are as follows: -0.0028 (absolute) or -0.23% (relative) before 10 years, and -0.0030 (absolute) or -0.25% (relative) after 10 years. The results of these scenario analyses are presented in Table 7 (comment 12; scenario 12).
7	**Carer disutility (3.11): The committee "would like to see scenarios in which disutility is halved, or absent, and also in which carer disutility ends at age 25".** Sanofi acknowledge the committee's comment that "the approach to modelling carer disutility is likely to be reasonable". In response to testimony provided by the patient expert during the committee meeting that carer "concern would not end at age 18", we have maintained our approach (-0.04 disutility) but increased the patient age from 18 years old to 25 years old in our revised base case. The impact of this change on the revised base case results is presented in Table 7 (comment 12; scenarios 8 to 11). The following adjustments to disutility have been provided as exploratory scenarios: • -0.02 disutility (halved) until age 25 • -0.04 disutility applied until age 18 • -0.02 disutility (halved) until age 18 No disutility applied has also been explored and we consider this an extreme scenario. Caregiving of children and young people with type 1 diabetes is associated with constant worry, social isolation, disruption to family life and routines and psychosocial maladjustment.[14,15] Removal of the carer disutility unreasonably suggests that carers of children and young people with type 1 diabetes experience no negative impact compared to the general population. The results of these scenario analyses are presented in Table 7 (comment 11; scenarios 8 to 11).
8	**Carer disutility (3.11): "The committee raised a concern that this disutility was not fully representative of carer disutility and may be an overestimate. This is because people in the model have a first-degree relative with type 1 diabetes."**

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	Patient population in the model We would like to clarify that, while the clinical trial population involved children with a first-degree relative with type 1 diabetes, the current appraisal represents a broader Stage 2 type 1 diabetes population, including people who do not have a first-degree relative with type 1 diabetes. Therefore, the Committee's interpretation that all carers in the model have a first-degree relative with type 1 diabetes is not applicable to this wider population. Indeed, approximately 90% of people diagnosed with type 1 diabetes do not have a first-degree relative with type 1 diabetes.[16] Application of the disutility The draft guidance states two example reasons why the committee are concerned the carer disutility may be overestimated: • "Someone could be a parent with type 1 diabetes caring for a child with type 1 diabetes, so the disutility captured is the relative effect of a parent having type 1 diabetes themselves." • "There could be multiple children in a family with type 1 diabetes, so the disutility may not be directly additive" The carer disutility of -0.04 is based upon a study published by Lopez-Bastida (2019).[17] Neither the type 1 diabetes status of the carer nor the number of children per carer is stated, therefore it cannot be known how many carer participants also had type 1 diabetes or multiple children with type 1 diabetes. Caregiver experiences and attitudes toward Stage 3 type 1 diabetes vary widely, with familiarity potentially increasing concern rather than reducing it. The study's recruitment strategy of randomly selecting centres across Spain and enrolling a representative cohort supports the inclusion of diverse carer situations, such as those with and without personal type 1 diabetes experience and varying family structures. Therefore, it is reasonable to consider that the sample reflects a broad spectrum of carer perspectives relevant to Stage 3 type 1 diabetes.
9	**Estimating costs in Stage 3 type 1 diabetes (3.12): The committee state two requests:** **1) Provision of "plausible estimates for the cost of managing Stage 3 type 1 diabetes based on a more recent data source"** **2) And "that this includes the costs and benefits of hybrid closed loop systems."** Description of the new approach Sanofi present a new approach to model increasing Stage 3 costs over time, adapting the data to include plausible estimates of hybrid closed loop impacts. The approach utilises Danish data with a follow-up of 19 years, which reflects the total healthcare cost experienced by individuals living with type 1 diabetes vs control individuals.[18] This approach addresses several concerns stated by the committee in the draft guidance: • "The committee also thought that the data used to model increasing costs for an incident population over time may not be appropriate": our new approach utilises a longitudinal study design, therefore concerns relating to applying costs from a cross-sectional prevalence study are no longer relevant. • The revised approach ensures that both the starting cost and its change over time are taken from the same data source. This removes the need to combine different datasets and helps reduce uncertainty linked to inconsistencies between sources.

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- "Although the data is based on a UK prevalent population, it is combined with modelled cost-trajectory data from an incident population in Taiwan that may not be applicable to the population seen in the NHS": our new approach utilises Danish data. Given the similarities in NICE Guidelines for Type 1 Diabetes Management[19,20] and equivalent Danish Endocrinological Society Type 1 Diabetes Guidelines[21] the Danish data is expected to be more generalisable to the UK than the original Taiwanese dataset.

An interim study summary providing additional information about the study design is provided as a supporting reference to this response.[18]

Implementation of the new approach into the model

1 Plotting the observed data
The Danish data were available as a chart (Figure 4) which was then digitized.

Figure 4. Average annual total healthcare costs (DKK) per person

DKK = Danish krone

Two adjusting factors were applied to the digitized data to estimate the equivalent costs in British pounds:

1) An exchange rate (0.099863 British pounds per Danish krone) was applied, based on purchasing power parity estimates provided by the Organisation for Economic Co-operation and Development.[22] The purchasing power parity exchange rate reported for hospital services was used given type 1 diabetes is usually managed in secondary care.
2) A factor to account for differences in health expenditures between Denmark and the UK was applied (0.95422, i.e., reflecting that costs in Denmark tend to be higher). This adjustment was also informed by data provided by the Organisation for Economic Co-operation and Development (health expenditures per person, current prices, reported in Euros).[23]

Scenarios in which the purchasing power parity exchange rate was increased and decreased by 10% were conducted, capturing potential uncertainty in exchange rates. The results of these scenario analyses are presented in Table 7 (comment 12; scenarios 2 and 3).

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2 Extrapolating the data

Given the model's lifetime time horizon, it was necessary to extrapolate costs beyond the 19 years of available observed data. Ordinary least squares regression was used to fit a polynomial equation to the data in Microsoft Excel. Given the spike in costs during the early years of living with Stage 3 type 1 diabetes, only the observations from Year 5 and onwards were used to inform the long-term projections as this is when the costs stabilised (Figure 4). Results from the regression exercise are shown in Figure 5.

Figure 5. Stage 3 type 1 diabetes cost projections

T1D = type 1 diabetes

It is important to note that:

- In the model the Stage 3 type 1 diabetes costs used are those resulting from subtracting the costs in the control group from the costs in the type 1 diabetes group. In this way only disease related costs are accounted for.
- The regression equations are only used to predict costs past 19 years from the onset of Stage 3 type 1 diabetes. Before this timepoint, the observed data are used directly.

Three Stage 3 type 1 diabetes costing scenarios were added to the model to aid the committee:

- Upper limit: corresponds to the Danish data (corrected by exchange rate and market healthcare expenditures) plus the hybrid closed loop acquisition cost
- Base case: corresponds to the Danish data (corrected by exchange rate and market healthcare expenditures), reduced accounting for the hybrid closed loop benefit on long-term care, plus the hybrid closed loop acquisition cost
- Lower limit: similar to the base case but accounting for twice the hybrid closed loop benefit on long-term care

The results of these scenario analyses are presented in Table 7 (comment 12; scenarios 4 and 5).

3 Adapting costs for hybrid closed loop

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	The acquisition costs of medical devices are not included in the Danish data set as this information is not captured in any of the Danish registers (see Section 4 of the Study Summary, provided separately).[18] In Denmark, medical devices are administered through closed regional procurement agreements, and therefore the associated costs are not publicly available. Additionally, given the infancy of hybrid closed loop availability, the Danish data set does not capture the long-term cost-impact that might be associated with their potential to reduce type 1 diabetes-associated complications. Therefore, the Danish data was further adjusted in two ways: 1) An estimated reduction in the total type 1 diabetes-related management costs was applied, and 2) Hybrid closed loop acquisition costs were added The reduction in the total type 1 diabetes-related management costs was estimated using an analysis conducted with the Core Diabetes Model v10. The model was run with baseline characteristics representing the population in the company's base case, and assuming treatment with hybrid closed loop decreases glycosylated haemoglobin (HbA1c) by 1.48% and that non-hybrid closed loop treatments will decrease glycosylated haemoglobin (HbA1c) by 0.98%.[28] This 0.5% difference between hybrid closed loop and no-hybrid closed loop was maintained for the duration of the time horizon (i.e. lifelong) and is in line with the NICE TA 943 which proposed a range between -0.23% and -0.59% depending on the comparator. Other risk factors such as body mass index, blood pressure and lipid levels are assumed not to be affected by the use of hybrid closed loop. The model reports type 1 diabetes-related management costs (excluding costs of the treatment to reduce glycosylated haemoglobin [HbA1c]) on a per annual cycle basis and these cycle costs were used to calculate a relative reduction attributable to hybrid closed loop use. Consequently, the relative reduction – applied on a cycle-by-cycle basis, was used to adjust downward the Danish type 1 diabetes-related management costs. Over the first 10 annual cycles, the Core Diabetes Model indicated that use of hybrid closed loop systems would be associated with lower type 1 diabetes-related management costs. By cycle 10 hybrid closed loop use had a lower cost profile; 89% relative to non- hybrid closed loop management costs. An 11% reduction at year 10. In later cycles, hybrid closed loop type 1 diabetes-related management costs continued to decline relative to non-hybrid closed loop cycle costs – falling to 75% at cycle 50. The adjustment to the Danish type 1 diabetes-related management costs to reflect the impact of hybrid closed loop devised was modified for sensitivity analyses in the following way: 1) Upper limit – no adjustment (i.e. the Danish costs as observed) 2) Lower limit – the Core Diabetes Model adjustment was doubled (i.e. twice the effect of hybrid closed loop on costs) Having used the Core Diabetes Model to model the potential cost-saving effect of hybrid closed loops on the Danish type 1 diabetes-related management costs, the acquisition costs of hybrid close loop devices themselves was then added. Adding these after adjustment of the Danish costs was necessary since the relative reduction estimated from the Core Diabetes Model would not logically make the device itself lower in cost. The acquisition costs for hybrid closed loop devices was taken as the average reported in the NICE guidance (TA943).[24] Whilst the value reported in

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	the guidance document was £5,684,[24] a 10% discount was nevertheless applied to this cost (£5,115.50) for the base case since it is known that the costs of these devices are subject to a confidential price arrangement. Sanofi is naturally not aware of the actual discounts in place, so two scenarios—where the discount is varied (20% and 30%)—are provided for information. The results of these scenario analyses are presented in Table 7 (comment 12; scenarios 6 and 7). The results of the revised base case are presented in Table 6 (comment 12).
10	**New data regarding Stage 2 disutility: Disease-modifying therapy availability improves health-related quality of life in Stage 2 type 1 diabetes relative to natural disease progression** Sanofi would like to present new data that has become available since the first committee meeting in relation to disutility associated with being in Stage 2 type 1 diabetes. A cross-sectional study examined health-related quality of life perceptions among [redacted] UK adults (mean age [redacted] years, [redacted] Caucasian) using the EQ-5D-5L questionnaire, comparing two groups' responses to type 1 diabetes progression scenarios.[25] While participants' baseline EQ-5D index was [redacted], those presented with a disease-modifying therapy scenario showed significantly less health-related quality of life decline when progressing to Stage 2 compared to the non-disease-modifying therapy group (reduction of [redacted]), with both groups showing further decline in Stage 3 ([redacted]). The findings demonstrate that pre-symptomatic type 1 diabetes was associated with lower health-related quality of life than the general population, with further decreases in clinical type 1 diabetes. Critically, disease-modifying therapy availability correlated with better health-related quality of life outcomes compared to natural disease progression. Therefore, Sanofi have revised the original base case to include a disutility associated with Stage 2 type 1 diabetes, but reflective of the relative benefit associated with the administration of a disease-modifying therapy (teplizumab = -[redacted]) vs no-disease-modifying therapy (established clinical management = [redacted]). Further information is supplied as a supporting reference and an abstract supplementary to this response.[25,26] The results of a scenario with no disutility applied are presented in Table 7 (comment 12; scenario 1).
11	**Company and EAG cost-effectiveness estimates (3.14):** In line with the NICE health technology evaluations manual (PMG36, 2022; updated 2025), we have included a non-reference-case scenario in which health benefits are discounted at 1.5% per annum and costs remain discounted at 3.5% per annum. NICE allows this alternative scenario to be presented where the health benefits of a technology are expected to be substantial, sustained over the long term, and reflective of a return to full or near-full health. While this scenario is not intended to replace the reference case, it offers relevant context for interpreting the potential long-term value of teplizumab. As noted in the draft guidance, although uncertain, "the clinical experts explained that short-term control of T1D can reduce the risk of complications in the long term despite diabetes progression." The scenario results are shown below (Table 4).

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Table 4. Non-reference-case scenario analysis results and impact to base case

Scenario description	Incremental Cost (£)	Incremental quality-adjusted life-years	Incremental cost-effectiveness ratio	Incremental cost-effectiveness ratio % change vs. base case
1.5% annual discount rate applied to health benefits *Base case: 3.5%*	[redacted]	[redacted]	£17,830	-29.2%

12

Company and EAG cost-effectiveness estimates (3.14): "In the company's base case, the deterministic incremental cost-effectiveness ratio (ICER) was £27,534 and the probabilistic ICER was £29,488". In response to the draft guidance, Sanofi are submitting a revised base case and simple Patient Access Scheme:

The revised base case aligns with comments 1-10 of this draft guidance response. For further information on any of the inputs/assumptions, please refer to the relevant comment. An updated cost-effectiveness model reflecting the revised base case and scenarios discussed has also been provided alongside this response. Please see below for a summary of the updated base case assumptions (Table 5), revised base case results (Table 6), and deterministic scenario analyses results (Table 7). Additionally, the impacts of specific changes to the revised base case, including zeroing out cytokine release syndrome inputs and using a single disutility decline for Stage 3 type 1 diabetes utility, are also shown in Table 7.

The list price has now been finalised and approved by the Department of Health & Social Care as [redacted] per 14-vial treatment course. In line with this revised base case, Sanofi would like to offer a revised Patient Access Scheme via a simple discount of [redacted] off the finalised list price for teplizumab. With the Patient Access Scheme, the cost of treatment is reduced to [redacted] per 14-vial treatment course.

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Table 5. Summary of revised base-case variables applied in the updated economic model

Variable	Value	Measurement of uncertainty (distribution, standard error)[a]	Source(s)
Clinical inputs			
Time to onset of Stage 3 type 1 diabetes	Log-normal distribution fitted to the teplizumab arm and gamma distribution fitted to the established clinical management arm, derived from participant-level data from the TN-10 study	*Multivariate normal (standard error from variance/covariance matrix)*	TN-10 study extended follow-up analysis[27]
Mortality for Stage 2 type 1 diabetes	UK general population life tables 2017-2018	*N/A*	ONS UK life tables
Incidence of cytokine release syndrome	4.60%	*N/A*	Integrated safety analysis[7]
Duration of cytokine release syndrome	2.5 days	*N/A*	Integrated safety analysis[7]
Utilities			
Utility estimates for Stage 2 type 1 diabetes			
Disutility vs. general population, teplizumab:[b] 0-17 years ≥18 years	 [redacted] [redacted]	*Beta*	Guenther et al. 2025[25] and study report (Sanofi Data on File)[26]
Disutility vs. general population, established clinical management:[b] 0-17 years ≥18 years	 [redacted] [redacted]	*Beta*	Guenther et al. 2025[25] and study report (Sanofi Data on File)[26]
Utility estimates for Stage 3 type 1 diabetes			
Disutility based on time from onset of Stage 3 type 1 diabetes: 10 years ≥11 years	 -0.0026 (relative: -0.28%) -0.0028 (relative: -0.30%)	*Beta*	Sparring et al. 2013[13]
Carer/parent disutility for people with Stage 3 type 1 diabetes <25 years	-0.040	*Beta*	López-Bastida et al. 2019[17]
Adverse reaction disutilities			
Cytokine release syndrome	-0.028	*Beta*	Falk Hvidberg et al. 2023[9] and TN-10 study[10]
Costs			
Teplizumab acquisition and administration cost			

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Teplizumab acquisition cost per 14-vial treatment course	[redacted] (including a simple discount of [redacted])	*N/A*	N/A
Disease management costs and healthcare resource utilisation			
Healthcare resource utilisation cost after onset of Stage 3 type 1 diabetes	Danish data (corrected by exchange rate and market healthcare expenditures), reduced accounting for the HCL benefit on long-term care, plus the HCL acquisition cost	*Gamma*	Danish cohort study (Data on File)[18] Organisation for Economic Co-operation and Development[22,23]
Adverse reaction management costs			
Cytokine release syndrome	£526.65	*Gamma*	National Schedule of NHS Costs[11] and integrated safety analysis[7]

[a] Where standard error is not reported it was assumed to be 20% of the mean value
[b] Captured using a piece-wise linear approach

Table 6. Revised base case results

Technologies	Total costs (£)	Total life-years gained	Total quality-adjusted life-years	Incremental costs (£)	Incremental life-years gained	Incremental quality-adjusted life-years	Incremental cost-effectiveness ratio vs. baseline (£/quality-adjusted life-year)	Incremental cost-effectiveness ratio incremental (£/quality-adjusted life-years)
Deterministic results								
Established clinical management	[redacted]	[redacted]	[redacted]					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£25,195
Probabilistic results								
Established clinical management	[redacted]	[redacted]	[redacted]					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£23,862

Table 7. Deterministic scenario analysis results and impact of specific changes to base case

	Scenario description	Incremental Cost (£)	Incremental quality-adjusted life-years	Incremental cost-effectiveness ratio	Incremental cost-effectiveness ratio % change vs. base case
0	Base case	[redacted]	[redacted]	£25,195	Not applicable

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	1	Stage 2 type 1 diabetes disutility vs general population = 0 *Base case uses disutilities by treatment*	[redacted]	[redacted]	£29,280	16.2%
	2	Purchasing power parity exchange rate increased by 10% *Base case = 0.0999*	[redacted]	[redacted]	£24,459	-2.9%
	3	Purchasing power parity exchange rate decreased by 10% *Base case = 0.0999*	[redacted]	[redacted]	£25,932	2.9%
	4	Stage 3 type 1 diabetes costs based on unadjusted (by hybrid closed loop benefit) Danish data *Base cases uses Danish data adjusted by hybrid closed loop benefit*	[redacted]	[redacted]	£19,770	-21.5%

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	5	Stage 3 type 1 diabetes costs based on corrected (by hybrid closed loop benefit) Danish data, doubling the hybrid closed loop benefit *Base cases uses Danish data adjusted by hybrid closed loop use*	[redacted]	[redacted]	£30,621	21.5%	
	6	Hybrid closed loop acquisition cost rebate = 20% *Base case uses 10%*	[redacted]	[redacted]	£27,668	9.8%	
	7	Hybrid closed loop acquisition cost rebate = 30% *Base case uses 10%*	[redacted]	[redacted]	£30,141	19.6%	
	8	Carer disutility = -0.02 *Base case = -0.04*	[redacted]	[redacted]	£28,510	13.2%	
	9	Age threshold for carer = 18 years *Base case = 25 years*	[redacted]	[redacted]	£28,533	13.2%	

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	10	Carer disutility = −0.02 Age threshold for carer = 18 years *Base case disutility= −0.04* *Base case threshold = 25 years*	[redacted]	[redacted]	£30,531	21.2%
	11	No carer disutility *Base case disutility= −0.04* *Base case threshold = 25 years*	[redacted]	[redacted]	£32,829	30.3%
	12	Stage 3 type 1 diabetes disutility decline: -0.23% up to year 10, -0.25% afterwards *Base case: -0.28% up to year 10, -0.30% afterwards*	[redacted]	[redacted]	£26,373	4.7%
	13	Time to stage 3 type 1 diabetes curves: log-normal for teplizumab vs normal spline 3 knots for established clinical management *Base case: log-normal for teplizumab, Gamma for established clinical management*	[redacted]	[redacted]	£26,438	4.9%

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	14	Time to stage 3 type 1 diabetes curves: normal spline 3 knots for both teplizumab and established clinical management *Base case: log-normal for teplizumab, Gamma for established clinical management*	[redacted]	[redacted]	£25,432	0.9%
	Impact of specific changes to base case					
	Cytokine release syndrome	Zeroing out cytokine release syndrome inputs from current base case	[redacted]	[redacted]	£25,155	-0.2%
	Stage 3 type 1 diabetes utility	Using single disutility decline (as per initial company submission)	[redacted]	[redacted]	£24,161	-4.1%

Insert extra rows as needed

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NICE 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]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on [insert consultation deadline]. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breakthrough T1D, the type 1 diabetes charity

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Sanofi – £82,000 for policy work unrelated to teplizumab (ongoing) Sanofi - £97,000 for information and support work unrelated to teplizumab (ongoing) Sanofi - £5,000 for consultancy on disease awareness unrelated to teplizumab (concluded)
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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1	Breakthrough T1D does not agree with the draft recommendation to not recommend teplizumab to delay the onset of stage 3 type 1 diabetes in people eight years and over with stage 2 type 1 diabetes and is concerned that NICE has not taken into account fully the effects of stage 3 type 1 diabetes on quality of life.
2	Despite advancements in technology, which has made managing type 1 diabetes (T1D) more convenient than ever before, blood glucose management is still fundamentally reliant on insulin therapy. This will always be a persistent challenge for people living with T1D, one that is characterised by physical, emotional and social burdens. Even with access to the latest technology, the reality of living with T1D is far from 'good enough'. Managing glucose levels is a burdensome, intensive and demanding experience. The physical health of those living with T1D is impacted, with often significantly higher prevalence of heart disease, kidney disease, eye damage and nerve damage.[1234] Given the mental load associated with managing T1D, burnout is also common amongst those with the condition. Ultimately, the quality of life for someone who lives with T1D but is otherwise healthy will inevitably be worse than someone that does not have T1D and is healthy in all other respects.
3	The same is true of care givers for those with T1D. As most people living with T1D are diagnosed under the age of 18, parents and care givers are often as intensely involved in managing blood glucose as the individual with the condition. This frequently presents as care givers reducing their working hours to help take on additional caring responsibilities. Indeed, in a survey of 2712 people for NPDA's First Year of Care Parent and Patient Reported Experience Measures report, 30% of care givers report that they or their partner had reduced their working hours whilst 11% said that they or their partner left employment entirely.[5] This is likely to cause additional financial strain within households. Additionally, this is often unevenly split with the mother being more likely to step back from employment. The same report highlights the impact on the carer's sleep. 74% of parents/carers report that their sleep is disrupted more than once a week due to attending to their child's diabetes health care needs. This of course not only has an impact on the quality of life of the child and the care givers but also on other children in the household as parent's attention is, by necessity, focused on the child with greater needs. There is therefore an unmet need in treating T1D. As new treatments which can modify the course of T1D become available, insulin replacement should no longer be seen as the only option for T1D. The positive impact of immunotherapies such as teplizumab in granting someone an additional few years of not being on insulin therapy cannot be overstated.
4	With regards to section 3.11 of the draft guideline, the Committee requested different caregiver scenarios. We spoke to three families who shared their experiences with us.

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	Julie has 16 year old twins with type 1 diabetes, they were diagnosed six months apart as toddlers and don't know what life is like without type 1 diabetes. Julie explained that it was not easy managing two teenagers with type 1 – she has to manage two different sets of diabetes technology, and each child has their unique circumstances, for instance, one is allergic to the adhesive in one particular pump, and the other child spent time not wanting to use technology at all, meaning Julie had to wake up numerous times a night to test their blood glucose, while still helping their twin manage their technology. Geri was diagnosed with type 1 diabetes post-pregnancy, and when her son became ill at the age of eight, she took him to the GP and discovered he was already in diabetic ketoacidosis (DKA). After a harrowing time in the hospital where she was left to get on with managing her son's newly diagnosed type 1, as she had it herself, she has found the experience isolating, and even though managing her own type 1 can be difficult, she has to be strong for her child. When she is unwell because of her type 1 diabetes, she still has to care for her child and his type 1. She never has a day off. She has found health care professionals dismissive of her family's needs, expecting her to manage as she already has the condition. Rather than making things easier, she told us that having two people with type 1 in the family meant double the hospital appointments, double the type 1 diabetes technology to manage and think about and double the worry. Roland is the father of a 20 year old with type 1 diabetes who lives at home with her parents. He explained that rather worrying about her less now she is an adult, he still has constant anxiety about his daughter when she's out by herself, particularly when she is driving. When they go away, they have to have a contingency plan, to ensure someone can check in on her in the case of a hypo or hyper. He finds the family's situation isolating – people don't understand type 1 diabetes, and he doesn't have anyone to talk to about it. He explained how helpless he feels when she is having a hypo – there is constant worry at night with sensors going off, and the experience of her diagnosis at 18 plays on his mind a lot. He described type 1 diabetes as relentless.
5	With regards to equalities, as stated above 30% of care givers report that they or their partner has reduced their working hours whilst 11% said that they or their partner left employment entirely. This is likely to cause additional financial strain within households. Additionally, this is often unevenly split with the mother being more likely to step back from employment.
6	

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.

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- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

1 Diabetes Control and Complications Trial, and Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Risk factors for cardiovascular disease in type 1 diabetes. 2016

2 Perkins, Bruce A., et al. Risk factors for kidney disease in type 1 diabetes. 2019.

3 Grauslund, Jakob. Eye complications and markers of morbidity and mortality in long-term type 1 diabetes. 2011

4 Vincent, Andrea M., et al. Diabetic neuropathy: cellular mechanisms as therapeutic targets. 2011.

5 National Paediatric Diabetes Audit. First Year of Care Parent and Patient Reported Experience Measures (PREMs) 2024.

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Diabetes (type 1, delaying stage 3 onset, 8 years and over) - teplizumab [ID6259

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 08/09/25
Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BSPED - British Society for Paedatric Endocrinology and Diabetes

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Diabetes (type 1, delaying stage 3 onset, 8 years and over) - teplizumab [ID6259

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that by not including the costs of screening and associated follow up required, this will increase equality gaps

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2	We are pleased that the committee considered that individuals/groups who historically have had higher glucose levels, lower use of diabetes technology may benefit from disease modifying therapy (RCPCH NPDA data). Without NHS access to Teplizumab, only children, young people and families able to fund treatment privately will gain from the treatment, further widening the health inequalities. The health inequalities in children with type 1 diabetes is clearly evidenced in the NPDA reports.
3	We are concerned that the recommendation implies that there are just as many individuals identified from routine clinical care as research – this is not the case. Our survey published in 2024 (PMID: 40407402) suggests that 35/124 paediatric diabetes units reported identifying children positive with IAb; of those, half of the units had children identified form clinical care and half from research; however the overall number of children identified were greater from research (n=97/145 (67%) islet autoantibody positive children came from a research setting).
4	We would like to update the committee that there is now a nationally recognised pathway for the follow up of children and young people identified with positive islet autoantibodies (Besser et al, on behalf of BSPED, Diab Medicine, in press) – available on request
5	We agree that costs of starting hybrid closed loop should be captured in the model; but starting on hybrid closed loop is imperfect with only 34% achieving a target HbA1c under 48mmol/mol or less over a 4-year period (data form CLOuD); Ware et al Diab Care 2024 PMID: 38924772

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Diabetes UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Whilst we understand the principle of using the costs associated with managing people with stage 2 type 1 diabetes as a comparator, we would suggest an alternative comparison focusing on the preventative benefits of offering this treatment and delaying the onset of stage 3 type 1 diabetes for an average of three years. Without teplizumab, people at stage 2 type 1 diabetes would progress to symptomatic stage 3 type 1 diabetes - requiring insulin therapy and technology like continuous glucose monitoring (CGM) and hybrid closed loops (HCL) - an average of three years earlier than those who'd received teplizumab. We propose that the costs of managing stage 3 type 1 diabetes for three years with no teplizumab treatment should be compared with the costs of managing stage 2 type 1 diabetes for the same period with teplizumab treatment.
2	Following the publication of NICE TA943 guidance on hybrid closed loop systems for managing type 1 diabetes, this technology has been recommended for a broad population in the UK including all children and young people aged 18 and under and people who are pregnant or planning a pregnancy. The total eligible population was estimated at 152,309 during the variation of funding period consultation during the appraisal and a phased five-year implementation developed by NHS England is underway to offer this technology widely. Latest figures at the end of the first year of implementation report that 62% of children and young people in England and Wales are using this technology, with an intention to offer it to all eligible people by the end of the five-year period. The costs of hybrid closed loop should be included in the costs of managing stage 3 type 1 diabetes and, though costs to the NHS are confidential, approximate costs for funding this technology are approximately £5,000 per year. This includes the cost of the insulin pump, consumables like tubing and a compatible CGM device. Reference: https://www.rcpch.ac.uk/resources/NPDA-dashboards

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3	We received 47 survey responses from people living with type 1 diabetes in the UK. A thematic analysis of their experience of diagnosis highlights several significant clinical and psychological challenges that could be mitigated by enabling a slower and managed progression to stage 3 type 1 diabetes. 12 respondents said they were diagnosed when in diabetic ketoacidosis (DKA) and reflected on their experience of this critical, life-threatening condition: [redacted] [redacted] Respondents were also diagnosed at various life stages, from childhood to adulthood, affecting their experiences. The impact of a diagnosis during more turbulent stages of life, such as when living away from home for the first time and at stage of transition to adulthood were key factors in a number of experiences shared with us: [redacted] [redacted]
4	47% of survey respondents said they felt "not so confident" or "not at all confident" in the first few years after diagnosis with type 1 diabetes. The reasons for this provided in free text responses highlight that type 1 diabetes is a condition that presents complex technical, practical and social challenges, such as monitoring blood glucose levels, administering and adjusting insulin doses, dietary changes, managing blood sugar highs and lows, and adapting to different situations and life stages that impact on blood sugars such as exercise, illness and puberty. Understanding the complexity of type 1 diabetes management can take years. [redacted] [redacted] Even those who felt they were well supported by their family and healthcare professionals highlight the burden of coming to terms with type 1 diabetes diagnosis in the midst of a busy life with other responsibilities.

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	[redacted]
5	Type 1 diabetes is a chronic condition that affects people over their whole life course and, though improvements in care and advances in technology have made management easier, it still requires round-the-clock self-management. Moreover, far too many people go on to develop devasting diabetes complications - such as cardiovascular disease, blindness, kidney disease and lower limb amputations – and live a shorter life because of the condition. Evidence from a range of studies undertaken across the world also report that one in four people with type 1 diabetes experience high levels of diabetes distress - the emotional distress resulting from living with diabetes and the burden of relentless daily self-management - that is likely to negatively affect how they manage their condition. The experiences of people who have lived with type 1 diabetes long-term illustrate the persistent burden of managing it, where improvements in care are often offset by evolving challenges like changes in work and family life and hormonal changes over time. [redacted] References: https://jamanetwork.com/journals/jama/fullarticle/2088852 https://www.diabetes.org.uk/for-professionals/improving-care/good-practice/psychological-care/emotional-health-professionals-guide/chapter-3-diabetes-distress
6	Being the parent or carer of someone with type 1 diabetes is an enormous challenge - one that could be eased by a treatment offering crucial extra years to prepare. We asked parents and carers of an adult or child with type 1 diabetes in the UK about their experiences in a recent survey, and 94% of respondents said they find it very or extremely challenging. Amongst the challenges described by respondents, the sudden onset of type 1 diabetes and difficulty in adjusting to the many demands it involves with little or no preparation is a key theme: [redacted] Furthermore, a number of respondents also noted how the difficulty to adjusting to relentless demands of managing type 1 diabetes was exacerbated by the unpredictability of its onset, which can negatively impact wellbeing in childhood and cause sudden physical and mental health needs that require professional support which is not always readily available.

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	[redacted]
7	The latest National Paediatric Diabetes Audit (NPDA) Patient Reported Experience Measures (PREM) report provides further insights into the negative impacts on quality of life when a child is diagnosed with type 1 diabetes. 42% of parents and carers of children aged 8-11 reported disruption to their employment in the first year after their child's diagnosis. Additionally, 47% of all parents and carers reported sleep disturbance three or more times a week due to attending to their child's diabetes health needs and 37% reported sleep disturbance because of stress related to their child's health. Reference: https://www.rcpch.ac.uk/work-we-do/clinical-audits/npda/PREM
8	The rate of people being diagnosed with type 1 diabetes in diabetic ketoacidosis (DKA) – requiring emergency care - has remained persistently high despite national campaigns to raise awareness of the symptoms of onset such as Diabetes UK's '4Ts' campaign. The 2023/24 National Paediatric Diabetes Audit reported that 26% of children and young people were diagnosed in DKA – a figure that has remained relatively unchanged or at points sharply increased during previous audit years. Studies suggest that approximately 10% of adults in the UK are diagnosed in DKA. DKA is a life-threatening complication that requires hospital admission and can be fatal. An emergency admission for DKA is estimated to cost the NHS over £2,000. The widespread use of teplizumab would reduce the number of people who experience DKA when diagnosed with type 1 diabetes and avoid people "crash-landing" into symptomatic onset of the condition. This would both help people avoid the trauma and harms of DKA and generate significant cost-savings for the NHS. References: https://www.rcpch.ac.uk/sites/default/files/2025-03/rcpch_npda_summary_report_on_2025_data_r4_0.pdf https://diabetesonthenet.com/wp-content/uploads/JDN_29-2_JDN373.pdf https://www.cprd.com/approved-studies/diabetic-ketoacidosis-dka-adults-newly-diagnosed-type-1-diabetes-t1d https://pubmed.ncbi.nlm.nih.gov/28727175/
9	The ELSA research study offers type 1 diabetes autoantibody screening to children and young people aged 3-13 years in the UK and provides further insights into the scale of the UK population with autoantibodies. It found [redacted]

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NICE 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]

Draft guidance comments form

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10	[redacted]
11	There are multiple ongoing studies offering screening for early stage type 1 diabetes autoantibodies in the UK, including ELSA, co-funded by Diabetes UK and Breakthrough T1D, and Type 1 Diabetes Risk in Adults (T1DRA). ELSA currently offers screening to children and young people aged between 3-13 years, and T1DRA to those aged 18 to 70 years. [redacted] In addition to the various research settings offering screening, a British Society of Paediatric Endocrinology and Diabetes (BSPED) survey of paediatric diabetes units (PDUs) in the UK found that nearly half (49%) of cases of people with two or more positive autoantibodies were identified outside of research settings. Respondents from 124 PDUs also reported managing a total of 145 children and young people with one or more autoantibody. Reference: https://onlinelibrary.wiley.com/doi/10.1111/dme.70069
12	We wish to clarify that type 1 diabetes is an auto-immune condition, and though it affects the metabolism it is caused by the immune system attacking insulin-producing cells.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not Applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not Applicable
Name of commentator person completing form:	[redacted]

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1	NHS England notes that committee acknowledged that there would be a potential increase in demand for ad-hoc autoantibody testing and the associated costs, if teplizumab were recommended and that this should have been captured in the model (paragraph 3.3.). NHS England has undertaken analysis to estimate the number of individuals within the identified populations who may present for autoantibody testing, along with the associated costs. This analysis is based solely on existing evidence-based sources. It is acknowledged that some cost components—particularly those linked to HRG codes for the referral stage—may not accurately reflect future costs should a new autoantibody screening programme be established and national tariffs updated accordingly. NHS England have modelled three scenarios: 1) First degree relatives (FDR)*: Proactive engagement with T1D and families. Assumes between 2&5 FDRs are tested, 30% adult and 70% child presentation. Low (2), central (2.5) and high (5) estimates considered. 2) Ad Hoc*: FDR tested population plus a % uplift to take account of ad-hoc requests for autoantibody testing or clinical concerns, 30% adult and 70% child presentation. Low, central and high estimates considered. 3) Systematic general population*: Autoantibody testing offered to general population. Lower estimate – people aged 8 to 11, central estimate – people aged 8-16, and higher estimate – people aged 8-29. *Assumes the inclusion of those patients who were identified in research studies Please note that the current modelling assumes a single autoantibody test per patient and does not account for any potential follow-up testing. A summary of the associated population estimates and costs is included below: 1) Scenario 1: First degree relatives (FDR) Low (620k patients) - £330M Central (775k patients) - £412M High (1.5M patients) - £825M 2) Scenario 2: Ad Hoc Low (1.1M patients) - £578M

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	Central (1.3M patients) - £656M High (2.1M patients) - £1.0B 3) Scenario 3: Systematic general population Low (2.8M patients) - £1.6B Central (6.2M patients) - £3.6B High (15.5M patients) - £7.1B In terms of impact on NHS testing capacity: 1) Scenario 1: First degree relatives (FDR) = ~310,000 tests. Testing capacity would need to increase 3.2 times 2) Scenario 2: Ad hoc = ~1,300,000 tests. Testing capacity would need to expand 13.6 times 3) Scenario 3: Systematic general population = ~6,270,000 tests. Testing capacity would need to expand 66 times The costs are for the testing only. The costs do not include patient identification, patient follow up and education in the event of a positive test, and ongoing treatment regimens and maintenance. The per-patient cost of autoantibody testing reflects the absence of an existing routine testing pathway within the NHS. NHS England anticipates that, over time, process efficiencies could be achieved through a review of clinical time spent on patient consultations and referrals, alongside the development of national infrastructure and optimisation of testing methods—such as online referrals and home testing options. However, at the time of this submission, there is no established evidence base to support a projected timeframe for the development and implementation of routine testing pathways, nor to estimate potential cost reductions. Note: Supporting excel spreadsheet submitted.
2	NHS England notes that committee would also like more information on how autoantibody testing would be commissioned in practice (paragraph 3.3). If teplizumab receives a positive recommendation, the establishment of a new autoantibody screening service and pathway within Integrated Care Boards (ICBs) would be necessary. This would present both affordability and capacity challenges for the NHS. Implementing such a service would require an expansion of

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<table>
<tr><td></td><td>laboratory infrastructure, alongside workforce planning to support the development and delivery of the new pathway.

The commissioning responsibility for this service would lie with ICBs. In the short term, without a formally commissioned and funded pathway, ad hoc patient presentations are likely to default to Trust-level management, placing additional resource and financial pressures on ICBs. This could lead to inconsistent approaches to care delivery and result in inequitable implementation, potentially exacerbating existing health inequalities. A funding variation is likely to be needed, in order to support implementation of a new testing and treatment pathway over time giving consideration to capacity, resource and affordability impact across the system.</td></tr>
<tr><td>3</td><td>NHS England notes that committee would like to see plausible estimates for the cost of managing stage 3 T1D based on a more recent data source that includes the costs and benefits of hybrid closed loop systems (paragraph 3.12).

NHS England would like to share current uptake data on hybrid closed loop systems for consideration by committee to further inform the costs associated with the management of stage 3 T1D.

<table>
<tr><th></th><th>0-12 years old</th><th>13-18 years old</th><th>19-25 years old</th><th>26-40 years old</th><th>41-60 years old</th><th>61-80 years old</th><th>>80 years old</th><th>All ages</th></tr>
<tr><td>Total patients</td><td>12,725</td><td>19,085</td><td>26,115</td><td>71,065</td><td>91,785</td><td>61,320</td><td>8,595</td><td>290,685</td></tr>
<tr><td>Tech usage at end of 2024/25</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hybrid Closed Loop (HCL)</td><td>68.0%</td><td>59.0%</td><td>18.1%</td><td>12.9%</td><td>9.0%</td><td>4.8%</td><td>0.9%</td><td>15.5%</td></tr>
<tr><td>Pump and CGM</td><td>4.2%</td><td>4.7%</td><td>7.1%</td><td>5.4%</td><td>4.4%</td><td>3.0%</td><td>1.3%</td><td>4.5%</td></tr>
<tr><td>Pump no CGM</td><td>0.7%</td><td>1.1%</td><td>6.9%</td><td>4.3%</td><td>3.2%</td><td>1.9%</td><td>0.6%</td><td>3.2%</td></tr>
<tr><td>CGM</td><td>23.2%</td><td>29.8%</td><td>48.3%</td><td>56.6%</td><td>59.1%</td><td>57.7%</td><td>44.0%</td><td>53.3%</td></tr>
<tr><td>No tech</td><td>2.1%</td><td>4.0%</td><td>13.5%</td><td>14.7%</td><td>18.3%</td><td>24.5%</td><td>35.5%</td><td>17.1%</td></tr>
<tr><td>Unknown</td><td>1.8%</td><td>1.3%</td><td>5.9%</td><td>6.2%</td><td>6.0%</td><td>8.2%</td><td>17.7%</td><td>6.4%</td></tr>
</table>

<table>
<tr><th></th><th>0-12 years old</th><th>13-18 years old</th><th>19-25 years old</th><th>26-40 years old</th><th>41-60 years old</th><th>61-80 years old</th><th>>80 years old</th><th>All ages</th></tr>
<tr><td>Estimated new diagnosis a year (based on 2024/25 values)</td><td>2,300</td><td>1,340</td><td>985</td><td>1,735</td><td>1,130</td><td>355</td><td>30</td><td>7,870</td></tr>
<tr><td>Proportion of new patient's eligible*</td><td>100%</td><td>100%</td><td>69%</td><td>72%</td><td>73%</td><td>70%</td><td>53%</td><td>85%</td></tr>
<tr><td>Intended HCL uptake from strategy assumptions**</td><td>90%</td><td>75%</td><td>50%</td><td>25%</td><td>20%</td><td>1%</td><td>1%</td><td>54%</td></tr>
<tr><td>Assumed annual volume starting HCL</td><td>2,070</td><td>1,005</td><td>341</td><td>311</td><td>165</td><td>2</td><td>0</td><td>3,894</td></tr>
<tr><td>Assumed rest go to CGM and manual insulin***</td><td>230</td><td>335</td><td>645</td><td>1,424</td><td>965</td><td>353</td><td>30</td><td>3,976</td></tr>
</table>

*For aged 0-18 100% are eligible, for 19 and over it is difficult to determine as do not have HbA1c measures for all, and do not track disabling hypos or if tried another tech first. For 19 and over assume those with HbA1c greater than or equal to 58mmol/mol in 2024/25 (year diagnosed) equates too eligible.
**The values for 19 and over equate to 27% when combined but have weighted higher update in younger groups. These assumptions are constrained by available funding for the 5-year strategy.
***Assume everyone who doesn't go on HCL does go on CGM and manual insulin administrating. Rationale being that most type 1 using CGM now and if started on a pump probably would be on HCL (so no need to assume a pump only group for this high-level estimates).</td></tr>
</table>

NICE National Institute for Health and Care Excellence

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	Uptake trajectories for hybrid closed loop (HCL) technology should not be assumed to follow a linear pattern, due to limitations in the availability of national funding. Once this funding is exhausted, Integrated Care Boards (ICBs) will be responsible for making local decisions regarding continued implementation and resource allocation. For example, national funding is expected to support access for approximately 30% of the adult population. The remaining 70% will require funding through local commissioning arrangements, which may result in variable uptake depending on local priorities and budgets.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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NICE 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]

Draft guidance comments form

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The West Yorkshire Integrated Care Board (ICB) and the West Yorkshire Association of Acute trusts (WYATT).

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]. West Yorskhire Integrated Care Board.

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The committee has noted the lack of a robust screening programme to identify people in stage 2 Type 1 diabetes and we agree that the national health system is not ready to take on the

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NICE National Institute for Health and Care Excellence

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	widespread use of a treatment without an adequate screening programme. There needs to be comparison of the cost effectiveness of using an expensive novel drug, or utilising health resource on regular glucose testing and education around type 1 diabetes, especially diabetic ketoacidosis. The overall costs to the health service, of a widespread screening programme, would need to be considered when weighing up whether teplizumab is cost effective or not.
3	The results from the ongoing screening for type 1 research studies in the UK - ELSA study in children and type 1 Diabetes Risk in Adults (T1DRA) study in adults, should be used to guide future practice. In particular, we need to consider the impact on people's mental health following the results of screening and readiness of health services to intervene with keeping people mentally safe following screening results.
3	We are concerned that the committee may not have fully taken into account the guidance produced and about to be published on clinical management following positive antibody screening. It has been circulated to children and young people's diabetes networks so draft copies are available. This guidance includes regular monitoring, education and psychological support. This means the comparator suggested by the company is appropriate instead of the no management suggested by the external assessment group.
4	Teplizumab has demonstrated it can delay the progression to stage 3 type 1 diabetes approximately doubling the median time to diagnosis and delaying progression up to approx.2 years. We note that the evidence is based on the results of one small clinical trial of 77 participants who were predominately white and relatives of people with stage 3 Type 1 diabetes, which may limit generalisability in the wider population. We are concerned about the widespread roll out of a drug without long term outcome data, and further data on treatment-emergent adverse events of special interest.
5	There appears to be significant uncertainty in the economic model prior to making a final decision the committee should consider the additional analysis stated in 3.15
6	We are concerned that the significant burden of living with type 1 diabetes, especially in children and young adults, hasn't been fully considered in the cost effectiveness model and there is no clear data on the impact on diabetes distress, emotional impact, stigma, mental health, injection fear, and resultant impact on education (time out for hospital appointments and admissions). More input from people with lived experience and their carer, advocates and charities is needed. The committee states in 3.16 there may be additional benefit to young people compared to the general Type 1 diabetes population, therefore we feel a separate should be performed looking at this cohort. Not offering teplizumab to cohorts which could benefit significantly could discriminate against this group.
7	As well as children and young adults, the appraisal could consider if there are other specific defined cohorts who may benefit more from treatment in future cost analysis reviews, for example people with learning difficulties or visual impairment in whom self-management with insulin may be more challenging. However, it would be important to consider gather feedback from people with diabetes and their advocates and charities, to ensure their views are considered before targeting specific cohorts.
8	We are concerned that the estimated costs of managing stage 2 T1 diabetes (the comparator) did not include hybrid closed loop therapy treatment and its associated healthcare professional cost, which is standard treatment in most paediatrics and many adults with T1 diabetes. The initial cost of initiating hybrid closed loop, as well as ongoing maintenance costs and workforce costs should be considered in the cost effectiveness analysis
9..	The Equality impact assessment – did not give special consideration to people with visual impairment (who may struggle to independently manage insulin) or children who reside in care settings, weren't considered separately. The assessment didn't consider the impact on travelling communities and other nomadic groups, where insulin supplies and storage and access to consistent healthcare can be problematic.

Insert extra rows as needed

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NICE 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]

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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)

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	Association of British Clinical Diabetologists

Comments on the DG:

My friend lives with the constant anxiety of being on the brink of Type 1 diabetes. Every meal, every decision feels like a source of worry, and so much of their energy is spent simply trying to stay well. The possibility of starting insulin therapy with its injections, carb counting, and relentless monitoring makes the future feel daunting and uncertain.

Teplizumab offers hope. It could delay that burden and give my friend valuable years of freedom before insulin becomes necessary. NICE should approve this treatment so that people like my friend can look to the future with hope rather than fear.

Name	[redacted]

Comments on the DG:

I am the partner of someone recently diagnosed with stage 2 type 1 diabetes. This stage brings a lot of uncertainty, especially not knowing when insulin will be needed. It is something that affects not only her but also our daily lives and our plans for the future.

Teplizumab could give my girlfriend valuable extra time before insulin becomes necessary. Even a delay of two years would make a real difference, giving her a better quality of life in the short term and giving us both more time to prepare emotionally and medically.

Approving teplizumab would offer meaningful hope for people at risk of type 1 diabetes and their families. It could help reduce the emotional and practical burden while also lessening the long-term impact on NHS resources by delaying progression to insulin dependence.

I strongly support the approval of teplizumab so that people like my girlfriend and their families can benefit from this treatment.

Name	[redacted]

Comments on the DG:

Type 1 Diabetes is not just medical, it's psychological. Carb counting every meal, injecting, and constant monitoring creates stress, anxiety, and risks of depression or eating disorders. NICE should consider the huge mental health benefit of delaying this burden. NICE says screening could stress the NHS, but many people with Stage 2 are already identified and waiting. They deserve access now, not rejection. Without NHS approval, only wealthy families will access teplizumab privately. That creates deep inequality in healthcare. NICE should ensure fair access for everyone. This topic concerns me as a health professional, but also as a friend of someone who has just been diagnosed with type 1 diabetes and could be accessing this kind of life changing therapy.

Name	[redacted]

Comments on the DG:

I see my friend living every day with the fear of progressing to Stage 3 Diabetes. Even now, she is constantly worrying about what to eat, how to look after herself, and what the future holds. It's exhausting to watch, and I can only imagine how much harder it will be when insulin and carb counting at every meal become unavoidable. Teplizumab could give her precious extra years before that burden — years of relief, health, and peace of mind. NICE should approve this treatment so people like my friend aren't left waiting helplessly for their health to get worse.

Name	[redacted]

Comments on the DG:

As someone already in Stage 2 Type 1 Diabetes, I am living with the knowledge that I am on a countdown to Stage 3. I know what is coming—lifelong insulin, carb counting at every meal, constant monitoring, and the risk of acute complications. Teplizumab offers the chance to delay this reality and gain precious years before being forced into a condition that consumes every part of daily life.

NICE's draft decision feels like it is taking away the possibility of a better life. The committee cites concerns about NHS pressures from screening, but people like me already exist—we are already identified, we are already waiting, and we should not be denied an intervention that has been proven to delay disease progression.

The physiological burden of living with Type 1 Diabetes is not fully captured in cost-effectiveness modelling. Having to count carbohydrates and inject insulin at every meal is exhausting, and over time increases risk of depression, anxiety, and eating disorders. It is not simply "manageable"—it is relentless. On top of this mental load, we face elevated risks of metabolic complications, cardiovascular disease, and reduced life expectancy. Delaying this for even a few years makes a profound difference to quality of life, mental health, and social participation.

I urge NICE to reconsider by:

- Recognising the real mental health toll of Stage 3 Type 1 Diabetes and how delaying onset transforms lives, not just numbers.
- Prioritising people already identified as Stage 2, who are waiting in fear of progression and deserve timely access to teplizumab.
- Exploring managed access or conditional approval rather than outright refusal, while evidence continues to grow.

I am asking NICE to look beyond the spreadsheets and see the people behind them. For me, and many others like me, teplizumab represents the difference between years of freedom and an early transition into a lifetime of clinical and psychological burden. Please don't deny us this opportunity.

Name	[redacted]
Organisation	Primary care diabetes and obesity society

Comments on the DG:

Whilst we welcome the innovation and the chance of early diagnosis and the potential to delay onset of T1D and the positive aspects of this, we in primary care and other HCPs will still utilise ELSA & T1DRA for the majority of testing and will not fully endorse wider testing without a fully commissioned pathway in place.

Name	[redacted]

Comments on the DG:

As a diabetes consultant managing patients with pre-clinical type 1 diabetes I treated the first adult in the UK under the managing access scheme. This made an unmeasurable difference to my patient. She was identified as having early type 1 diabetes in routine clinical care during pregnancy. She knows how hard the future is in terms of managing the disease with insulin as this was her life with type 1 diabetes during pregnancy. After delivery the natural reduction in insulin resistance meant she could stop insulin treatment, but she will inevitably need it in due course. She said to me "any extra time without insulin would be a blessing as i know what is in store and how much insulin treatment will impact my life". Whilst 2-3 years of insulin may not feel much it is massive to my patients. Additionally, this is the start of a new world. Having Teplizumab treatment would drive the development of strategies to find individuals to benefit which in turn would drive further drug discovery. We all want to stop type 1 diabetes developing but we wont get there in one step it needs to be stages. We are a long way behind other specialties using immunotherapies in autoimmune diseases (inflammatory bowel disease, rheumatoid arthritis etc). But theirs have symptomatic early stages. This is a unique situation where we need to define an entirely new asymptomatic patient group to allow us to improve type 1 diabetes care. Having the option of a proven therapy available on the NHS will be a massively positive step towards making this a reality for our future patients.

Name	[redacted]
Organisation	Association of British Clinical Diabetologists

Comments on the DG:

There is a desperate need from parents of children identified with early T1D for teplizumab therapy. This decision by NICE will go against this need, and create an unequal market with inequitable access.

We have undertaken qualitative work with families identified through the ELSA screening programme who are eligible for therapy (reference below). Some quotations from families are below.

Quotation 1:
“It is, it's really frustrating to be honest. I think we spoke didn't we and said it was available in America for £200 000? And it's so frustrating that we don't have that sort of funds available to be able to get something like that, and it's just so frustrating that something that is available there isn't available here yet, something that can delay the onset of it as well, and it is it's frustrating and upsetting to be honest.” A1, Mother of an 8 year old girl

Quotation 2:

“I was prepared to travel to the US if I had to, to get involved in these studies if it wasn't going to be in the UK
and stuff like that. So there's I remember articulating it as I'm just prepared to do anything right now, just to help in whatever way is possible in terms of making this an easier transition for him.” A7, Mother and Father of a 9 year old boy

Reference:
Quinn LM, Boiko O, Elliott J, Randell M, Litchfield I, Boardman F, Dias RP, Greenfield SM, Narendran P. Treatment acceptability for disease-modifying therapy for type 1 diabetes (T1D)-Views from parents of children with presymptomatic T1D. Diabetes Obes Metab. 2025 Oct;27(10):6059-6067. doi: 10.1111/dom.16639. Epub 2025 Jul 23.

2. The mean 2-3 year delay that follows treatment is very meaningful for patients. Qualitative research undertaken by ourselves has demonstrated this clearly.

Quote 1:
“If you have diabetes or you're a caregiver with somebody… for somebody with diabetes, three years is a lifetime, especially in terms of getting all the mechanisms in place to deal with it. You're not rushing through trying to get pumps and your medication, and furniture, whatever. So three years is huge, it really is.” A4, Father of an 8 year old boy

Quote 2:
Absolutely, because as I said it could be a gateway to a further treatment, if we can keep her at stage two, and then they make another amazing development that… got to take any opportunity I think that is offered.” A2, Mother of a 10 year old girl.

Reference
Quinn LM, Boiko O, Elliott J, Randell M, Litchfield I, Boardman F, Dias RP, Greenfield SM, Narendran P. Treatment acceptability for disease-modifying therapy for type 1 diabetes (T1D)-Views from parents of children with presymptomatic T1D. Diabetes Obes Metab. 2025 Oct;27(10):6059-6067. doi: 10.1111/dom.16639. Epub 2025 Jul 23. PMID: 40698578; PMCID: PMC12409228.

3. Some research suggests that health care professionals are likely to increase screening of first degree relatives if disease modifying therapy becomes available (Reference below). However the uplift in screening is highly unlikely to be significant until and unless there is a structured screening programme embedded into NHS healthcare because:

- organising tests for patients not under the care of the health care physician organising the test (i.e. relatives of the index patient) is not permissible and will need the development of a pathway

- first degree relatives account for a minority (only 15%) of the total T1D population

- in this population of relatives, a very small population will be screened positive (3% of first degree relatives, 2% of second degree relatives)

Reference
Quinn LM, Narendran P, Randell MJ, Bhavra K, Boardman F, Greenfield SM, Litchfield I. General population screening for paediatric type 1 diabetes-A qualitative study of UK professional stakeholders. Diabet Med. 2023 Oct;40(10):e15131. doi: 10.1111/dme.15131. Epub 2023 May 25.

4. Currently, people with early T1D are identified through research programmes such as ELSA and T1DRA, and this is likely to be a primary route until a formal screening programme is established in the UK.

Preliminary results from the ELSA study demonstrate that screening processes are generally feasible and acceptable. Please find a summary of these results below, courtesy of ELSA study team, unpublished results.

Between November 2022–2024, 24,875 children were recruited; 17,283 valid dried blood spot (DBS) samples were analysed; median age 8 years (IQR 5–10); 51.61% male; White (80.96%); 18.26% minority ethnic backgrounds; 32.47% with a family history of T1D, with greater equity through community-screening approaches. In total, 308 (1.78%) screened positive, including 160 (0.93%) with multiple autoantibodies and 75 with a single autoantibody (0.43%). Of 151 children staged, 69.54% were stage 1, 20.53% stage 2 and 4.64% stage 3. The screening model appeared feasible (90.91% of families completed confirmatory testing, 94.97% completed staging and 84.26% attended follow-up education) as well as acceptable (98% of families rated the experience positively).

THE FULL RESULTS OF THE ELSA STUDY CAN BE MADE AVAILABLE IF USEFUL FOR THE NICE CONSULTATION. PLEASE LET US KNOW.

5. We are not aware of any evidence that the natural history of T1D is different in people with and without relatives with this condition. Therefore we would not expect a different treatment response in people without relatives with T1D.

6. Interviews with families suggest that families are able to manage the 14days of treatment for the expected gain in years without the need for insulin treatment.

Quote 1:
I'm just prepared to do anything right now, just to help in whatever way is possible in terms of making this an easier transition for him. A7, Mother and Father of a 9 year old boy with stage 2 T1D

Reference:
Quinn LM, Boiko O, Elliott J, Randell M, Litchfield I, Boardman F, Dias RP, Greenfield SM, Narendran P. Treatment acceptability for disease-modifying therapy for type 1 diabetes (T1D)-Views from parents of children with presymptomatic T1D. Diabetes Obes Metab. 2025 Oct;27(10):6059-6067. doi: 10.1111/dom.16639. Epub 2025 Jul 23. PMID: 40698578; PMCID: PMC12409228.

Name	[redacted]

Comments on the DG:
I highly anticipate initiating this treatment to potentially delaying patients progressing to stage 3 type 1 diabetes would be life changing. The quality of life this could provide this patient group I am in support of, I hope this can be NICE recommended.

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

Kidney.Research.UK.response.to.Draft.consultation.document.

The duration of type 1 diabetes (T1D) is associated with an increased risk of acute kidney injury (AKI) and kidney disease. One study [Cumulative Kidney Complication Risk by 50 Years of Type 1 Diabetes: The Effects of Sex, Age, and Calendar Year at Onset - PMC] found that after 50 years of having T1D, some 60% of patients have end stage renal disease (ESRD); 72% have macroalbuminuria and 88% have microalbuminuria.

With modern management increasing T1D patient longevity, it is estimated almost everyone with T1D may develop impaired kidney function, to a greater or lesser degree [Kidney Disease: The Forgotten Legacy of Type 1 Diabetes | Diabetes Care | American Diabetes Association].

Kidney Research UK calls for tighter control and management of T1D in patients to prevent the onset of pathophysiological changes and protect kidneys in this vulnerable population.

We believe that any interventions that delay the clinical onset of T1D in paediatric populations, including teplizumab, may significantly preserve long-term cardiometabolic health [see recent results from a retrospective study presented at the American Diabetes Association's (ADA) 85th Scientific Sessions in Chicago from Delayed T1D Onset Linked to Lower CV, Renal Risks]

It is also important that urine albumin-to-creatinine ratio (uACR) testing and renal follow-up is continued in this T1D patient population to fully understand any renal benefits of teplizumab and to delay the onset of kidney damage and potentially chronic kidney disease (CKD).

The health economic benefits of screening for T1D include preventing diabetic ketoacidosis (DKA) and associated acute, vascular and kidney complications, as well as hospitalisation at clinical diagnosis [Health economic considerations of screening for early type 1 diabetes - PMC].

The potential benefits of teplizumab should therefore be considered in the context of cost savings from delaying the development of diabetic kidney disease. These savings would not only be economical (based on the high costs of dialysis for patients in end-stage renal failure – estimated to be £34,000 per patient per year [Economics-of-Kidney-Disease-summary-report_accessible.pdf]) but also in quality of live for T1D patients who may be able to avoid the gruelling nature of dialysis and ESRD.

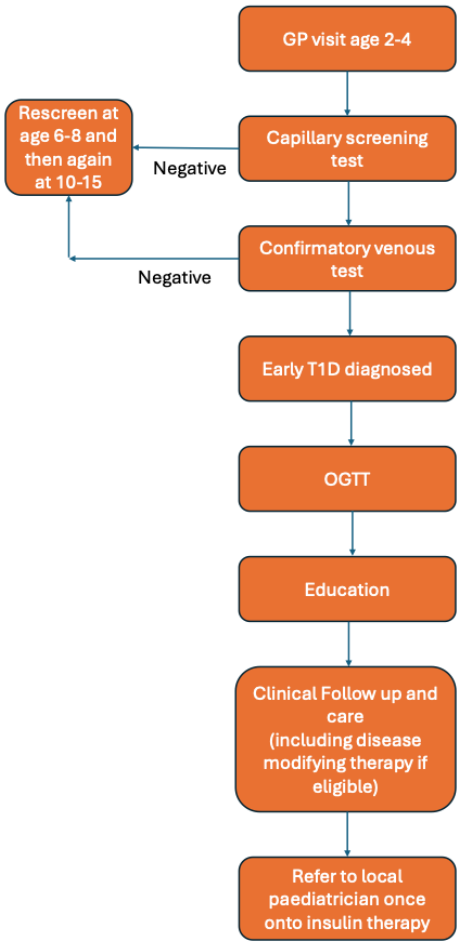
Proposed 5-year plan for screening, follow up and treatment of early T1D in children

Early detection of T1D, before insulin treatment is required, offers significant benefits including improved long-term glucose control, preparation time for insulin therapy, and a reduced risk of diabetic emergencies like diabetic ketoacidosis. Furthermore, the advent of disease modifying therapies to delay the need for insulin makes it crucial to identify T1D at these presymptomatic stages.

Teplizumab is the first licensed disease-modifying therapy for people with early-stage T1D. It reduces by half the rate of progression to insulin dependence. The UK is the first country in Europe to make this treatment available, providing a unique opportunity to deliver substantial benefits for our patients. This plan outlines how the NHS could identify, support and treat this population.

Family Screening

Initial efforts will focus on first-degree relatives (FDRs) of people with T1D. Screening begins with a finger-prick blood test for islet antibodies at their GP, followed by confirmatory venous testing and glucose assessment at regional centres. FDR screening is expected to identify ~15% of the early T1D population and will allow the NHS to test and refine systems before wider rollout. Screening will take place at ages 2–4, and then again at 6–8, and 10–15 years. Children who have never been tested should join the schedule at the earliest opportunity.



Follow-Up and Care

Regional centres will provide specialist follow-up for children and adults identified with early T1D. Care will be guided by national recommendations, with audit and feedback to ensure best practice is shared and clinics are optimised. Broadly, current guidelines suggest 3-6 monthly follow up in secondary care paediatric centres, with education, testing for HbA1c and provision of glucose monitoring equipment for a sub-population. These pathways have been published.

Treatment Pathway

Individuals eligible for teplizumab will be treated in regional centres in line with national guidelines and managed there until insulin is required. Once insulin therapy is started, care will be transferred back to local secondary care T1D teams for long-term management and support.

THE FUTURE

General Population Screening

After learning from FDR screening over the first 5 years, testing will expand to second degree relatives and those with other autoimmune diseases. This will then roll out to the general

population. We propose GP-led screening, which the ELSA study has shown to be equitable, engaging families across socio-economic and ethnic backgrounds. Screening will continue to take place at ages 2–4, 6–8, and 10–15 years. Children who have never been tested should join the schedule at the earliest opportunity.

Assumptions for FDR screening and monitoring -also see Excel sheet

Assumptions:
24,500 children with T1D in England
2 FDRs per index case of which half are under age 16
Therefore, need to test 24,500 children

Testing 24,500 children will identify:
680 children with stage 1
181 children with stage 2
102 will also move from stage 1 to 2 every year – total 408 over the 5 years

Monitoring as per international guidelines:
Stage 2 will need 4 visits per year to secondary care over 5 years
Stage 1 will need 2 visits per year to secondary care over 5 years

Treatment assumptions:
Half will be over the age of 8
Half of these will be treated
Teplizumab will be at cost price with no patient access scheme (i.e. full cost)

Total costs over 5 years:
Screening FDRs)including rescreening those initially testing negative): £1.7M
Monitoring those with early T1D for 5 years: £4M
Treating those identified at stage 2 (including those that move from stage 1 to 2 over the 5 years): £78M

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]

Draft guidance company response EAG critique

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. EAG critique of company response to the draft guidance

The following is the EAG critique of the company response to the draft guidance (DG).[1, 2]

1.1 Comment 1: Treatment pathway (3.2): Sanofi consider that the language in section 3.2 confuses the infrastructure required for teplizumab infusion with requirements for the wider pre-symptomatic type 1 diabetes pathway.

The company states:[1] *"When considering the treatment pathway for teplizumab in Stage 2 type 1 diabetes, it is important to separate the resources that are required for administering teplizumab from the wider management of pre-symptomatic type 1 (Stage 1 and Stage 2) diabetes (independent of immunotherapy)."*

With regards to the costs that should be included in the economic model, the company identities:[1] *"We request that discussion of the treatment pathway by the committee focuses on the pathway associated with teplizumab treatment, rather than being conflated with the wider pre-symptomatic type 1 diabetes pathway"* This means that only costs associated with the administration (infusion) of teplizumab need to be included.

EAG comment: The DG states the following:[2] *"The consideration of a national screening programme is outside the committee's remit, so it agreed the costs of a national screening programme should not be included in the model. But it decided that the potential increase in demand for ad-hoc autoantibody testing and the associated costs, if teplizumab were recommended, should have been captured in the model."* This is discussed further in Comment 2, and is in accordance with the EAG recommendation that the cost of testing should be included.

1.2 Comment 2: Identifying the eligible population for teplizumab (3.3): "It [the committee] decided that the potential increase in demand for ad-hoc autoantibody testing and the associated costs, if teplizumab were recommended, should have been captured in the model". Sanofi is concerned that it would be inappropriate to capture these costs in the model.

The company argue that the cost of autoantibody testing should not be in included, stating:[1] *"Any additional costs related to patient identification should be considered as occurring prior to, or 'upstream of', the point at which individuals are included in the model, and would therefore apply equally to both the teplizumab arm and the established clinical management arm."*

EAG comment: The EAG continue to make the point that established clinical management does not include autoantibody testing for all patients who might be identified should teplizumab be recommended, unless the means of identification does not change (see Comment 3 as to the company's view as to how the number of patients tested might increase).

1.3 Comment 3: Identifying the eligible population for teplizumab (3.3): "The committee also decided that the lack of data on the size and composition of the population eligible for teplizumab was a significant uncertainty. It concluded that it needed more information on the number of people in each of the identified

populations that might present for autoantibody testing." Sanofi have sought additional clarification:

The company stated that they convened an Advisory Board to seek information on the following:[1] *"…four distinct populations defined in the draft guidance that may be tested and subsequently identified as having Stage 2 type 1 diabetes"* With the approval of teplizumab, they anticipated the following changes in these populations:

- Those identified in research studies: "modest increase"
- Those tested due to clinical concern about hypoglycaemia: no increase given that they are diagnosed incidentally.
- Those who have a first-degree relative with type 1 diabetes: "mild to moderate increase"
- Those requesting testing: mostly first-degree relatives with type 1 diabetes

The company then cited an ongoing study started in 2025, which is a collaboration between the company and University Hospitals of Morecombe Bay NHS Foundation Trust, which shows a:[1] "[redacted]"

Following this, the company then presented a scenario to estimate the budget impact of a "mild to moderate" increase in the number of first-degree relatives tested if teplizumab was approved.[1] This is based on estimates of the numbers of both incident and prevalent type 1 diabetes patients, an assumption of two first-degree relatives to be tested per patient, and four possible levels of percentage uptake ([redacted]).

EAG comment: The EAG would agree that the largest increase in uptake would probably be in the first-degree relatives of those with type 1 diabetes. However, there might be a substantial increase in those detected via research studies of by those requesting testing without a first-degree relative.

The EAG also notes that NHS England (NHSE) submitted a response to the DG, which also provides estimates of testing costs if teplizumab was recommended by NICE, for the following scenarios:[3]

1) First degree relatives (FDR)*: Proactive engagement with T1D and families. Assumes between 2&5 FDRs are tested, 30% adult and 70% child presentation. Low (2), central (2.5) and high (5) estimates considered.
2) Ad Hoc*: FDR tested population plus a % uplift to take account of ad-hoc requests for autoantibody testing or clinical concerns, 30% adult and 70% child presentation. Low, central and high estimates considered.
3) Systematic general population*: Autoantibody testing offered to general population. Lower estimate – people aged 8 to 11, central estimate – people aged 8-16, and higher estimate – people aged 8-29.

*Assumes the inclusion of those patients who were identified in research studies

(1) seems to align with the company's scenario (see above). (2) seems to overlap with those tested due to a clinical concern, with the addition of "ad-hoc request". (3) seems to be effectively population screening, which the DG stated was not applicable to this technology appraisal. NHSE also present an

Excel workbook with details as to the cost calculations, including the total number of FDG relatives that would be tested in Scenario 1. The table below shows a comparison between the company and NHSE data/assumptions.

Table 1.1: Parameters to calculate total number tested autoantibodies in England

	NHSE		Company	
Parameter	**Estimate**	**Source**	**Estimate**	**Source**
Adults with T1DM	276,750	NHS Digital 2025	N/A	N/A
Children with T1DM	38,787		N/A	N/A
Patients with T1DM	310,187**		280,401*	NHS digital 2023
People presenting (low value) per patient with FDR	2	Assumption	2	Assumption
People presenting (high value) per patient with FDR	5		N/A	
People presenting (central) per patient with FDR	2.5		N/A	
Proportion of people presenting (adults)	30%		[redacted]	
Proportion of people presenting (children)	70%			
Proportion of people who are aged 8 and over	N/A	N/A	91%	Office for National Statistics
Source: company response to the draft guidance, and submission from NHS England.[3] *Based on sum of incident and prevalent population. **Unclear why this is not the sum of adults and children, which is 315,537.				

Note that the NHSE calculations omit the 91% who are aged 8 and over. They also include higher numbers for all other inputs, that for number of people with T1DM most likely due to a more recent data source (2025 vs. 2023), but they also assume a greater uptake (minimum of 30% as opposed to [redacted]).

It is beyond the remit of the EAG to comment any further on the budget impact. However, the EAG notes that any change to how those with Stage 2 type 1 diabetes are identified for treatment with teplizumab implies an increase in the cost per patient treated with teplizumab. The size of the increase will depend on the proportion of those tested who would have stage 2 T1D, which the DG reports to vary between 1 in 10 to 20 in FDRs to 1 in 300 to 400 in the general population.[2]

1.4 Comment 4: Adverse events (3.7): In response to the committee's request that "The costs of cytokine release syndrome should be included in the teplizumab arm of the model, in line with the incidence rate of 5.8% from the integrated safety analysis", this has been considered in the revised cost-effectiveness model.

The company explained that the 5.8% incidence rate that the committee refers to is the incidence rate of cytokine release syndrome (CRS) for patients receiving teplizumab in the integrated safety analysis of five clinical trials of teplizumab.[4] The same analysis indicated that CRS was reported in 1.2% of

patients receiving control, and since the company's economic model captures the excess risk of adverse events occurring, 4.6% CRS was assumed for teplizumab. CRS events resolved within 2 to 3 days from onset in the integrated safety analysis; thus, a duration of 2.5 days was assumed by the company. The utility decrement applied for CRS was informed by Hvidberg et al. 2023.[5] Values of -0.0288 and -0.0267 were reported for males and females, respectively, for disorders involving the immune mechanism. A weighted disutility of -0.028 for CRS was calculated based on the male/female proportion in the TN-10 trial (44.68% female).[6] Finally, the cost for CRS management was informed by the NHS costing code WJ11Z (disorders of immunity), with a day case cost of £526.65.[7]

EAG comment: The EAG agrees with the company's approach and would like to point out that the model results are not sensitive to changes in CRS-related parameters – changes in percentage CRS, duration, costs or utility decrements lead to minimal changes to the ICER.

1.5 Comment 5: Modelling progression to stage 3 type 1 diabetes (3.9): Sanofi maintain that the log-normal distribution for teplizumab and the gamma distribution for established clinical management remain the most suitable curve fits for modelling progression to Stage 3 type 1 diabetes.

The company used flexible parametric survival methods incorporating splines to fit curves to the data from the TN-10 trial, addressing the committee's concerns particularly regarding the use of an exponential model, which assumes a constant hazard, for the placebo arm.

Models with 1 or more knots can be viewed as more flexible versions of the corresponding parametric model, may show a better fit to the data than standard models, but the performance of the splines over the long term requires face validity checks.

Analyses were run based on models fitted with hazard, odds, and normal scales and 0, 1, 2, and 3 knots. Results showing goodness of fit statistics indicated that for teplizumab, the log-normal standard parametric distribution, that were applied in the company's original base case submission, still has the best fit based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Based on AIC, log-normal was the best fit, while spline Normal with 1 knot was the second-best. Based on BIC, log-normal was the best fit and log-logistic was the second-best. For placebo, the splines models showed a better fit than the standard models (lower overall AIC/BIC). Spline Normal with 3 knots was ranked as the best fit and Spline Normal with 2 knots was the second-best. Based on BIC, only exponential and log-normal were the best fits.

Considering all the original and new analyses, the company concluded that a log-normal model for teplizumab is still appropriate (in line with the original company submission), given that a log-normal model retained the best goodness-of-fit statistics. For established clinical management, the company assumed a gamma distribution in their revised base-case, indicating that although the gamma model did not exhibit the best goodness of fit statistics, the long-term projections from the gamma model and those projections derived from the best fit model were aligned. Assuming flexible parametric models was explored by the company in scenario analyses.

EAG comment: The EAG would like to thank the company for the additional analyses conducted, even though it is unclear why these were based on models fitted with hazard, odds, and normal scales and 0, 1, 2, and 3 knots. The selection of the number of knots for example seems not properly justified.

The EAG still maintains that most of the concerns highlighted in the EAG report are not resolved:

- The company still assumed different types of parametric distributions for the intervention and comparator arms (log-normal for teplizumab and gamma for ECM), which in general is not recommended. The EAG prefers the same type of parametric distributions for both treatment arms.
- While the company emphasised the choice of the log-normal distribution based on the best goodness of fit, the company is missing to report that the difference in goodness of fit statistics for many of the distributions is minor (e.g., less than 2 AIC points). This means that in practice AIC or BIC cannot really be used to discriminate between distributions.
- The EAG previously suggested using additional data and/or clearer and more detailed elicitation of expert opinion to validate long-term projections. Since these have not been provided, the EAG still considers that there is uncertainty about the long-term effects assumed for teplizumab and prefers a more conservative approach for long-term extrapolations (e.g., a gamma distribution for both arms), noting that the choice of parametric distribution can still have a major impact on the model results.

On another point, the option to select spline extrapolations in the economic model does not seem to work properly (or the EAG is not able to select the right settings).

1.6 Comment 6: Approach to estimating decline in disutility (3.10): In response to the committees request that they "would like to see exploration of the rate of disutility over time in stage 3 type 1 diabetes, and how this interacts with the one-off disutility and constant disutility values applied", Sanofi have explored a new approach to estimate disutility over time in Stage 3 type 1 diabetes.

In line with the committee's comments that "a time-dependent disutility was appropriate", and that Sparring 2013 is an appropriate data source that is not "double counting age-related effects on utility",[8] the company retained a time-dependent disutility from Sparring 2013 but adapted the rate of decline as described below.

In the original model, Stage 3 T1D disutilities increased linearly with disease duration, to reflect the increased risk for comorbidities for these patients. The economic model has been updated to use a piece-wise linear approach where two different utility decline rates can be selected: it is possible to define an inflexion point and the two different rates (before and after the inflexion point) of utility decline.

The company assumed a lower utility decline, -0.0026 (absolute) or -0.28% (relative), through the initial 10 years of living with Stage 3 T1D. Afterwards, the utility decline increases to -0.0028 (absolute) or -0.30% (relative). A baseline utility of 0.93 was used for the estimation of relative decline, in line with the original submission.[8]

The selection of an inflexion point at year 10 and the utility decline rates were informed by a simulation analysis conducted using the Core Diabetes Model, to reflect the anticipated impact of hybrid closed loop systems on the long-term quality of life trajectory:

- For the first 10 years, the simulation was run with a 10-year time horizon. The analysis indicated that mean annual utility was 0.005 higher for patients using hybrid closed loops compared to those without it.
- For the period beyond 10 years, the simulation was run with an 80-year time horizon. This indicated a 0.03 higher mean annual utility for hybrid closed loop users.

The company indicated that these utility differences were used to inform downward adjustments to the slope of the original linear decline function, reflecting the positive impact of hybrid closed loops on patient quality of life.

The 10-year inflexion point was selected in line with the committee's statement that "*complications associated with stage 3 T1D take 10 years to manifest*".[2]

The company conducted an exploratory scenario where the same inflexion point was used (10 years), but the utility declines were changed as follows: -0.0028 (absolute) or -0.23% (relative) before 10 years, and -0.0030 (absolute) or -0.25% (relative) after 10 years. This scenario had a minor impact on the model results.

EAG comment: The company's updated approach is more flexible than original approach and it seems to be in line with Committee's requests. However, the EAG is unclear how the utility decline rates were calculated. This is important because changes in these rates can have moderate/major impact on the model results. Changing the inflexion point has minimal impact on results.

1.7 Comment 7: Carer disutility (3.11): The committee "would like to see scenarios in which disutility is halved, or absent, and also in which carer disutility ends at age 25".

Based on the testimony provided by the patient expert during the committee meeting that carer "concern would not end at age 18", the company still apply the same utility decrement as in the original submission (-0.04) but increased the patient age from 18 years old to 25 years old in their revised base case. This change resulted in an ICER decreased by approximately 12%.

In addition, the company explored the following scenarios:

- -0.02 disutility (halved) until age 25 (ICER increased by 13.2%)
- -0.04 disutility applied until age 18 (ICER increased by 13.2%)
- -0.02 disutility (halved) until age 18 (ICER increased by 21.2%)
- No caregiver disutility - considered an extreme scenario (ICER increased by 30.3%).

EAG comment: The company's additional analyses illustrated the remaining uncertainty, and the impact on the model results, around assumptions about caregiver disutilities. The age threshold to which the caregiver disutility applies still seems arbitrary. However, the EAG cannot select a preferred threshold since this would also be arbitrary.

The EAG is still unsure about the following:

- If the caregiving burden is higher in younger patients, the disutility assumed (-0.04) might be high given that the model population is 13.58 years at the start.
- 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. Assuming disutility to one caregiver increased the ICER by 11.2%.

The results of the scenario analyses conducted by the company indicated that the model was also sensitive to changes in these assumptions.

1.8 Comment 8: Carer disutility (3.11): "The committee raised a concern that this disutility was not fully representative of carer disutility and may be an overestimate. This is because people in the model have a first-degree relative with type 1 diabetes."

First, the company explained that while all participants in TN-10 were children with a first-degree relative with Stage 3 T1D, the current appraisal represents a broader Stage 2 T1D, including people who do not have a first-degree relative with Stage 3 T1D. Therefore, the company considers that the Committee's interpretation that all carers in the model have a first-degree relative with Stage 3 T1D is not applicable to this wider population. The company further referred to Sims et al. 2022 to indicate that approximately 90% of people diagnosed with T1D do not have a first-degree relative with T1D.[9]

Furthermore, regarding the following reasons why the Committee were concerned the carer disutility may be overestimated:

- "*Someone could be a parent with type 1 diabetes caring for a child with type 1 diabetes, so the disutility captured is the relative effect of a parent having type 1 diabetes themselves*".
- "*There could be multiple children in a family with type 1 diabetes, so the disutility may not be directly additive*".

The company indicated the following:

- The carer disutility of -0.04 was sourced from Lopez-Bastida et al. 2019.[10] In that study the type 1 diabetes status of the carer nor the number of children per carer is reported. Therefore, it is unknown how many caregivers also had type 1 diabetes or multiple children with type 1 diabetes.
- Caregiver experiences and attitudes toward Stage 3 type 1 diabetes can vary widely, with familiarity potentially increasing concern rather than reducing it. The study's recruitment strategy of randomly selecting centres across Spain and enrolling a representative cohort supports the inclusion of diverse carer situations. Therefore, the company consider it reasonable to assume that the sample reflects a broad spectrum of carer perspectives relevant to Stage 3 type 1 diabetes.

EAG comment: The company concluded that their approach is appropriate. The EAG acknowledges the uncertainty around this point, but with the current evidence it is not possible to select an alternative preferred assumption. For further details on caregiver disutility, we refer to Comment 7.

1.9 Comment 9: Estimating costs in Stage 3 type 1 diabetes (3.12): The committee state two requests:

- ***Provision of "plausible estimates for the cost of managing Stage 3 type 1 diabetes based on a more recent data source"***

- ***And "that this includes the costs and benefits of hybrid closed loop systems."***

The company proposed an entirely new approach to estimating costs of stage 3 T1D over time compared to the original submission. In the original submission, the company used data from Hex et al. 2024 to estimate initial costs of being diagnosed with stage 3 T1D,[11] and then extended this over time based on fitting regression models to cost trajectories from Taiwan provided by Ou et al. 2016.[12] The EAG considered this approach inappropriate as it led to a large overestimation of stage 3 T1D costs over

time, unduly favouring teplizumab. The main issue was that the Hex et al. 2024 estimate of monthly costs was based on the prevalent UK population and not the incident population as assumed in the company's modelling. The EAG considered Hex et al. 2024 to provide the most robust estimate of stage 3 T1D costs but it was not used appropriately in the model. In addition, the committee were concerned that the current approach did not include the costs and benefits from hybrid closed loop (HCL) systems which were recommended by NICE in 2023.[13]

The company provided updated estimates of stage 3 T1D costs over time including costs from the use of hybrid closed loop systems. They first estimated costs of managing stage 3 T1D using data from the national Danish registers. A case control study containing [redacted] cases (patients diagnosed with stage 3 T1D) and [redacted] controls. Costs were observed for up to 19 years after diagnosis. Patients were matched using a combination of exact matching and nearest neighbour matching with a 1:3 ratio. For the base case estimates patients were matched on age, sex, region of residence, presence of comorbidities, income and educational level at baseline. For patients aged less than 18 years at diagnoses the income and educational level of their parents was used. Observed costs for cases and controls were then converted to UK pounds using the OECD exchange rate from Danish krone to pounds of 0.099863, and a factor reflecting higher expenditure on healthcare in Denmark of 0.95422.[14, 15]

Once costs were converted to UK pounds, linear regression models including a quadratic term were applied to the data between years 5 and 19 to extrapolate beyond 19 years. Figure 1.1 shows the observed costs against the fitted models. The observed data was used in the economic model up to 19 years after which the regression-modelled cost estimates were used. Costs of managing stage 3 T1D were estimated by subtracting the estimated costs for controls from the costs among cases.

Figure 1.1: Average annual total healthcare costs (DKK) per person

Based on Figure 4 in the company's comments on Draft Guidance.[1]
DKK = Danish krone; KM = Kaplan-Meier; T1D = type 1 diabetes

The costs estimated from the Danish national registers did not include direct or indirect costs of HCL systems. To include these in the model the company performed simulations using the Core Diabetes Model v10. The model reports T1D-related management costs (excluding the costs of treatment to reduce HbA1c). To simulate the impact of HCL systems the company ran the model using the baseline characteristics of the population in the base case and assumed that HCL decreases HbA1c by 1.48% compared to 0.98% for non-hybrid closed loop systems, giving a difference of 0.5%. This was

considered in line with NICE TA943, which proposed a range of 0.23% to 0.59% depending on the comparator.[13] This difference is assumed to remain constant over a 50-year period. The company calculated the relative net reduction in costs of T1D management and applied this to the estimated costs from the Danish national registers. In addition, the company added the device costs for HCL systems. The company assumed a 10% price discount on the average reported price in the NICE TA943 guidance of £5,684 giving £5,115.50.[13] The company applied 100% eligibility and uptake to model the upper estimate of effectiveness for HCL. Applying it this way ensures HCL has the maximally 'cost-offsetting' benefit on long-term Stage 3 costs (i.e., by reducing long term outcomes maximally). The company explained that they did not seek to capture a mix of HCL and non-HCL uptake, which would be too complex and open to false precision. This is in line with modelling approach taken for the NICE HCL appraisal (TA943).

Probabilistic sensitivity analysis was performed using a gamma distribution and assuming a standard error equal to 20% of the mean cost.

EAG comment:

Hex et al. 2024 provide a top-down estimate of the total and average costs of managing stage 3 T1D in England.[11] As such, it provides the most relevant estimate of the costs of managing stage 3 T1D prior to the use of HCL systems. However, this estimate is limited for modelling since it does not reflect cost trajectories over time, present costs for patients diagnosed at different ages, or include the net costs of HCL systems. It nevertheless serves as useful benchmark to assess the appropriateness of other modelling approaches.

The company's updated approach to estimating stage 3 T1D costs using real world data from the Danish national registry is preferred during the period in which costs were observed. However, the extrapolation beyond this leads to similar limitations as in the original submission. In particular, the approach to extrapolating costs beyond the 19-year observation period of the Danish national register study lacks face validity and leads to an overestimation of long-term costs which unduly favours teplizumab.

To inform the long-term extrapolation the company fitted a regression model including a linear and quadratic term to costs for cases and controls from the Danish national register study between years 5 to 19. While the model fits well to the observed data the quadratic term leads to large increases in costs at an increasing rate after this period, especially for the teplizumab arm. Figure 1.2 shows the observed data versus the extrapolated data up to 65 years, which is the average additional life expectancy in the economic model. Costs of stage 3 T1D are given as the difference between modelled costs for cases and controls. The average estimated monthly costs of stage 3 T1D from this model over 65 years is £[redacted] which is substantially higher than the estimate of £415.22 from Hex et al. 2024.[11]

Figure 1.2: Average annual total healthcare costs (GBP) per person – observed vs. extrapolated data

GBP = Great Britain pounds; T1D = type 1 diabetes

The EAG considers the conceptual approach to adding costs of HCL systems appropriate. However, the percentage cost reduction from the CORE diabetes model v10 is applied to the estimated costs of stage 3 T1D from the extrapolated model which are considered overestimates. The costs of stage 3 T1D from the CORE diabetes model are also substantially below the estimates provided by the company. It is not explained why these costs would not be appropriate to use in the model. In addition, the company applied 100% uptake of hybrid closed loop systems as mentioned above. In comments on the draft guidance document, NHSE provided recent data on the uptake of hybrid closed loop systems in the NHS.[3] Around 100% of patients aged less than 19 years would be eligible for hybrid closed loop systems and current uptake is 60-70%. For patients aged 19 years or older, around 27% are expected to be eligible, with eligibility rate decreasing with patient age. Across the entire population, the weighted average eligibility is 85% and current uptake approximately 15.5%. Intended uptake based on NHS England strategy assumptions is 54%. In the EAG base-case a 54% uptake is applied.

Finally, while the estimation from the Danish national registers seems broadly appropriate, the reporting of the case control study design is limited. For instance, it is not clearly articulated how cases and controls were selected over time and how the index date for controls were determined. In particular, it is not clear whether patients could be both controls and cases at different points in time and whether controls who went on to be later diagnosed with T1D were then censored.

The EAG consider it necessary to reanalyse the data from the Danish national register study. We consider using a single linear term for time in the extrapolation model, excluding the quadratic term. Otherwise, we follow the approach used in the company submission i.e., using observed data up to 19 years and extrapolating after including the costs of HCL. Table 1.2 shows the regression models from the company and the alternative simpler model from the EAG.

Table 1.2: Regression models used to estimate stage 3 T1D costs

	Cost regression models with quadratic term (CS)		Cost regression models with only linear term (EAG)	
	Cases (T1D)	**Controls**	**Cases (T1D)**	**Controls**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Linear term	[redacted]	[redacted]	[redacted]	[redacted]
Quadratic term	[redacted]	[redacted]	n/a	n/a
CS = company submission; EAG = External Assessment Group; T1D = type 1 diabetes				

Figure 1.3 presents different estimates of long-term stage 3 T1D costs from Hex et al. 2024, the company's original submission, the company's updated submission including and excluding costs of HCL, and the EAG estimates including and excluding the HCL. It is evident that the company's original and updated models substantially overestimate the costs of stage 3 T1D and unduly favour teplizumab.

Figure 1.3: Comparison of different approaches to estimate Stage 3 T1D costs

[redacted]

1.10 Comment 10: New data regarding Stage 2 disutility: Disease-modifying therapy availability improves health-related quality of life in Stage 2 type 1 diabetes relative to natural disease progression

The company presented new disutility data associated with being in Stage 2 T1D that have become available since the first Committee meeting.

Guenther et al. 2025 reports the findings of a cross-sectional study examining health-related quality of life perceptions among 300 UK adults (mean age 42.5 years, 90% Caucasian) using the EQ-5D-5L questionnaire, comparing two groups' responses to type 1 diabetes progression scenarios.[16] Participants'

baseline EQ-5D index was 0.837. Those presented with a disease-modifying therapy scenario showed significantly less health-related quality of life decline when progressing to Stage 2 compared to the non-disease-modifying therapy group (reduction of -0.049 vs -0.124, p=0.004), with both groups showing further decline in Stage 3 (0.553 vs. 0.527).

The company considered that these findings demonstrate that pre-symptomatic (Stage 2) T1D was associated with lower health-related quality of life than the general population, with further decreases in clinical (Stage 3) T1D.

Also, disease-modifying therapy availability was correlated with better health-related quality of life outcomes compared to natural disease progression. Therefore, the company revised their original base-case to include a disutility associated with Stage 2 T1D, but reflective of the relative benefit associated with the administration of a disease-modifying therapy (teplizumab = -0.049) vs no-disease-modifying therapy (established clinical management = -0.124).

EAG comment: Guenther et al. 2025 is an abstract only publication. While the company indicated that additional information (Data on file) was supplied as a supporting reference, the EAG was unable to find this information. Therefore, the EAG cannot properly assess the applicability or the validity of the study.

Considering the values reported in the abstract, the EAG has concerns regarding their face validity. While it is reasonable to assume that patients might prefer a health state where progression to symptomatic disease is slowed due to treatment, the EAG is concerned about the magnitude of the utility decrements estimated from the study.

For the disutility associated to being in Stage 3 T1D, the company used Sullivan et al. 2011, in which an UK-based catalogue of EQ-5D index scores was presented.[17] 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. The EAG would like the company to clarify the following:

- Why is the disutility for ECM in Stage 2 from Guenther et al. 2025 approximately twice larger than the one from Sullivan et al. 20111 used for Stage 3? Even if untreated, Stage 2 is asymptomatic and less severe than Stage 3. Therefore, it seems unrealistic to apply those values to Stage 2 patients.
- Likewise, the disutility applied to teplizumab patients seems large at face value since it is not far from the one used for stage 3.
- Finally, the utilities estimated for Stage 3 seem low as these are typical values used for progressed cancers for example.

For these reasons, the EAG prefers using no disutility associated with Stage 2 T1D as in the original submission.

1.11 Comment 11: Company and EAG cost-effectiveness estimates (3.14):

The company presented the results of a non-reference-case scenario in which health benefits are discounted at 1.5% per annum and costs remain discounted at 3.5% per annum. The company explained that this scenario is not intended to replace their base-case, but it offers relevant context for interpreting the potential long-term value of teplizumab. This scenario results in an ICER decreased by 29.2% compared to the company's base-case.

EAG comment: The EAG has no additional comments regarding this point.

1.12 Comment 12: Company and EAG cost-effectiveness estimates (3.14): "In the company's base case, the deterministic incremental cost-effectiveness ratio (ICER) was £27,534 and the probabilistic ICER was £29,488". In response to the draft guidance, Sanofi are submitting a revised base case and simple Patient Access Scheme

The revised company's base-case was defined after considering comments 1-10 above. Teplizumab's list price has been approved by the Department of Health & Social Care as £[redacted] per 14-vial treatment course. The company has offered a revised Patient Access Scheme (PAS) via a simple discount of [redacted]% off the finalised list price for teplizumab. With the new PAS, the cost of treatment is reduced to £[redacted] per 14-vial treatment course. The company's updated base-case results can be seen in Table 1.3.

Table 1.3: Updated company base-case deterministic CE results (teplizumab updated 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]	25,195
ECM	[redacted]	[redacted]	[redacted]				

Based on Table 6 the company's comments on Draft Guidance.[1]
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

EAG comment: Based on this revised base-case, the company also presented the results of several scenarios, which can be seen in Table 7 of the company's comments on Draft Guidance.[1] Overall, the model results were still sensitive to some alternative assumptions regarding costs and utilities. The scenarios considering different extrapolations for time to progression showed a minor impact on the model results, but other choices not explored by the company can have a larger impact.

The adjustments made by the EAG, to define an updated EAG base-case (using the revised base-above as starting point) are listed below:

1. 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 a parametric distribution with non-constant hazard function is preferred. Given the uncertainty regarding the long-term extrapolations, the EAG prefers a more conservative approach for teplizumab. Since the gamma distribution also showed a good fit to teplizumab data, the EAG prefers using this distribution for its base-case.
2. Given the EAG concerns about the validity of the findings in Guenther et al. 2025, the EAG prefers assuming no disutility associated to Stage 2 T1D.
3. Stage 3 T1D costs increase in time according to linear equation (instead of quadratic).
4. Assume an HCL uptake of 54% in line with NHSE estimate.

The cumulative step-by-step changes made by the EAG to derive its updated base-case, using the updated company's model submitted with their comments on Draft Guidance, can be seen in Table 1.4. The change with the largest impact on the results was assuming a gamma distribution (individual fitting)

for both treatment arms to model time to Stage 3 T1D onset (the ICER increased by approximately £15,000). The other changes included in the EAG base-case had a similar impact on the results, increasing the ICER by approximately £10,000 at each step.

Table 1.4: Cumulative impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's updated base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	25,195
ECM	[redacted]	[redacted]			
Change 1 - Time to Stage 3 T1D onset – individual fitting Gamma (both arms)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	41,080
ECM	[redacted]	[redacted]			
Change 2 - No utility decrement associated with Stage 2 T1D + change 1					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	52,828
ECM	[redacted]	[redacted]			
Change 3 - Type 1 diabetes costs increase linearly + changes 1-2					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	63,394
ECM	[redacted]	[redacted]			
Change 4 - EAG's updated base-case – 45% HCL uptake + changes 1-3					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	72,911
ECM	[redacted]	[redacted]			

Based on the model submitted following the clarification phase.
EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; HCL = hybrid closed loop; QALY = quality-adjusted life year; T1D = type 1 diabetes

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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]

Scenarios including testing requested by NICE after PMB

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. Summary of company and EAG base-case results

The revised company's and EAG's base-case results are summarised in Table 1.1 and 1.2, respectively. Note in these scenarios, the comparator is ECM, which includes management of Stage 2 T1D.

Table 1.1: Revised company base-case deterministic CE results (teplizumab updated 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]	25,195
ECM	[redacted]	[redacted]	[redacted]				

Based on Table 6 the company's comments on Draft Guidance.[1]

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 1.2: Revised EAG base-case deterministic CE results (teplizumab updated 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]	72,911
ECM	[redacted]	[redacted]	[redacted]				

Based on Table 6 the company's comments on Draft Guidance.[1]

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

2. Scenarios including testing/screening costs

If testing/screening costs were to be included in the economic model, the following changes need to be made to the economic model:

- The number of patients needed to be tested to detect one case is required. The DG states that the proportion of patients that would have stage 2 T1D would be 1 in 10 to 1 in 20 in people with FDRs, and 1 in 300 to 400 in the general population.
- The number of patients needed to be tested to detect one case is multiplied by the cost of the test (£29.04 – antibody test as in the CS).
- The comparator in this (asymptomatic and undiagnosed) population is placebo/no treatment plus no screening/no testing.
- Placebo/no treatment is different from ECM since these patients not detected and hence not treated. Thus, ECM costs associated to Stage 2 T1D in the economic model are equal to £0.
- Also, since the comparator arm in TN-10 included at least close monitoring for Stage 3 T1D development in addition to placebo (clarification Question B3), it might be expected that the comparator in the model (ECM) is more effective than no treatment. To approximate this, the EAG assumed for ECM the parametric curve with lowest efficacy (exponential).

The results of the scenarios including screening/testing costs under the company's and EAG's preferred assumptions are summarised in Table 2.1 and 2.2, respectively.

Table 2.1: Scenarios including screening/testing costs (company's preferred assumptions)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's updated base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	25,195
ECM	[redacted]	[redacted]			
Scenario 1 – 10 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	28,527
Placebo	[redacted]	[redacted]			
Scenario 2 – 15 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	28,766
Placebo	[redacted]	[redacted]			
Scenario 3 – 20 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	29,006
Placebo	[redacted]	[redacted]			
Scenario 4 – 300 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	42,400
Placebo	[redacted]	[redacted]			
Scenario 5 – 400 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	47,184
Placebo	[redacted]	[redacted]			
Based on the model submitted following the clarification phase.					

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1D = type 1 diabetes					

Table 2.2: Scenarios including screening/testing costs (EAG's preferred assumptions)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG's updated base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	72,911
ECM	[redacted]	[redacted]			
Scenario 1 – 10 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	76,653
Placebo	[redacted]	[redacted]			
Scenario 2 – 15 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	76,991
Placebo	[redacted]	[redacted]			
Scenario 3 – 20 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	77,329
Placebo	[redacted]	[redacted]			
Scenario 4 – 300 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	96,273
Placebo	[redacted]	[redacted]			
Scenario 5 – 400 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	103,039
Placebo	[redacted]	[redacted]			
Based on the model submitted following the clarification phase. EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1D = type 1 diabetes					

In order to observe the impact of including testing/screening costs on the model results, NICE requested the EAG to conduct the testing scenarios with ECM as comparator. In these scenarios, the ECM costs associated to Stage 2 T1D and the ECM parametric curve used to extrapolate progression are set back to the company's and EAG's preferred options. The EAG considers these scenarios conceptually incorrect since assuming ECM as comparator implies that these patients have also been identified (through testing). Therefore, these scenarios should be interpreted with caution. The results of these scenarios under the company's and EAG's preferred assumptions are presented in Table 2.3 and 2.4, respectively.

Table 2.3: Scenarios including screening/testing costs with ECM as comparator (company's preferred assumptions)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's updated base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	25,195

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]			
Scenario 1 – 10 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	25,628
ECM	[redacted]	[redacted]			
Scenario 2 – 15 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	25,869
ECM	[redacted]	[redacted]			
Scenario 3 – 20 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	26,109
ECM	[redacted]	[redacted]			
Scenario 4 – 300 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	39,572
ECM	[redacted]	[redacted]			
Scenario 5 – 400 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	44,380
ECM	[redacted]	[redacted]			
Based on the model submitted following the clarification phase. ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1D = type 1 diabetes					

Table 2.4: Scenarios including screening/testing costs with ECM as comparator (EAG's preferred assumptions)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG's updated base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	72,911
ECM	[redacted]	[redacted]			
Scenario 1 – 10 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	73,534
ECM	[redacted]	[redacted]			
Scenario 2 – 15 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	73,880
ECM	[redacted]	[redacted]			
Scenario 3 – 20 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	74,226
ECM	[redacted]	[redacted]			
Scenario 4 – 300 patients tested to detect one case with T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	93,595
ECM	[redacted]	[redacted]			
Scenario 5 – 400 patients tested to detect one case with T1D					

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	100,512
ECM	[redacted]	[redacted]			

Based on the model submitted following the clarification phase.

EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1D = type 1 diabetes

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 3 October 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 Errors in the marking of confidential information in "ID6259 DG Company comments form Sanofi 080925 v1.0_EAG critique_final_021025 [CON].docx"

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG comment</th></tr>
<tr><td>Section 1.9, Pg 10 (Final EAG Critique v1.0)</td><td>Data from the unpublished Danish study should be marked as confidential in this sentence:
'A case control study containing [redacted] cases (patients diagnosed with stage 3 T1D) and [redacted] controls.'.'</td><td>The amended sentence should be:
'A case control study containing [redacted] cases (patients diagnosed with stage 3 T1D) and [redacted] controls.'</td><td>Amended</td></tr>
<tr><td>Section 1.9, Pg 11 (Final EAG Critique v1.0)</td><td>Monthly costs of stage 3 T1D over 65 years (model results) should be marked as confidential in this sentence:
'The average estimated monthly costs of stage 3 T1D from this model over 65 years is [redacted] which is substantially higher than the estimate of £415.22 from Hex et al. 2024'</td><td>The amended sentence should be:
'The average estimated monthly costs of stage 3 T1D from this model over 65 years is [redacted] which is substantially higher than the estimate of £415.22 from Hex et al. 2024'</td><td>Amended</td></tr>
<tr><td>Section 1.9, Table 1.2, Pg 13 (Final EAG Critique v1.0)</td><td>The following model regression coefficients in Table 1.2 should be marked as confidential.
<table><tr><th></th><th>Cost regression models with</th><th>Cost regression models with only</th></tr></table></td><td>The revised table should be:
<table><tr><th></th><th>Cost regression models with quadratic term (CS)</th><th>Cost regression models with only linear term (EAG)</th></tr></table></td><td>Amended</td></tr>
</table>

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG comment</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th colspan="2">quadratic term (CS)</th><th colspan="2">linear term (EAG)</th></tr>
<tr><th></th><th>Cases (T1D)</th><th>Controls</th><th>Cases (T1D)</th><th>Controls</th></tr>
<tr><td>Intercept</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Linear term</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Quadratic term</td><td>[redacted]</td><td>[redacted]</td><td>n/a</td><td>n/a</td></tr>
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<tr><td>Intercept</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Quadratic term</td><td>[redacted]</td><td>[redacted]</td><td>n/a</td><td>n/a</td></tr>
</table>
</td><td></td></tr>
</table>

Issue 2 Factual inaccuracies in "ID6259 DG Company comments form Sanofi 080925 v1.0_EAG critique_final_021025 [CON].docx"

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
<u>Data error</u> • Section 1.7, Pg. 8 (Final EAG Critique v1.0) Two of the percentages are reported incorrectly in the following text: 'In addition, the company explored the following scenarios: • -0.02 disutility (halved) until age 25 (ICER increased by 13.2%) • -0.04 disutility applied until age 18 (ICER increased by 21.2%) • -0.02 disutility (halved) until age 18 (ICER increased by 13.2%)	The ICER percentage increase in the second bullet should be changed from '21.2%' to '13.2%'. The ICER percentage increase in the third bullet should be changed from '13.2%' to 21.2%'.	The percentage values are incorrect based on Table 7 of the company DG response.	Amended

• No caregiver disutility - considered an extreme scenario (ICER increased by 30.3%).'			
<u>Factually inaccurate claim</u> • Section 1.5, Pg. 7 (EAG Final Critique v1.0) The text incorrectly indicates that the log-normal distribution for teplizumab is at the upper-end of choices, which is incorrect: "A log-normal distribution for teplizumab results in the long-term extrapolations at the upper end compared to other choices."	The text is removed, or additional text is added (as per the justification) to explain why a log-normal distribution is in fact a "mid" choice for teplizumab.	Given log-normal is the best statistical fit to teplizumab, this fit produces estimates that capture a middle point for several years past the follow up period captured in the trial and estimates on the lower end in the long-term (eg. past 30 years of disease duration). When the full spectrum of standard and flexible projections are plotted, ~50% (n=8-9/17) would be more favourable to teplizumab (please see figure 1 at end of section).	Sentence removed as suggested. Note however that Figure 1 below was not originally provided by the company and that the electronic model does not seem to work when splines are selected. Therefore, the EAG referred to the standard distributions only.
<u>Factual inaccuracy</u> • Section 1.9, Pg. 11 (EAG Final Critique v1.0) The text incorrectly indicates that the company assumed a 100% uptake of hybrid closed	The text is removed, or additional text is added (as per the justification) to explain why the Company did not assume 100% uptake of HCL.	The Company applied 100% to model the upper estimate of effectiveness for HCL. Applying it this way ensures HCL has the maximally 'cost-offsetting' benefit on long-term Stage 3 costs (ie by reducing long term outcomes maximally). The Company did not seek to capture a mix of HCL and non-HCL uptake,	Amended as suggested by the company. The EAG agree that this is a reasonable scenario to perform. The EAG explored additional scenarios based on NHS England estimates of eligibility and intended uptake.

loop (HCL) systems, which is incorrect: "This approach implicitly assumes 100% eligibility and uptake of hybrid closed loop systems"		which would be too complex and open to false precision. This is in line with modelling approach taken for the NICE HCL appraisal (TA943).	
<u>Factually inaccurate comparison</u> • Section 1.9, Pg. 12 (Final EAG Critique v1.0) The text indicates that the two average monthly cost figures are directly comparable, which is incorrect: "The average estimated monthly costs of stage 3 T1D from this model over 65 years is [redacted] which is substantially higher than the estimate of £415.22 from Hex et al. 2024"	The text is removed, or additional text is added (as per the justification) to explain why these averages are not directly comparable.	The two figures measure different things: • £415.22 per month, derived from Hex et al (2024), is an approximate cross-sectional average of the cost of a Stage 3 T1D population over one year (2021-2022). • [redacted] is the average monthly costs for an individual living with Stage 3 T1D for 65 years as estimated in the company's model. A cross-sectional average reflects costs observed across a population at a single point in time, with different individuals contributing data at varying stages of their disease course. Direct comparison with longitudinal model estimates is therefore inappropriate. To enable a like-for-like comparison, costs should be derived using the estimated prevalence of T1D and the Stage 3	Not a factual inaccuracy. The Hex et al. (2024) estimate is a reasonable proxy for the average costs of stage 3 T1D over the patient lifetime as it reflects the real distribution of patients at different ages in England with stage 3 T1D. The EAG agrees that it is not the most suitable estimate for modelling (given that it is fixed regardless of age or time with stage 3 T1D) but it nevertheless serves as a useful benchmark. If average costs from the modelling are substantially higher this requires clear justification. The estimate of [redacted] does not include HCL costs. It is unclear which model adjustments the company is referring to here.

		cost extrapolation alone (excluding HCL costs and model adjustments), which would yield an estimated cost of [redacted]. It is therefore inappropriate to state the average is “substantially higher”, given it is in fact significantly lower.	

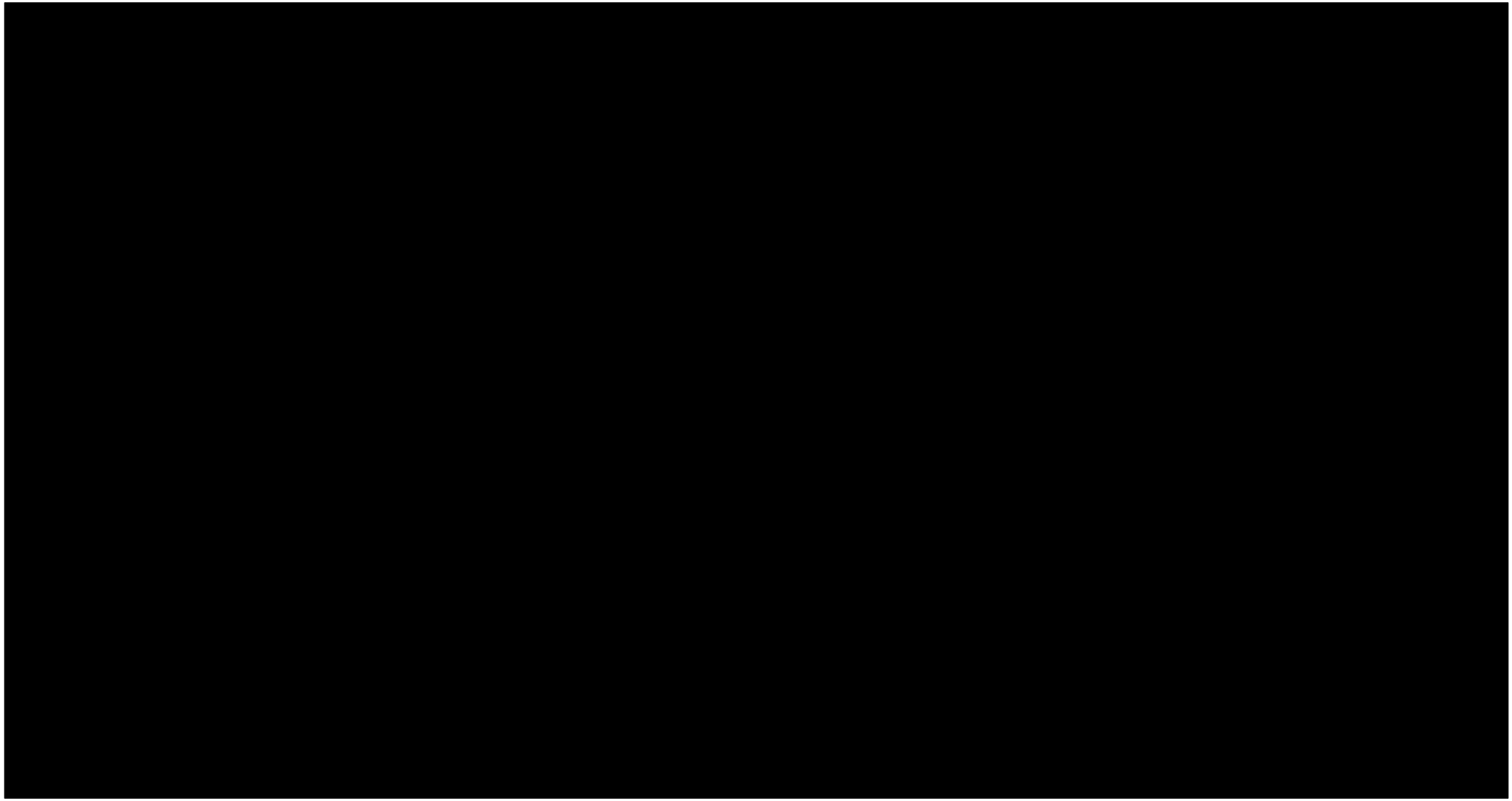


Figure 1. All standard and flexible parametric projections modelled for Teplizumab

Issue 3 Formatting clarification in "ID6259 DG Company comments form Sanofi 080925 v1.0_EAG critique_final_021025 [CON].docx"

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Reference formatting error • Section 1.4, Pg. 6 Reference formatting error in the following text: 'Finally, the cost for CRS management was informed by the NHS costing code WJ11Z (disorders of immunity), with a day case cost of £526.65.11'	The day case cost should be amended to '£526.65', from '£526.65.11'. The following reference should be inserted (which was reference number 11 in the company's Draft Guidance response): National Health Services (NHS). *National Schedule of NHS Costs 2022/23*. 2024. https://www.england.nhs.uk/publication/2022-23-national-cost-collection-data-publication-2/	Reference formatting error	Amended.

Issue 4 Factual inaccuracies in "ID6259 EAG testing scenarios revised 031025 [CON]"

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
<u>Incorrect implementation of screening/testing costs</u> • Section 2, Pg. 4-7	Tables 2.1-2.4 should be removed, or the content amended (as per the justification) to accurately reflect the cost of testing in the context of this decision problem.	The scenarios presented in Tables 2.1–2.4 are conceptually inconsistent with the NICE decision problem, which is to assess teplizumab versus established clinical management (ECM) in identified Stage 2 T1D. The validity of ECM as the correct comparator was confirmed in the draft guidance (DG). **Tables 2.1–2.2** use placebo/no treatment + no testing as the comparator, effectively reframing the question as a population screening programme (testing + treatment vs no testing/no treatment). This is outside the appraisal scope,	Not a factual inaccuracy. The EAG was requested to conduct these scenarios. Despite their limitations (highlighted by the EAG), they can still be useful for the appraisal committee.

		and is inconsistent with the DG. In these analyses, Stage 2 costs were removed and testing costs applied only to the teplizumab arm, inflating incremental costs without changing QALYs. **Tables 2.3–2.4** re-introduce ECM but still add testing costs to one arm only. The EAG itself notes that this is "conceptually incorrect," as testing would apply equally to both arms and cancel out in the incremental comparison. These analyses therefore do not provide a valid estimate of cost-effectiveness and should be excluded from decision-making.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Call for additional evidence

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

Committee discussion and call for additional evidence

The evaluation committee discussed this appraisal at committee meetings in May 2025 and October 2025. It considered evidence submitted Sanofi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. It also heard evidence raised by experts during the meetings.

The committee was unable to make a recommendation because it was considered that additional evidence is needed before it could make a fully informed decision. It requested additional information and analyses it would need to determine whether teplizumab should be recommended for use in the NHS.

The company is invited to submit additional evidence to support the committee's decision making, in line with the issues and requests outlined in this document.

Identifying the eligible population for teplizumab

At the first committee meeting, the clinical experts explained that there are 4 distinct subpopulations that may be tested and subsequently identified as having stage 2 T1D. These are people who:

- are identified in research studies
- are tested because of clinical concerns about hyperglycaemia (for example, as a consequence of steroid use for other autoimmune conditions)
- have a first-degree relative with T1D
- request autoantibody testing.

At the first committee meeting it was outlined by the clinical experts that the current demand for antibody testing is low because there is no available treatment to delay the onset of stage 3 T1D. They highlighted that if a treatment to delay stage 3 T1D becomes available there would likely be an increase in the number of people coming forward for autoantibody testing. In responses to draft guidance consultation and at

the second committee meeting, the company and experts from NHS England also agreed that there would be an increase in testing if teplizumab was recommended.

At the second committee meeting, the company explained that the results of the recently published ELSA study indicated that the expected risk of having T1D in the first-degree relative cohort was closer to 1 in 30, with a general population rate of about 1 in 200.

The committee acknowledged that if teplizumab were recommended, there would be expected to be an increase in people requesting autoantibody testing with subsequent diagnosis of stage 2 T1D. The consideration of a national screening programme is outside the committee's remit, so it agreed the costs of a national screening programme should not be included in the model. At the second committee meeting, the committee noted that some people in the 4 subpopulations may already be identified in practice because of clinical concerns or identified in a research study. But it decided that additional testing costs specifically for first-degree relatives and people requesting autoantibody testing should be captured in the model to account for the increase in demand for autoantibody testing if teplizumab was recommended. It understood that, in practice, it was unlikely that people in the general population would be able to request an antibody test in the NHS, and that most additional NHS-funded tests would be for first-degree relatives.

The committee concluded that although the size of the eligible population and the number of people being tested is still uncertain, the costs of additional antibody testing associated with introducing teplizumab should be included in the economic model. It concluded that it would like to see:

- Cost-effectiveness estimates based on testing with population risk of 1 in 30 (for the first-degree relative population), and without testing
- Blended cost-effectiveness estimates for the full population based on differing proportions of each of the 4 subpopulations eligible for teplizumab

Testing costs

In its response to the draft guidance consultation, NHS England submitted the estimated testing costs associated with the testing of the populations outlined in the draft guidance. It assumed 1 autoantibody test per person and that the cost of testing would include phlebotomy appointments, blood tests, an oral glucose tolerance test and diabetes service costs. The overall testing costs per person were:

- first-degree relatives: £668.53 for children, £212.73 for adults
- first-degree relatives plus ad-hoc uplift: £637.35 for children, £193.26 for adults.

The company stated that NHS England's approach to estimating testing costs was an overestimate and included costs that went beyond the scope of testing and into the diagnostic pathway. The company also noted that the existing tariff costs for diabetes specialist appointments are based on management of stage 3 T1D rather than stage 2 T1D, and that stage 2 costs are likely to be lower. The NHS England expert agreed that the NHS England estimated costs cover a wider context than testing alone. They explained that the tariffs used for diabetes service costs, which are based on a person seeing a consultant for testing, are the only tariffs currently available. They advised that the costs may change over time if a treatment pathway for stage 2 T1D is set up. The committee also heard from the ICB expert that the costs presented by NHS England were likely to be an overestimate of the costs of the testing pathway for stage 2 T1D, because testing would likely be delivered in community hubs and not require a consultant appointment.

The committee concluded that any costs of testing included in the model should incorporate the wider costs of testing for stage 2 T1D in addition to autoantibody testing in any populations identified through testing (for example, first degree relatives). But it thought that the costs provided by NHS England may be an overestimate, and requested:

- Testing costs based on the costs of additional services related to testing for T1D in addition to autoantibody testing, with more plausible costs for these services. This may include the costs of glucose testing and blood tests carried out in a community clinic.
- Inclusion of these updated costs (including the full costs of testing) in the requested additional analyses that include testing costs (that is, using a risk proportion of 1 in 30 and blended cost effectiveness estimates).

Generalisability of ELSA and health inequalities

The clinical experts explained that people identified from research studies (such as ELSA) would be eligible to receive teplizumab if it were recommended. They advised

that the ELSA study has been extended until 2028, which could help to provide the NHS with time to set up the necessary infrastructure for testing.

But the committee was concerned about the impact on health inequalities if people from disadvantaged groups do not have sufficient access to or are not represented in research studies. It requested:

- Additional evidence on the generalisability of the ELSA study to the UK population, and to what extent disadvantaged groups are represented in the study.

Carer disutility

The committee considered that applying caregiver disutility of -0.04 up to age 25 was likely to be reasonable and heard from the patient and clinical experts that a parent's involvement in care may continue past the age of 18.

But it also noted that the evidence provided for carer disutility was based only on primary caregivers. So it decided that applying the same disutility to someone other than a primary caregiver may not be appropriate. So, it concluded that the caregiver disutility of -0.04 should be applied up to the age of 25 for 1 caregiver only.

Stage 2 disutility

The committee decided that it was uncertain about the validity of a disutility for stage 2 type 1 diabetes. It understood that this stage was asymptomatic, and the argued effect on utility from diagnosis and adjustment may already be captured in the one-off disutility applied at stage 3 T1D in the model. It also noted that because the results of vignette studies can be highly sensitive to how the questions asked are framed, if values from a vignette study are to be used it was essential to evaluate the full methods used in that vignette study. The committee concluded that it could not accept the inclusion of a stage 2 disutility without a clear explanation of the rationale for and validity of applying a disutility to an asymptomatic stage of disease, and without full information on the methods used to estimate that disutility.

Managing stage 3 costs

At the first committee meeting, the committee concluded that the costs of managing stage 3 T1D increase over time, but requested an updated modelling approach with

more plausible costs. It also considered that the impact of the cost of hybrid closed loops should be captured.

Following draft guidance consultation, the company submitted new data on stage 3 costs based on a Danish registry study with 19 years of data available. It applied a linear regression model with a quadratic term to data collected between 5 and 19 years of follow up to extrapolate stage 3 costs beyond this point. It also included the additional costs of hybrid closed loops using the Core Diabetes Model and assumed a 100% uptake of hybrid closed loop systems. The EAG preferred to apply a linear extrapolation of costs without a quadratic term and assumed a 54% uptake of hybrid closed loop systems based on uptake data submitted by NHS England.

The committee acknowledged that stage 3 T1D costs were likely to increase over time, and considered that the costs in the EAG's approach were too low and unlikely to align with the expected increase in complications over time. But it noted that the rapid and large increase in the extrapolated stage 3 T1D costs in the company's approach may not be appropriate, lacked face validity and had not been validated against any real-world sources of data. The committee concluded that in the absence of more suitable data, it had no choice but to use the EAG's approach to modelling stage 3 costs. It requested:

- More suitable approach to model the expected increase in costs beyond 20 years.

Committee other considerations and preferred assumptions

The committee reached conclusions on some issues and preferred assumptions. It requested that analyses be presented using the following conclusions and preferred assumptions in addition to those outlined in the previous sections:

- Using an incidence rate of 4.6% for cytokine release syndrome (CRS) in the teplizumab arm of the model
- Using the log-normal distribution for time to onset of stage 3 T1D in the teplizumab arm
- Using the gamma distribution for time to onset of stage 3 T1D in the teplizumab arm

- Using the company’s revised approach to stage 3 disutility in the model (that is, the piece wise approach for time dependent disutility presented at the second committee meeting).

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

(ID:6259)

Call for Additional Evidence

Company Submission

28th November 2025

Contents

Executive Summary

We are grateful to the committee for the opportunity to respond to the call for additional evidence following ACM2 for teplizumab (received 29th October 2025). Below is a summary of how we have addressed the key committee topics:

Topic 1: Additional costs related to patient identification should be included in both arms of the model.

Individuals enter the model in each arm with a diagnosis of Stage 2 T1D. Testing is known to have outcome benefits such as avoidance of diabetic ketoacidosis (DKA), and so costs should **not** be imposed only on the teplizumab arm whilst the benefits associated with identification remain in the ECM arm.

- At a 1:30 population risk for first-degree relatives, total estimated costs to test 30 individuals and diagnose one Early-T1D individual are £1,724.26.
- Additional testing costs incurred by the NHS are applied to 13% of the tested population. 87% are assumed to be covered by research and testing for other clinical concern (supported by Swaby et al., 2025 and expert clinical opinion). This results in the blended cost of £224.15 used in the model.
- ELSA demonstrates strong UK population representativeness, with future recruitment strategies continuing to support equity of access for disadvantaged and minority groups.

Topic 2: Carer disutility should be applied to more than one caregiver

Our base case maintains a ratio of 1.76 : 1 (Carer : Dependent). We have collected further supporting evidence to show that more than 1 carer is involved in the support of children and young people with T1D.

- Our survey in collaboration with Breakthrough T1D (n=[redacted] caregivers), indicates [redacted]% of primary caregivers have secondary caregiver support.
- When two carers are involved, secondary caregivers contribute [redacted]% relative to primary caregiver time. This corresponds to [redacted] caregivers per dependent.
- This ratio is [redacted] when sole carers are included (tested in scenario analysis).

Topic 3: Disutility for Stage 2 T1D should be included to reflect the impact associated with seemingly healthy individuals receiving a diagnosis of a chronic and progressive disease.

It is clinically plausible that the disutility associated with Stage 2 T1D diagnosis will be larger than for the transition from Stage 2 to 3 T1D. This is because whilst individuals still carry the diagnosis there is time for adaptation and watchful waiting. Hence it is wholly appropriate to include a disutility at diagnosis even though Stage 2 T1D is

asymptomatic. Disutility at the onset of Stage 3 T1D remains important to reflect the transition to symptomatic disease that must now be constantly and diligently managed.

- The UK general population vignette study (Guenther et al., 2025) shows there is a health-related quality of life (HRQoL) impact of Stage 2 T1D diagnosis, and that teplizumab helps to mitigate this (teplizumab: -0.049 vs ECM -0.124; p=0.004).
- This is supported by expert clinical validation.
- To address committee concerns we have provided a scenario in which the Stage 3 T1D onset disutility is removed. This captures the more important impact of a shock Stage 2 diagnosis for an apparently health individual vs. Stage 2 to 3 disutility for patients already carrying a Stage 2 diagnosis.

Topic 4: Costs for the management of Stage 3 T1D will increase over time.

The costs based on Danish real-world evidence have been accepted as the best available source by the committee and the clinical experts have confirmed that the quadratic extrapolation of this RWE is more appropriate than the EAG linear approach.

- Despite HCL availability Stage 3 T1D remains a chronic disease where costly complications accumulate over time. Hence our projections are most suitable.
- Leading UK clinicians confirmed the EAG projections significantly underestimate the cost of long-term complications.
- Comparing like-for-like with the £415.22 monthly figure from Hex et al (2024), our unadjusted extrapolation results in a lower monthly average of £368.80.
- HCL uptake is assumed to be 85% in the expected patient population (National Specialty Advisor for Diabetes with NHS England personal communication).
- Even with HCL suboptimal control persists at the population level (average HbA1c on HCL is 7.2% vs ≤6.5% target).
- Acquisition costs and expected long-term benefits associated with HCL, based on a HbA1c reduction of -0.5% (Edgvist, 2021; TA943) are included in the model.

Willingness to pay should be towards the higher end of the threshold.

It is important to recognise the benefits to unmet need, equality and innovation that teplizumab represents. In the context of the imminent WTP update and the important step change that teplizumab represents, WTP should be considerably higher than the midpoint of the current range, which is the lower bound of the new WTP envelope.

- Teplizumab addresses a significant unmet need. It is the first and only disease-modifying therapy to delay the onset of Stage 3 T1D whilst also preserving C-peptide response.
- T1D is a disease of inequality in outcomes across different sectors of society with worse glycaemic control experienced in populations with lower socioeconomic status and certain ethnicities.

- Uncertainty in the key inputs and assumptions identified by NICE have been resolved (patient identification and testing, Stage 2 quality of life, carer burden and costs for the management of Stage 3 T1D).
- The increase to the cost-effectiveness threshold from £20k - £30k/QALY to £25k - £35k/QALY may be informally in place at the time of decision making.

1.5% discount rate is justified for this appraisal.

The reduction of -84.6% in the ICER in moving from a discount rate of 3.5% (Probabilistic ICER = £26,342) to 1.5% (Probabilistic ICER = £4,076) amply illustrates the long-term impact of delaying Stage 3 T1D onset and the validity of employing a more appropriate discount rate.

- Delaying Stage 3 T1D onset and preserving β-cell function in children and young people during key formative years (a critical developmental window early in life when T1D is often poorly managed), means that teplizumab is expected to alter the lifetime trajectory of disease burden.
- The full value of these future health gains must be appropriately captured to avoid undervaluing an important preventive intervention with enduring impact.
- This meets the spirit of the NICE criteria for the application of the non-reference case and plausibly supports the case for 1.5% discounting.

Key assumptions and inputs applied in the updated base case.

- **Patient identification and testing:** Blended testing cost of £224.15 in both arms
- **Caregivers:** 1.76 caregivers for those aged <25 years old (-0.04 disutility)
- **Stage 2 disutility**: applied at -0.049 (teplizumab) vs -0.124 (ECM)
- **Stage 3 costs**: Quadratic extrapolation assuming 85% HCL uptake

Revised base case results

Table 1. Revised base case in response to call for additional evidence

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
ECM*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£27,720
Teplizumab	[redacted]	[redacted]	[redacted]					
Probabilistic results								
ECM	[redacted]	[redacted]	[redacted]					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	£26,342

ECM: Established clinical management

Topic 1. Identification and Testing

The committee have asked us to consider three elements in relation to patient identification and testing. This is in the context of a potential increase in autoantibody (AAB) testing of first degree relatives (FDRs) if teplizumab is recommended:

- 1.1. Capturing testing costs in the model
- 1.2. Testing costs, including:
    - 1.2.1) The wider testing and diagnosis pathway in a community clinic and
    - 1.2.2) The associated costs
    - 1.2.3) Estimated cost blends between additional individuals that would have testing costs attributable to the NHS (FDRs) and those that would not (captured via research studies or tested for other clinical concerns)
- 1.3. Generalisability of ELSA

1.1 Capturing testing costs in the model

Additional costs related to patient identification should be applied equally to both arms (teplizumab and established clinical management) in the cost-effectiveness analysis.

Any additional costs related to patient identification, if they must be included in the cost-effectiveness model (CEM), should be applied equally to both arms (teplizumab and Established Clinical Management (ECM)) in the cost-effectiveness analysis. This is because the analysis begins with individuals already identified as Stage 2 T1D and apportions either ECM OR teplizumab + ECM to them in the model to make the comparison between treatments. Testing is known to have outcome benefits such as avoidance of diabetic ketoacidosis (DKA), and so costs should not be imposed only on the teplizumab arm whilst the benefits associated with identification and ECM remain in the counterfactual. For example, without identification and ECM, DKA at diagnosis would expect to rise to ~25% from 2.5%,[3] incurring higher costs both in the short and long term, reducing quality of life and increasing mortality risk for individuals in the comparator arm.

The inclusion of exploratory and confirmatory testing costs in the model is contrary to NICE precedent set in other appraisals (see Appendix 1).

1.2 Testing costs

- The estimated cost to test 30 individuals and confirm diagnosis of Early-T1D in 1 individual is £1,724 (Table 2). This represents a 1 in 30 population risk rate and is aligned to the requested NHS community clinic setting (Figure 1).
- Our base case assumes 13% of additional testing costs are attributable to the NHS and 87% will be carried out in research studies and testing due to clinical concern, based on recent UK evidence (Swaby et al, 2025) and expert opinion.
- This results in a blended cost estimate to the NHS of £224.15 per individual identified for application in the cost-effectiveness model (Table 3).

1.2.1 Testing costs associated with each sub-population

The four sub-populations described in the committee discussion document are:

- Identified in research studies (ELSA/T1DRA)
- Tested because of clinical concerns about hyperglycaemia
- Have a first-degree relative with T1D
- Request autoantibody testing

Any increase in demand for additional testing will be in the FDRs sub-population. To calculate blended cost estimates of testing, the above four sub-populations were subdivided:

1. Those where an **additional** testing cost **would** be attributable to the NHS:
    a. First-degree relative (FDR), at a 1 in 30 population risk rate
2. Those where an **additional** testing cost **would not** be attributable to the NHS:
    a. Identified in research (ELSA/T1DRA studies)
    b. Tested because of clinical concerns about hyperglycaemia: the availability of teplizumab is not expected to have an impact on autoantibody (AAB) testing in this cohort. The individuals will present independent of teplizumab availability.
    c. Request autoantibody testing (general population): In the absence of a national screening programme, individuals would be refused NHS

testing based on eligibility, pay privately or be directed to a research study (ELSA/T1DRA).

Given that the additional costs of testing relate only to FDRs, the testing pathway in an NHS community setting has been agreed with clinical experts to be as follows (Figure 1):

FDRs will enter community testing either via a proactive request from an individual, or via suggestion from their relative's secondary care team. Given the FDR risk proportion is 1 in 30:

- 30 individuals receive an exploratory AAB test
- 1.1 individuals (3.7%)[4] proceed to confirmatory testing
- 1 individual (91.9%; corresponding to overall 3.4% of the original population personal communication from [redacted]) proceeds to staging to confirm a diagnosis of Early-T1D

Once diagnosed with Early-T1D, the individual would be referred to a specialist diabetes service. Service and treatment costs from this point onwards (monitoring, education and teplizumab administration costs) are already captured in the model.

It is important to note that given the nature of T1D progression, individuals who enter the specialist diabetes service at Stage 2 are **not** additional individuals for the overall diabetes service; these individuals would have presented at Stage 3 T1D, often in DKA, but are instead being managed earlier in their disease, potentially reducing costs due to the improved management that results from earlier identification.[5]

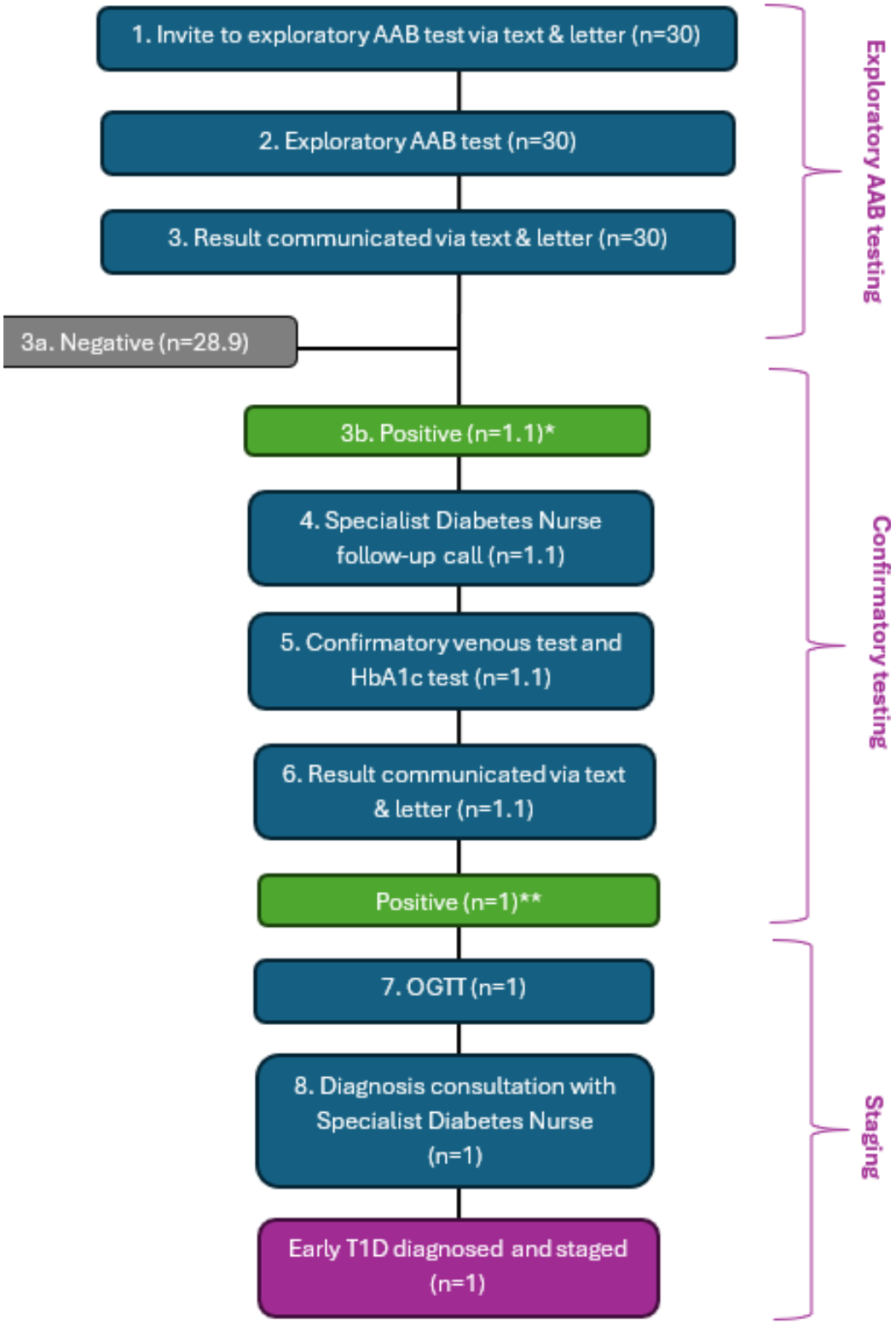


Figure 1. Testing pathway in an NHS Community Clinic Setting.
*3.7%[4] are ≥2 AAB positive at this stage
**91.9% (corresponding to overall 3.4% of the original population; personal communication from [redacted]) are ≥2 AAB positive at this stage
AAB: autoantibody; HbA1c: haemoglobin A1c (glycated haemoglobin); OGTT: Oral Glucose Tolerance Test; T1D: Type 1 Diabetes

1.2.2 Estimated additional testing and service costs

At a 1:30 population risk rate, the wider costs related to testing for Early-T1D are £1,710.24 (Table 2). This comprises the cost of exploratory AAB tests in 30 individuals (£1,386.00), confirmatory testing in 1.1 individuals (£154.26) and staging in 1 individual (£184.00).

Importantly, these costs will reduce over time with the introduction of more cost-effective methods of testing, for example, dried blood spot tests which are expected to remove the need for phlebotomy appointments at the exploratory stage (expert personal communication). Similarly, OGTTs are expected to be replaced by cheaper and more routinely used glycaemic measures, given that they are also more patient-friendly (expert personal communication).

Table 2. Total estimated costs incurred by the NHS to diagnose and stage Early-T1D at a 1 in 30 population risk

#	Step	Cost per individual	Total cost for 30 individuals	Source/Assumption
Exploratory AAB testing in 30 FDRs (n=30)		**£46.20**	**£1,386.00**	
1	Invite to exploratory AAB test	£1.44	£43.20	Original and chasing invite sent
	SMS message*2	£0.04	£1.20	£0.02 per text[6]
	Letter*2	£1.40	£42.00	£0.70 per letter[7]
2	Exploratory AAB Test	£44.76	£1,342.80	
	Phlebotomy appointment	£15.00	£450.00	15 mins nurse appointment with assumed uplift for add'l time for paediatric individuals [8]
	AAB test	£29.04	£871.20	Cost of GAD antibodies testing[9]
3	Communicating result	£0.72	£21.60	1 Letter and 1 SMS message[6,7]
1.1* <u>suspected</u> individual with ≥2 AAB+ of 30 tested (proceed to steps 4-6)				
#	**Step**	**Cost per individual**	**Total cost for 1.1 individuals**	**Source/Assumption**
Confirmatory testing in 1.1 FDR (n=1.1)		**£140.24**	**£154.26**	
4	Specialist Diabetes Nurse Consultation	£22.00	£24.20	Community; 1 appointment per positive individual (assumed 10 mins)[10]
5	Confirmatory AAB Test	£118.24	£130.06	
	Phlebotomy appointment	£15.00	£16.50	15 mins nurse appointment with assumed uplift for add'l time for paediatric individuals[8]
	Confirmatory tests	£102.52	£112.77	
	Confirmatory venous test and analysis	*£97.52*	*£107.27*	As per model submitted by [redacted] in response to ACM1 DG
	HbA1c test	*£5.00*	*£5.50*	As per model submitted by [redacted] in response to ACM1 DG
6	Communicating result	£0.72	£0.79	1 Letter and 1 SMS message[6,7]
1 ** **<u>confirmed</u> individual with ≥2 AAB+ of 30 tested**				
#	**Step**	**Cost per individual**	**Total cost for 1 individual**	**Source/Assumption**
Staging in 1 FDR (n=1)		-	£184.00	
7	OGTT	-	£112.00	As per model submitted by [redacted] in response to ACM1 DG
8	Diagnosis consultation with Specialist Diabetes Nurse	-	£72.00	30 min appointment by secondary care team; as per model submitted by [redacted] in response to ACM1 DG
Total Early T1D diagnosed and staged in 1 individual (from 30 tested)		-	**£1,724.26**	Costs of exploratory testing in 30 individuals, confirmatory testing in 1.1 individuals and staging in 1 individual

Aligned to NHS community clinic pathway in Figure 1.

AAB: autoantibody; GAD: glutamic acid decarboxylase; DG: draft guidance; OGTT: Oral Glucose Tolerance Test; HbA1c: haemoglobin A1c (glycated haemoglobin)

**3.7%[4] are ≥2 AAB positive at this stage; **91.9% (corresponding to 3.4% of the original population; personal communication from [redacted]) are ≥2 AAB positive at this stage*

1.2.3 Blended testing cost estimate

A blend between populations when additional testing costs are and are not attributable to the NHS were explored in line with the committee request to include these costs in the CEM. The two costs used to calculate the blended cost estimates are:

- **£1,724.26:** Where an **additional** testing cost **would** be attributable to the NHS, in the FDR subpopulation, £1,724.26 is the maximum total pathway cost per individual diagnosed (at 1 in 30 population risk; Table 2).
- **£0:** Where an **additional** testing cost **would not** be attributable to the NHS (identified in research, tested because of clinical concerns about hyperglycaemia, and general population request for autoantibody testing).

Cost estimates to the NHS at different blends of additional testing attributable and not attributable to the NHS were explored using weighted averages (Table 3).

Table 3. Cost estimates to the NHS at different blends of additional testing attributable and not attributable to the NHS

Additional costs attributable to the NHS: Maximum additional cost attributable to the NHS at a 1 in 30 population risk (FDRs)	**£1,724.26**
Additional costs not attributable to the NHS: Those tested in research studies, incidentally identified and Gen Pop requesting AAB testing	**£0.00**

Additional costs attributable	**Additional costs not attributable**	**Blended Cost Estimate to the NHS**
0%	100%	£0.00
5%	95%	£86.21
10%	90%	£172.43
13%	87%	£224.15
15%	85%	£258.64
20%	80%	£344.85
25%	75%	£431.07

Blue fill indicates company base case

Our base case assumes 13% of additional testing costs are attributable to the NHS and 87% will be carried out in research studies and testing due to clinical concern, based on recent evidence [11] and expert clinical opinion. This results in a blended cost estimate to the NHS of £224.15 per individual identified for application in the cost-effectiveness model.

Swaby et al (2025) surveyed 127/164 UK paediatric diabetes units, of which, 35 managed 145 children and young people with Early-T1D. AAB testing was conducted in

13% due to family screening in secondary care (FDRs) and 87% for reasons that would fall under no additional attributable cost to the NHS because of teplizumab (Figure 2).

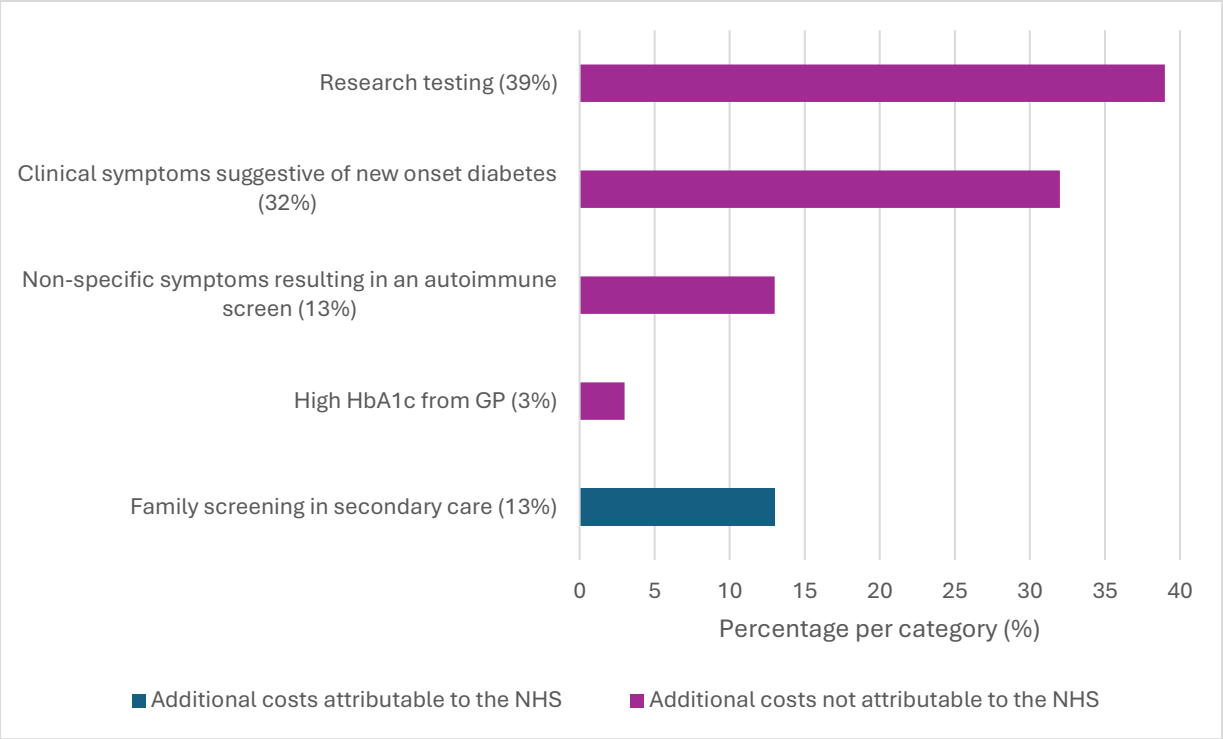


Figure 2. Reasons reported for autoantibody testing in children and young people in Swaby et al (2025). Figure adapted from Swaby et al (2025)[11]

Insight from the NICE committee meetings, advisory boards and expert clinical opinion indicates that research studies are expected to continue as the primary route for testing of individuals, especially whilst the NHS establish the required pathway. Capacity through ELSA & T1DRA stretches to 90k individuals which is adequate to accommodate estimated numbers (expert personal communication).

1.2.4 Scenario analysis

See section 7.2 for ICER impact of the following scenarios:

1. £224.15 applied to teplizumab arm only. It must be noted that no commensurate adjustment to the comparator arm of the model was made to account for the disbenefits and costs associated with that population not being tested and identified.

1.3 Generalisability of ELSA

The recent ELSA publication (Quinn et al, 2025) indicates that the ELSA study is generalisable to the UK population (Table 4), with recruitment and testing outside the home setting increasing access for disadvantaged groups.

The committee was concerned whether people from disadvantaged groups had sufficient access and/or were represented in research studies.

Participants in ELSA are generalisable to the UK population, and individuals from disadvantaged groups had sufficient access and were represented (Table 4). Black and Asian individuals and individuals from lower socio-economic backgrounds were slightly underrepresented. 98.3% (n=115/117) of parents viewed the programme positively, which was consistent across ethnicities and socio-economic backgrounds.[4]

Table 4. Socio-demographic data from ELSA compared to the UK General Population

Characteristic	**ELSA (n=24,875)**	**UK General Population**	**UK Reference**
% Male	51.61%	49.00%	ONS 2022[12]
Median age	8.00 years (IQR 5.00-10.00)	-	
Reported Ethnicity			
White	*80.96%*	*81.70%*	ONS 2022[13]
Mixed	*7.08%*	*2.90%*	
Asian	*6.53%*	*9.30%*	
Black	*2.09%*	*4.00%*	
Other Groups	*2.55%*	*2.10%*	
Median index of multiple deprivation (IMD) decile for English postcodes	6 (IQR 4–9)	5.5	GOV.UK 2019[14]
Reported family history of T1D	32.47%	~10%	Sims 2022[15]
Affected first degree relative (parent or sibling)	*15.46%*	*~12%*	Parkkola 2013[16]

Information on the socio-demographics of ELSA was presented at the European Association for the Study of Diabetes (EASD) 2025 Annual Meeting and is available as a preprint publication whilst undergoing peer review for publication by The Lancet.[4]

The authors report that "recruitment and testing outside the home setting (e.g. schools, GP, hospitals, community forums)" supports recruitment from ethnic minority, more deprived populations, and those without a family history of T1D. ELSA will continue to focus on equity in recruitment ensuring access for individuals from ethnic minority groups, and those living in areas of high deprivation (personal communication with ELSA Lead on 21/11/25). For example, by recruiting from schools in more deprived areas and supporting community drives.

1.4 Conclusion

At a 1:30 population risk for FDRs, the total estimated costs to test 30 individuals and diagnose one Early-T1D individual in an NHS community setting is £1,724. Our base case assumes 13% of additional testing costs are attributable to the NHS and 87% will be carried out in research studies and testing due to clinical concern (supported by Swaby et al., 2025 and expert clinical opinion), resulting in a blended cost of £224.15 for application to the model. This additional cost related to patient identification should be included in both arms of the model.

ELSA demonstrates strong UK population representativeness, with future recruitment strategies continuing to support equity of access for disadvantaged and minority groups.

Topic 2. Carer Disutility (Number of Caregivers)

- More than one caregiver is involved in the care of a child or young person with T1D aged ≤ 25 years old.
- New evidence via a survey completed with Breakthrough T1D of [redacted] caregivers of a child or young person aged ≤ 25 years old indicates that [redacted] of primary caregivers have support from a secondary caregiver.
- When a secondary caregiver is involved, they spend approx. [redacted] the time ([redacted]) of a primary caregiver in physical caregiving activities ([redacted] vs [redacted] of an individual's total care; n=[redacted]). This corresponds to [redacted] caregivers per dependent.
- Including respondents who said they were the only carer, the ratio of caregivers to dependent is [redacted] A scenario is presented to reflect this new evidence (section 7.2).

More than one caregiver is involved in the care of a child or young person with T1D under the age of 25 years.[17] This is further supported by the results of a Sanofi-sponsored survey conducted with Breakthrough T1D for the purposes of this response to the call for evidence. The survey sought to understand how often a secondary caregiver is involved, and how that caregiving burden quantitively compares to the primary caregiver.

The survey flow is available in Appendix 2. The survey was open between 21/11/2025 and 26/11/2025. Respondents were eligible to take part in the survey if they were a caregiver of a child or young person with T1D aged ≤ 25 years old in line with the age agreed by the committee following ACM2. If the respondent had caregiving duties for more than one child or young person with T1D, they were only able to answer the survey

once from the perspective of the eldest dependent. [redacted] participants completed the survey with respondent characteristics detailed in Table 5.

Table 5. Secondary caregiver survey respondent characteristics

Characteristic	Data
Respondents	[redacted]
Average age of child/young person with T1D	[redacted]
Under 8 years	[redacted]
8-16 years	[redacted]
17-25 years	[redacted]
No. of secondary caregiver involved in care (%)	[redacted]

[redacted] percent (n=[redacted]) said another person is involved in the care of their child or young person with T1D. When a secondary caregiver is involved, they spend [redacted] the time ([redacted]) of a primary caregiver in physical caregiving activities ([redacted] vs [redacted] of an individual's total care; n=[redacted]). This corresponds to [redacted] care givers per dependent.

Overall, including respondents who said they were the only carer, the ratio of caregivers per dependent is [redacted] (see Appendix 2 for an explanation of the calculation of this ratio). This is implemented in scenario analysis.

The elements cited as contributing to the care burden were almost universal for all respondents. Around [redacted] of respondents reported time spent:

- ordering supplies ([redacted]),
- attending diabetes-related appointments ([redacted]),
- liaising with school/education or recreational settings ([redacted]),
- checking daytime glucose levels ([redacted]),
- participating in diabetes education ([redacted])

Caregivers also commonly reported administering insulin and maintaining technology (e.g., injections/pump site changes; [redacted]) and getting up at night for diabetes-related needs ([redacted]), indicating substantial around-the-clock involvement. Work impacts were prevalent, with approximately [redacted] caregivers taking time off work due to the child or young person's diabetes ([redacted]). The mental burden is also significant, with key themes of emotional strain ([redacted]), sleep and physical strain ([redacted]) and comprehensive care demands ([redacted]) cited by respondents.

2.1 Conclusion

Carer disutility should be applied to more than one caregiver as new evidence indicates [redacted] % of primary caregivers have secondary caregiver support (n=[redacted]). When involved, they spend approximately [redacted] the time of a primary caregiver in physical

caregiving activities. This corresponds to [redacted] care givers per dependent. When including respondents who said they were the only carer, the ratio of caregivers per dependent is [redacted].

Topic 3. Stage 2 Disutility

- Disutility for Stage 2 T1D (teplizumab: -0.049 vs ECM: -0.124) should be included in the model to reflect the impact associated with seemingly healthy individuals being told that they have a chronic and progressive disease.
    - This is different to the disutility applied at onset of Stage 3 T1D, which instead reflects the adjustment required to transition from an asymptomatic to symptomatic disease state that must now be constantly and diligently managed.
- Guenther et al. (2025) provides statistically significant (p=0.004) evidence that diagnosis of Stage 2 T1D has a measurable impact on health-related quality of life (HRQoL), and that the availability of a disease-modifying therapy (DMT) to delay the onset of Stage 3 T1D helps to mitigate this.
- The model utilises these representative utility data to describe the difference in HRQoL between the world with and without teplizumab for people diagnosed with Stage 2 T1D.
- The qualitative real-world experiences of individuals who have received teplizumab in the UK and in the US[1,2] support the findings from Guenther et al. (2025).

3.1 Information on the study and methods

Full information on the methods, including the vignette descriptions, were supplied to NICE on 22nd October 2025 (Stage 2 Disutility Report_BOD0249_version1_0.pdf).

To summarise; Guenther et al (2025) aimed to capture the HRQoL impact of transitioning from non-symptomatic to symptomatic T1D, and whether a DMT could mitigate this impact. It is a cross-sectional vignette-based survey conducted with a representative sample of the UK general population (n=300, aged ≥18 years). Using the EQ-5D-5L questionnaire, the participants first valued their own health followed by Stage 2 and Stage 3 T1D hypothetical health states. The responses were then converted into UK (EQ-5D-5L) index values.[18] We have assumed that the Decision Support Unit (DSU) mapping function to EQ-5D-3L based on the EEPRU dataset would likely yield very similar values.

Participants were randomly allocated into two groups of 150 in order to value any perceived benefit of a DMT, such as teplizumab, to delay the onset of Stage 3 disease. After random allocation, there was no statistically significant difference in terms of age, education and current knowledge about T1D between the two groups. Both groups were shown the same vignettes, with the only difference being whether a DMT was available or not:

- **Group A (DMT Scenario):** Assessed health states where a hypothetical DMT was available to delay the onset of Stage 3 T1D.
- **Group B (Natural History Scenario):** Assessed health states with **NO** DMT available to delay disease progression.

The vignette descriptions were developed using a structured, evidence-based approach:

1. A literature review of clinical guidelines, publications, and existing utility studies was completed to understand clinical differences, key symptoms, and standard treatments for Stage 2 and Stage 3 T1D.
2. Two T1D patients reviewed the draft vignettes, focusing on the most impacted HRQoL domains at each stage (e.g., anxiety/uncertainty in Stage 2; daily burden of insulin management and DKA risk in Stage 3).
3. A final medical review ensured symptoms and acute complications were medically accurate and appropriately emphasised for each stage, confirming alignment with current medical classifications and clinical practice guidelines.
4. A native speaker revised both vignettes to ensure clarity and neutral language.
5. A pilot study with [redacted] participants was conducted ([redacted] (n=[redacted]) female; [redacted] (n=[redacted]) had prior T1D knowledge). Participants read and summarised the vignettes to confirm understanding of the health status and differences between Stage 2 and Stage 3 T1D. The entire survey was piloted to ensure clarity and reasonable completion time.
6. In the final revision, minor linguistic changes were made, and vignette presentation was adjusted to ensure visibility throughout the online survey.

The accuracy of the disease health states has been validated by three leading UK clinical experts (personal expert communication), who all agreed with the descriptions. One clinician said that the language used in the Stage 2 vignette may have overstated how suddenly the onset of symptoms for Stage 3 T1D can occur (personal expert communication). However, it is important to note that the resulting disutility values used in the cost-effectiveness model are only those associated with the diagnosis of Stage 2 and not the transition to Stage 3 T1D.

The absolute values elicited in the study for 'Own health' and 'Stage 2 & 3 T1D' are also not used in the model, rather the incremental difference (disutility) following the

diagnosis of Stage 2 is the parameter which informs the cost-effectiveness analysis and is applied to the age specific utility estimates taken from the UK general population.[19]

3.2 Rationale for applying the disutility

Guenther et al (2025) is the first study to quantify the impact of pre-symptomatic T1D on HRQoL. This new evidence captures two elements:

1. There is a disutility associated with Stage 2 T1D, despite this being an asymptomatic disease state.
2. The availability of a DMT to delay the onset of Stage 3 disease, such as teplizumab, is perceived to significantly mitigate the decrease in HRQoL observed in the presymptomatic stage.

Whilst Stage 2 T1D is asymptomatic, this evidence indicates that there is an initial psychological burden with this diagnosis and regular follow-up in Stage 2 T1D. This is clinically plausible, given seemingly healthy individuals will be told that although currently asymptomatic, they have a chronic, lifelong and progressive disease. This is supported by the FRIDA study, which found that parental psychological stress (measured by PHQ-9 questionnaire) was significantly greater at the time of metabolic staging in mothers of children with Early-T1D compared to the control cohort (3 [1-7] vs 2 [1-4]; P = 0.002).[20]

This is different to the disutility applied at onset of Stage 3 T1D, which instead reflects the adjustment required to transition from an asymptomatic to symptomatic disease state that must now be constantly and diligently managed.

This study indicates that a DMT such as teplizumab is likely to provide a statistically significant relative improvement to the HRQoL associated with Stage 2 T1D (-0.049 vs -0.124 (p=0.004)). This is clinically plausible, illustrating that whilst individuals still carry the diagnosis the certainty and hope in slowing and managing the disease derived from treatment with a DMT is very important to them.

This concept is reinforced by qualitative real-world experiences of individuals who have received teplizumab in the US and hypothetically discussed treatment acceptability in the UK. For example, in the US, 72% of individuals and caregivers of children with T1D who had received teplizumab (n=34/47) felt teplizumab would help slow down the disease and 60% (n=28/47) felt teplizumab would make T1D easier to manage.[1] Similarly, in the UK, 9 parents from 8 families whose children were ≥ 8 years old and diagnosed with Stage 2 T1D were interviewed via the ELSA study.[2] When asked hypothetically about teplizumab, 89% (n=8/9) would accept teplizumab, with a 2-3 year delay being deemed as “meaningful and worth it for a two-week treatment course”. This reinforces historical US data, where delaying time until insulin dependence from two to four years was of high importance in parents of children with T1D (n=600).[21]

During our validation with clinical experts for the purposes of this response, they also agreed that:

1. An individual would experience a HRQoL impact in Stage 2 T1D, despite this being an asymptomatic disease.
2. This HRQoL impact would be expected to be reduced by the uptake of teplizumab.
3. An individual would expect to experience an HRQoL impact in Stage 2 T1D and again at the onset of Stage 3 T1D.

One clinician described that the disutility in Stage 2 T1D may in fact be greater than in the onset of Stage 3 T1D, as the 'shock' of diagnosis comes at Stage 2 T1D rather than Stage 3 T1D. By the time the individual reaches Stage 3 T1D, they are more accepting.

3.3 Scenario analysis

The committee has a concern that a disutility from diagnosis and adjustment may already be captured in the one-off disutility applied at the onset of Stage 3 T1D in the model. In the pathway relevant for teplizumab, individuals would be diagnosed at Stage 2 T1D not Stage 3 T1D. We have therefore provided a scenario in which the disutility at the onset of Stage 3 T1D is removed (section 7.2). This analysis captures the more important impact of a shock Stage 2 diagnosis for an apparently healthy individual vs. the transition from Stage 2 to 3 T1D for patients already carrying a Stage 2 diagnosis.

It is entirely inappropriate to disregard the impact of Stage 2 diagnosis and not to apply a disutility at this point. This ignores expert clinical opinion that the Stage 2 diagnosis has an impact on HRQoL and disregards the statistically significant evidence that diagnosis of Stage 2 T1D has a measurable impact on HRQoL. Furthermore, it is clear from the Guenther et al (2025) study described above that the availability of an effective DMT such as teplizumab helps to mitigate this. To exclude these disutilities would underestimate the real-world benefit of delaying Stage 3 T1D onset and bias the model against delay.

3.4 Conclusion

Disutility for Stage 2 T1D should be included to reflect the impact associated with seemingly healthy individuals receiving a diagnosis of a chronic and progressive disease. The UK general population vignette study (Guenther et al., 2025) provides significant evidence of a HRQoL impact from Stage 2 T1D diagnosis and demonstrates that a DMT, like teplizumab, provides a statistically significant benefit in reducing this impact. This finding is supported by expert clinical validation.

Topic 4. Managing Stage 3 Costs

- Costs are based on Danish real-world evidence (RWE). This has been accepted as the best available source by the committee.
- Clinical experts have confirmed that the quadratic extrapolation of this RWE is more appropriate than the linear approach taken by the EAG.
- Our unadjusted extrapolation for Stage 3 costs is more conservative at £368.80 per month than £415.22 derived from Hex et al. (2024; unadjusted for Hybrid Closed Loop (HCL) costs to ensure equivalence).
- HCL uptake is assumed to be 85% in the expected patient population based on correspondence with the [redacted].
- Acquisition costs and expected long-term benefits associated with HCL, based on a HbA1c reduction of -0.5% (Edgvist, 2021; TA943) are included in the model.
- Despite HCL availability and uptake (and adjustment in the model), costly complications are expected to persist and increase over time to relatively high levels in the outer years.

We note that the committee has accepted the use of the Danish real-world evidence (RWE) dataset presented at ACM2, and that there are no concerns regarding the observed data up to 19 years. Extrapolation beyond this point is required and our approach is discussed in detail below.

To model the Stage 3 T1D costs over a lifetime which includes Hybrid Closed Loop (HCL) availability as requested by the committee, we made three key assumptions that were presented at ACM2:

1. Extrapolation of costs beyond the 19 years of observed data using a quadratic approach.
2. Two adjustments for HCL:
    a. HCL acquisition costs (£5,115.10 inc. a notional 10% discount given confidentiality) added per annum.
    b. Reduction in costs to account for the expected benefit of HCL reducing long-term T1D complications. This reduction was estimated using the Core Diabetes Model (CDM) running with and without the expected HbA1c benefit observed with HCL (-0.5%; Edqvist 2021; TA943)[22], and

applying the net modelled reduction in complication-related costs (-11% at 10 years; -25% at 50 years) to the extrapolation.

More detail on, and justification for, this approach is provided below.

4.1 Extrapolation of costs beyond the observed data

4.1.1 Methodology and statistical fit

Ordinary least squares regression (OLS) models were used to estimate costs past the 19 years of follow up in the Danish RWE dataset for both people living with Stage 3 T1D (Figure 3) and healthy controls (Figure 4). Linear, quadratic, power and exponential models were tested. The goodness-of-fit of the OLS models were evaluated by the coefficient of determination R^2, with values closer to 1 indicating a better degree of fit. The quadratic models provided the best fits for both individuals with Stage 3 T1D (R^2 = 0.8871) and healthy controls (R^2 = 0.959; Table 6) and were validated by clinical opinion (see 4.3.1). These were used in our base case.

We note that the External Assessment Group (EAG) preferred linear extrapolations. These do not fit the observed data as well as the quadratic estimators and were considered to grossly underestimate likely costs by all the clinical experts we spoke to. The committee also had concerns with this approach acknowledging that the costs were likely to increase over time and the EAG costs are too low (Committee discussion document page 5 paragraph 3).

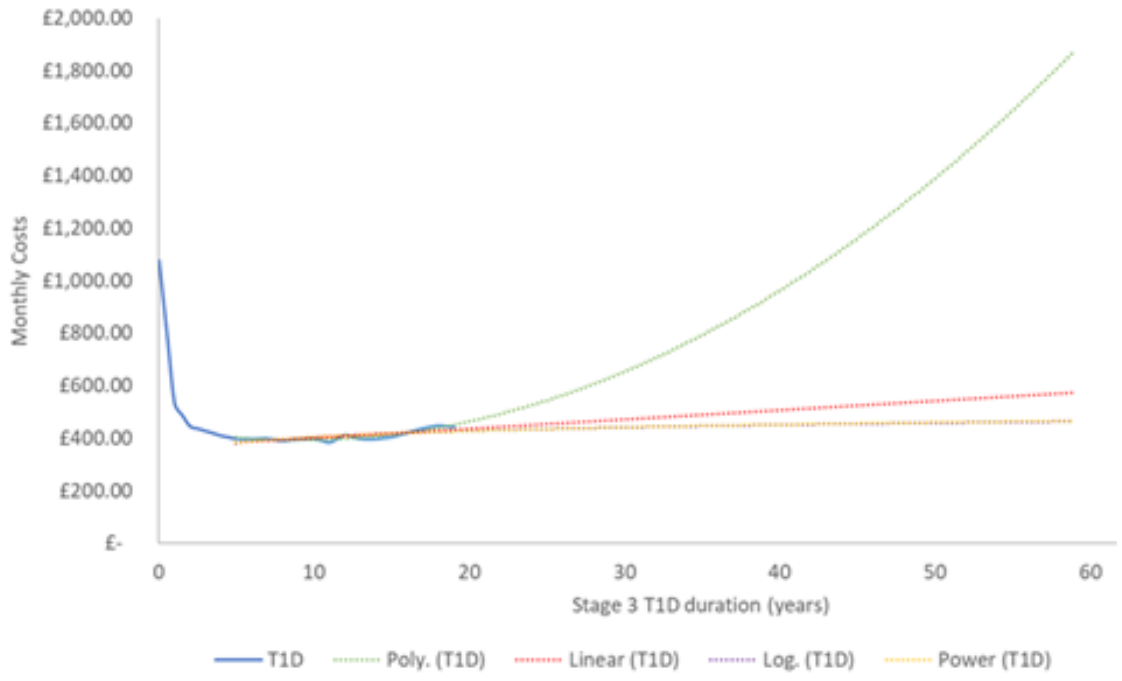


Figure 3. Extrapolations for costs over time for individuals with Stage 3 T1D
Note that the 'Log' and 'Power' extrapolations overlap

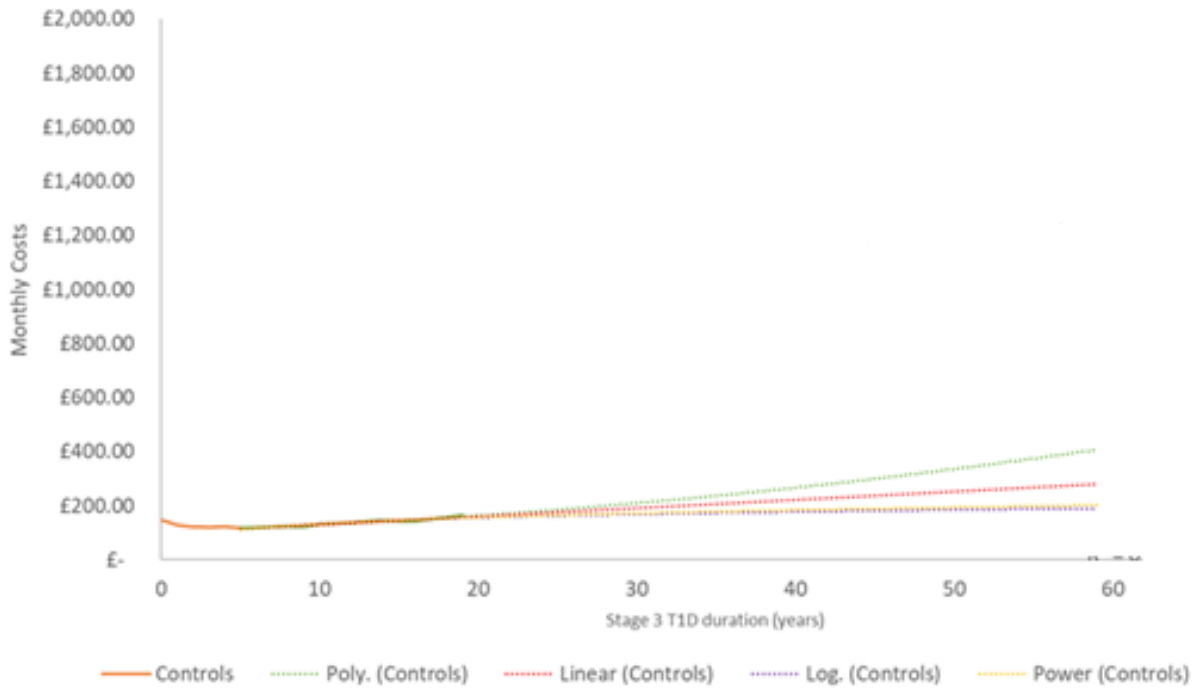


Figure 4. Extrapolations for costs over time for control individuals

Table 6. Extrapolations of Stage 3 T1D costs

Equation	Equation	R^2
Individuals with Stage 3 T1D		
Poly (Quadratic)	[redacted]	0.8871
Linear		0.6334
Log		0.4935
Power		0.5053
Controls		
Poly (Quadratic)		0.959
Linear		0.9541
Log		0.9038
Power		0.9209

4.1.2 Accruing costs in the model is contingent on survival

It is true that the cost for an individual patient will increase to relatively high levels if that person survives many decades after diagnosis, but it is important to remember that the accepted model structure is a cohort model and costs are applied according to the weighted average of duration since diagnosis and proportion alive at each time point. For this reason, the *average per person* cost of Stage 3 T1D in the model does not increase in the long run as shown in the depiction of the quadratic fit in Figure 5. The committee should be reassured that our approach does not overinflate costs in the outer years.

This is because accruing costs is contingent on survival to that time point. In practice after weighting for survival, the average cost per person used in the model diverges from the projected cost after ~35 years following diagnosis and again at ~60 years (Figure 5). The contribution to the cross-sectional population average does not increase significantly with the increasing cost in the outer years, because few patients are alive to contribute those higher costs. This is illustrated for both our (Figure 5) and EAG approaches (Figure 6).

The credibility of the linear approach to extrapolation using the EAG approach was questioned by the committee and the clinical experts because of the known increase in costly complications over time in Stage 3 T1D, even with HCL. The clinical implausibility of the EAG approach is further highlighted when the survival-weighted annual costs are plotted (Figure 6). Indeed, inspection of Figure 6 shows the contribution to the cross-sectional population costs used in the model decreases at every time point. This is not credible in a progressive, chronic disease characterised by costly complications several decades after diagnosis (see section 4.3.2).

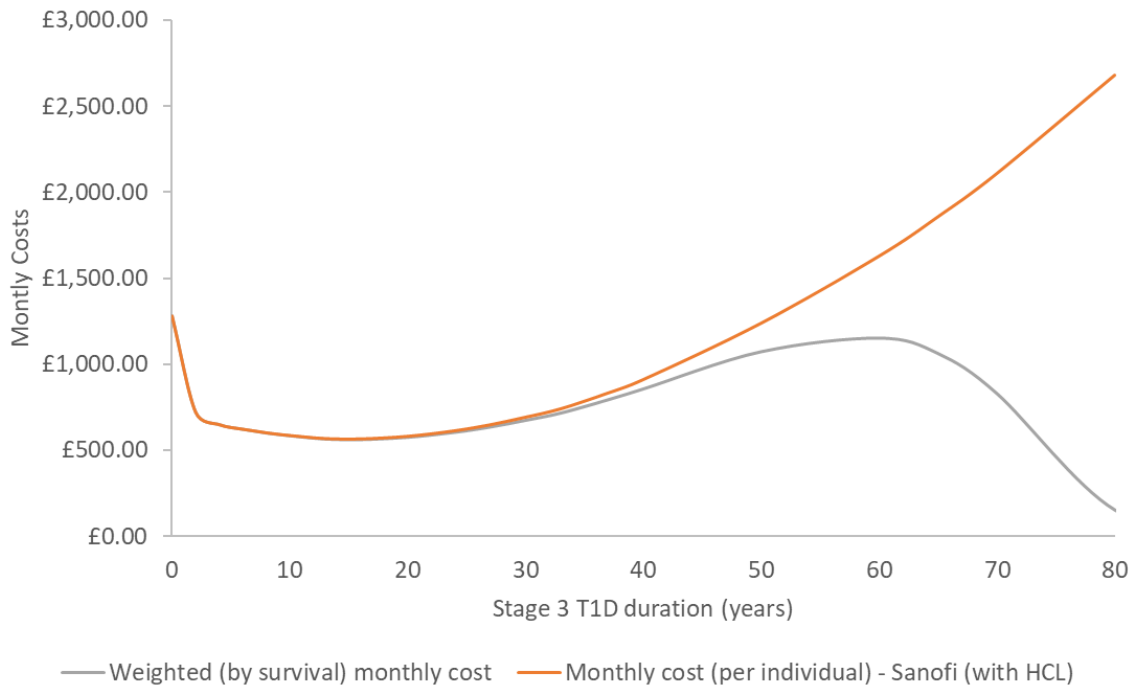


Figure 5. Company base case: monthly Stage 3 T1D costs when accounting and not accounting for survival

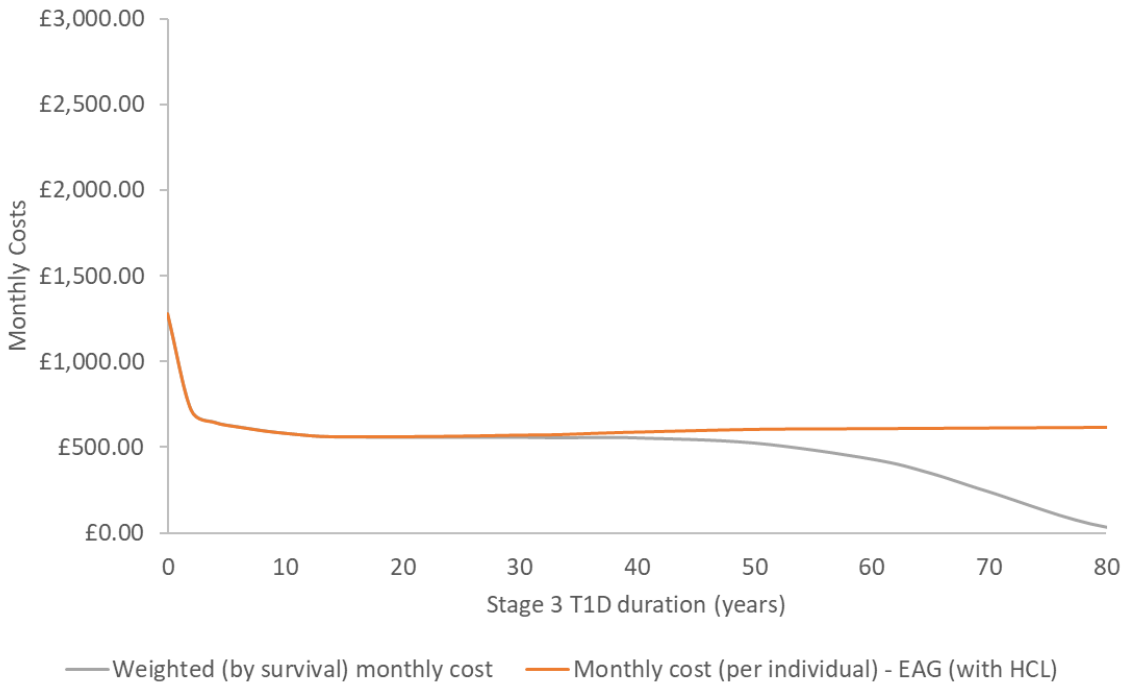


Figure 6. EAG base case: monthly Stage 3 T1D costs when accounting and not accounting for survival

4.2 Adjustments for HCL

4.2.1 Modelling HCL impact on long-term complications

The ACM2 committee document incorrectly states that the company approach "*included the additional costs of hybrid closed loops using the Core Diabetes Model (CDM)*".

HCL is expected to improve diabetes control. The CDM was used to model the impact on long-term complication costs in two scenarios: A) where an individual receives HCL and B) one where they do not. This was done to estimate the proportional reduction in costs that might be associated with better management through HCL and **not** to generate the absolute cost for use in the model. When the proportional reduction in costs is applied to the extrapolation of the Danish RWE to adjust for HCL uptake, the costs are decreased not increased (there are no '*additional*' costs).

We captured the impact of HCL using the CDM by considering the following:

1. HCL is expected to reduce HbA1c by -0.5% compared to those who do not use HCL (-1.48% vs -0.98%; Edgvist, 2021; TA943).[22]

2. When this is applied in the CDM the proportional reduction in costs is:
    a. At year 10: use of HCL reduces complication costs by 11%

b. By year 50: use of HCL reduces complication costs by 25%

These adjustments were applied to the extrapolated cost data to model the expected cost-saving associated with avoided complications with HCL.

4.2.2 HCL uptake from a healthcare service perspective

The recent NICE recommendation for HCL (TA943) has resulted in steep uptake for the technology over the last two years particularly in the paediatric population.[23] Our original submission included 100% uptake of the technology for the modelled population but with the recognition that this is likely an overestimate. We have revised our base case to reflect a more nuanced view of HCL in the population of interest. This is based on personal communication with [redacted], who explained that current uptake is ~72%, with expected plateau at 80-85%. Hence, we have chosen the upper limit of 85% for the revised base case. Note that we have removed any cost-saving associated with a reduction in long-term complications for the 15% who do not receive HCL in the base case to avoid double counting.

The EAG implementation of HCL uptake at 54% is a significant underestimate. This represents HCL uptake across the entire prevalent cohort, including all ages, and is taken from NHS England 2024/25 data. This is not the representative population for teplizumab who are likely to be younger (note the peak age of T1D diagnosis in England and Wales is 12 years (based on National Diabetes Audit [NDA] data from 2019-2020).[24]

4.3 Validation

4.3.1 Expert clinical opinion

In response to the call for additional evidence, expert clinical opinion was sought from three leading clinicians to validate the plausibility of the approaches to modelling Stage 3 T1D costs:

[redacted]

Table 7 compares the annual cost projections for the quadratic (Company base case) and linear (EAG base case) projections at various time points. These were used to anchor the conversations with the clinical experts. Before discussing the magnitude of the costs, we explained that the costs in Table 7 were contingent on surviving to those time points and noted that very few patients are alive in the outer years. For example, if a person was diagnosed with T1D 40 years ago our projection suggests that they would attract an annual cost of [redacted] but the EAG projected costs are [redacted] and so on.

Clinical experts strongly felt the EAG's cost projections were significantly underestimated. They raised concerns that estimates may be limited to HCL acquisition costs and appeared adjusted only for inflation, without accounting for rising diabetes-related complications. Experts also highlighted that not all patients will adopt HCL technology, and even those who do must maintain long-term adherence to achieve benefits, explaining even in this case complications are still expected. One expert cited data that average HbA1c for HCL users is 7.2%, well above the ≤6.5% target for optimal control. Experts explained that costs can vary considerably, where some people get fewer complications and some are very expensive to the system- typically those who fail to adhere to treatment. Even under good management, long-term outcomes for T1D are still associated with costly complications.

Therefore, there was consensus that the Sanofi projected costs were more reflective of real-world clinical practice. However, there was hesitancy that [redacted] at 80 years could be too high. Clearly some patients will attract very high costs in the outer years including renal failure, amputation and other complications, but not all patients will. The clinical experts were more comfortable with an annual cost closer to those estimated around 60 years than at 80 years. We have tested this assumption in scenario analysis by capping the projection at 65 years (see section 7.2).

Table 7. Annual cost projections for different projections

Stage 3 T1D duration	**% surviving at this point**	**Sanofi's projections for annual treatment cost (quadratic)***	**EAG's projections for annual treatment cost (linear)****
20 years	[redacted]	[redacted]	[redacted]
40 years	[redacted]	[redacted]	[redacted]
60 years	[redacted]	[redacted]	[redacted]
80 years	[redacted]	[redacted]	[redacted]

*Sanofi projection is adjusted to assume an 85% uptake in HCL

** EAG projection is adjusted to assume a 54% uptake in HCL

4.3.2 Clinical plausibility

T1D is a progressive, chronic disease characterised by costly complications several decades after diagnosis of/progression to Stage 3. Expected complications of long-term T1D are summarised in Table 8.

As Stage 3 T1D duration increases, both microvascular and macrovascular complications become more prevalent. Microvascular complications including diabetic retinopathy, nephropathy, and neuropathy show strong associations with disease

duration.[25] The risk of macrovascular complications, particularly cardiovascular disease increases significantly with age and T1D duration, with approximately 14-33% of T1D patients developing cardiovascular disease by age 65.[26] The EURODIAB study demonstrated that after 15 years of T1D, approximately 37% of patients had at least one complication, rising to over 70% after 30 years of disease duration.[27] The T1D Exchange Registry found that by age 50-65, nearly 32% of patients had at least two complications, regardless of age at diagnosis.[28] National Diabetes Audit data (2023) for England confirms an incremental elevated risk of stage 3 T1D associated complications with both age and diabetes duration.[74] Notably, the audit identifies elevated risk rates for chronic kidney disease (condition) and hospital admissions related to both micro and macrovascular complications with increasing age and disease duration (Table 8).

Increased prevalence of diabetes complications will be associated with an increased cost of diabetes care. Individuals with the most severe and advanced complications which require interventions, represent a significant proportion of patients with complications and present the greatest financial impact. Interventions, such as dialysis for end-stage renal disease, coronary intervention for myocardial infarction and lower limb amputation for severe neuropathy will represent the highest healthcare resource utilisation costs (see Appendix 4).

While HCL systems represent a significant advancement in T1D management and demonstrate improved glycaemic outcomes that may reduce long-term complication risk, they do not eliminate complications entirely, and residual risk remains. Meta-analyses of HCL systems show improvements in time-in-range (TIR) to approximately 70-75% and HbA1c reductions of 0.3-0.5% compared to standard insulin therapy [29,30], this suggests a potential offset and reduction in diabetes-associated complications with increased glycaemic control but not complete prevention.

Indeed, HCL use may not result in a TIR above 70% in all individuals. A UK observational study in adults switching from an insulin pump and intermittent scanned CGM to HCL technology showed that despite increased % TIR and HbA1c reductions over a median follow up of five months, 72% of HCL users did not reach the internationally recommended target of ≥70% TIR and <4% time below range.[31] A recent retrospective study in children with new HCL use, suggested that despite improved glycaemic control with HCL overall (increased time in range from 39% to 57%), 10% of children discontinued their use of HCL over a mean period of 9 months and 9% of children either had new onset or worsening retinopathy (mostly by one stage), highlighting that improved control may slow but does not halt complication development.[32]

Furthermore, HCL systems do not address non-glycaemic risk factors for complications including hypertension, dyslipidaemia, genetic susceptibility, and cumulative glycaemic exposure from years prior to HCL initiation.[28] Long-term data from the DCCT/EDIC study indicates that even individuals who achieved near-normal glucose control still

developed complications at rates substantially higher than non-diabetic populations, with legacy effects of earlier poor control persisting for decades.[25,33] Therefore, while HCL technology offers meaningful improvements in diabetes management and may attenuate complication progression, complications are not expected to be eliminated entirely.

Table 8. Summary of risk rate of long-term complications of Stage 3 T1D by age demographic and diabetes duration

	Risk Rate/1000 people grouped by age demographic			Risk Rate/1000 people grouped by diabetes duration			
Complication type	**20-49 years**	**50-74 years**	**75+ years**	**0-9 years**	**10-19 years**	**20-29 years**	**30+ years**
Chronic kidney disease – Condition	25.9	106.4	301.5	30.8	57.4	106.2	138.5
Renal Replacement Therapy - Hospital admissions	8.4	13.5	8.1	2.8	8.8	15.9	13.9
Minor Amputation - Hospital admissions	2.1	5.7	5.4	0.9	3.2	4.8	6.2
Major Amputation - Hospital admissions	0.8	2.2	1.9	0.4	1.0	2.0	2.4
Myocardial Infarction - Hospital admissions	1.9	9.2	18.3	2.4	3.9	7.6	11.6
Heart Failure - Hospital admissions	5.2	29.9	99.6	8.8	17.2	29.9	38.4
Stroke - Hospital admissions	1.9	10.5	28.1	3.1	5.4	9.6	12.7

Data is taken from national diabetes audit Complications and Mortality Outcomes dashboard, 2009-2023[74]. Data presented in the table uses the following filters: Organisation code: ENG, Organisation name: England, Organisation type: Country, Year: 2023, Complication type: Condition or Hospital admission (as specified in table) Admission type: any, Diabetes type: type 1 Sex: All.

4.3.3 Comparison with published estimates

The committee and the EAG have referred to the published estimate of £415.22 per month derived from Hex et al. (2024) because it represents UK specific costing data for T1D.[22] £415.22 is an approximate cross-sectional average of the monthly cost of a Stage 3 T1D population in one year (2021-22). This represents a weighted average across the entire prevalent population (all ages and duration of diagnosis) and crucially does not account for present-day HCL availability. Nonetheless we can use this figure to validate the unadjusted extrapolations, by applying the same calculation and comparing the weighted averages (see Appendix 2 for explanation of these calculations).

The equivalent figure for our unadjusted quadratic extrapolation is £368.80. This is similar but slightly lower than the Hex et al. (2024) estimate. In contrast, the linear extrapolation (preferred by the EAG) produces an equivalent value of £280.76 illustrating how this approach is likely to significantly underestimate the costs associated with Stage 3 T1D management by approximately a third (-32%). This projection lacks further face validity as it contradicts the known increasing incidence of costly Stage 3 T1D complications over time.

When adjusted for HCL as per committee requests our monthly estimate increases to £666.90 and the EAG to £595.50. These estimates include the impact of using HCL (both in terms of clinical benefit and acquisition cost; our assumption for uptake is 85% vs EAG uptake: 54%), which was not accounted for in the estimates published by Hex et al. (2024).[34]

4.4 Scenario analysis

The following scenarios were explored. The ICER impact of these scenarios are in section 7.2:

1. The costs for Stage 3 T1D management are capped in the model once an individual has lived with Stage 3 T1D for 65 years. After this point the same cost applies every year until death. This provides a scenario where the extrapolation of the costs to very high levels is attenuated in concordance with the views of the clinical experts.
2. HCL uptake at 100%, to illustrate the expected maximum benefit expected with the availability of HCL technology.

4.5 Conclusion

Clinical experts have confirmed that the quadratic extrapolation is more appropriate than the linear approach taken by the EAG for modelling Stage 3 costs over time. This is further validated by comparing the approaches to the monthly figure derived from Hex

et al. (2024; £415.22), whereby the unadjusted quadratic approach is conservative at £368.80 per month (-11% vs Hex), but the linear approach is a considerable underestimate at £280.76 per month (-32% vs Hex).

HCL uptake is assumed to be 85% in the expected patient population based on correspondence with the [redacted], with the model including acquisition costs and expected long-term benefits associated with HCL based on a HbA1c reduction of -0.5% (Edgvist, 2021; TA943). Despite HCL availability, uptake, and model adjustments, costly complications are expected to persist and increase over time to relatively high levels in the outer years.

Topic 5. Committee Other Considerations and Preferred Assumptions

We acknowledge and accept the committee position on the following issues/assumptions following ACM2, and have captured these in the revised base case:

1. Using an incidence rate of 4.6% for cytokine release syndrome (CRS) in the teplizumab arm of the model
2. Using the log-normal distribution for time to onset of Stage 3 T1D in the teplizumab arm
3. Using the gamma distribution for time to onset of Stage 3 T1D in the teplizumab arm
4. Using the company's revised approach to Stage 3 disutility in the model presented at ACM2

Topic 6. Willingness to Pay and Discounting

The willingness to pay (WTP) for teplizumab should be towards the higher end of the threshold.

Teplizumab addresses a significant unmet need. It is the first and only disease-modifying therapy to delay the onset of Stage 3 T1D.

- Median time to onset of Stage 3 T1D was 5.0 years vs 2.3 years in the placebo arm (while also preserving the C-peptide response).
- [redacted] as many people are expected to be Stage 3 T1D-free at 10 years when treated with teplizumab compared to established clinical management alone ([redacted] vs [redacted] respectively), well beyond the 2.7-year difference observed at the end of the trial extension.

T1D is a disease of inequality across socioeconomic and ethnic groups.

- Worse glycaemic control is experienced in populations with lower socioeconomic status and certain ethnicities.
- Diabetic ketoacidosis (DKA) is associated with lower socioeconomic status.
- Diabetes distress (DD) among caregivers of adolescents with T1D is associated with deprivation and protected characteristics.
- Teplizumab has the potential to address these issues and reduce inequality.

The forthcoming change to the NICE cost-effectiveness threshold means that the committee should exercise flexibility in setting the WTP for teplizumab.

1. It is important to recognise the benefits to unmet need, equality and innovation that teplizumab represents.
2. Uncertainty has been reduced though the NICE process.
3. The WTP should be considerably higher than the midpoint of the current threshold of £25k/QALY, which is the lower bound of the new WTP envelope.

Applying a 1.5% discount rate is justified.

- T1D is a lifelong disease with peak age of diagnosis of 12 years.
- Delay to onset and preservation of β-cell function in children means that teplizumab is expected to alter the lifetime trajectory of disease.
- The full value of future health gains must be appropriately captured to avoid undervaluing an important preventive intervention with enduring impact not

6.1 Willingness to pay

The willingness to pay (WTP) for teplizumab should be towards the higher end of the threshold.

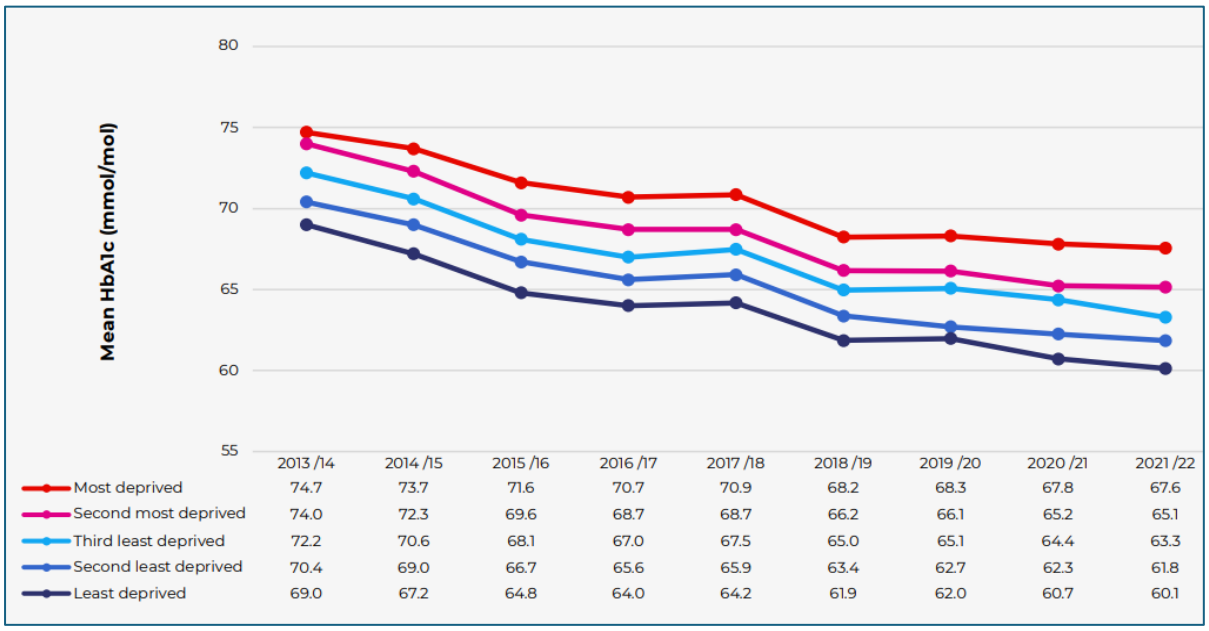
As yet the committee have not provided an indication of their willingness to pay (WTP). We provide more context below describing inequality in T1D, the reduction in uncertainty in the economic modelling following ACM2 and a discussion on the upcoming threshold change from £20k - £30k/QALY to £25k - £35k/QALY to help the committee reach a conclusion on the most appropriate WTP threshold.

6.1.1 Inequality in T1D

Whilst there is no quintile of the index of multiple deprivation (IMD) with a higher or lower likelihood of having T1D, nonetheless T1D is a disease of inequality in outcomes for patients and caregivers alike across different sectors of society. Expert clinical opinion gathered for this response indicated that teplizumab provides a therapy that people from disadvantaged backgrounds are more likely to adhere to (ie a 14 day treatment course vs a lifetime of insulin management/monitoring), with the benefits of teplizumab treatment persisting much longer than those 14 days.

6.1.2 Impact of deprivation on HbA1c control

National Paediatric Diabetes Audit (NPDA) data up to 2022 show that mean HbA1c has improved over the last 10 years or so, but deprivation remains a significant factor in achieving optimal control Figure 7.



	2013 /14	2014 /15	2015 /16	2016 /17	2017 /18	2018 /19	2019 /20	2020 /21	2021 /22
Most deprived	74.7	73.7	71.6	70.7	70.9	68.2	68.3	67.8	67.6
Second most deprived	74.0	72.3	69.6	68.7	68.7	66.2	66.1	65.2	65.1
Third least deprived	72.2	70.6	68.1	67.0	67.5	65.0	65.1	64.4	63.3
Second least deprived	70.4	69.0	66.7	65.6	65.9	63.4	62.7	62.3	61.8
Least deprived	69.0	67.2	64.8	64.0	64.2	61.9	62.0	60.7	60.1

Figure 7. Mean HbA1c by deprivation quintile for those with Type 1 diabetes, 2013- 2022
Figure reproduced from the National Paediatric Diabetes Audit Report on Care and outcomes 2021/22[35]

Similarly, whilst HbA1c control is improving across all ethnicities over time in England, persistent inequality in HbA1c outcomes associated with ethnicity remain and the gap

is not closing. Access to modern technologies such as real time continuous glucose monitoring (rtCGM) also remains an important discriminator between ethnicities and by IMD.[35]

6.1.3 Impact of deprivation on other important outcomes

Critically Stage 3 T1D is often diagnosed when patients present at hospital with Diabetic Ketoacidosis (DKA). This is a dangerous complication that requires hospital admission and can be fatal.

Whilst there is no evidence to suggest that the use of teplizumab may alter the rate of DKA per se, the testing likely to be established will help to reduce incidence of DKA. The committee have requested that the additional costs of testing are included and we have implemented them in several scenarios, however it is important to note that in all cases only the costs attributable to testing are included. For example, in the committee preferred scenario in which testing costs are added to the teplizumab arm alone, no additional quality of life benefit or cost offsets due to avoided DKA as a consequence of screening are modelled. This disproportionately benefits established clinical management in the modelling.

Given the preference of the committee to include testing costs in this way, it is critical to recognise at least qualitatively the potential for differentiated impact of DKA at the transition between Stage 2 and 3 T1D in different populations. This can be considered from an equity point of view.

There is a growing evidence base that shows there is a significant association between lower socioeconomic status and DKA at diagnosis. For example a very recently published multicentre observational study in England with data collected from nine paediatric diabetes units across five English regions (West Midlands, East Midlands, Yorkshire and Humber, London and the South East, and East of England) showed that children in the most deprived quintile (IMD1) had a 51.8% DKA rate compared to 28.0% in the least deprived quintile (IMD5) (p=0.0007). This study is the largest of its kind to date and found that centres serving more deprived communities had much higher rates of DKA than those serving more affluent populations. Notably these figures are higher than the reported national incidence of 23.3% in the National Paediatric Diabetes Audit (NPDA).[35] This further highlights the discrepancy in DKA outcomes according to IMD because the participating centres in the study serve populations with disproportionately high levels of deprivation.

The authors of the study point towards the need for multi-stage awareness campaigns targeting deprived areas, alongside consideration of targeted testing to support earlier diagnosis and education to prevent DKA.

A national reimbursement recommendation for teplizumab could help to address some of these concerns. In the responses to the draft guidance following ACM1 it was noted

by a respondent that: *'The widespread use of teplizumab would reduce the number of people who experience DKA when diagnosed with type 1 diabetes and avoid people "crash-landing" into symptomatic onset of the condition. This would both help people avoid the trauma and harms of DKA and generate significant cost-savings for the NHS'.*

Another important issue is diabetes distress (DD) among caregivers of adolescents with T1D. This is also associated with deprivation and protected characteristics. Indeed, family income, marital status, caregiver sex, and child age have been known for some time to be risk factors for caregiver DD.[36-38] Most recently a study directly addressing this issue was published in 2025 and was the first of its kind among caregivers of adolescents with T1D. This examined demographic, family, and diabetes factors associated with DD.[39] This US study was a two-site randomized clinical trial aimed at treating DD. It found that female caregivers, caregivers of younger adolescents, caregivers reporting lower household income, caregivers of lower subjective social status, and single/non-partnered caregivers reported significantly higher caregiver DD than their counterparts.

UK clinical expert advice provided to Sanofi during our preparation for this appraisal indicated that extended time in Stage 2 would provide more time to understand the diagnosis, prepare and more thoroughly learn how to manage Stage 3 T1D. All of which may help contribute to reducing DD and ultimately lead to improved outcomes by reducing the likelihood of DKA and reducing glycaemic exposure prior to and immediately after the onset of Stage 3 T1D.

6.1.4 Mitigation of uncertainty

Key uncertainties identified by the EAG and committee have been resolved at ACM2. These include:

- The appropriate parametric fitting methods for progression from Stage 2 to Stage 3 T1D. (Teplizumab: Log-Normal; Established clinical management: Gamma).
- Disutility for individuals living with Stage 3 T1D over the time horizon of the model (Absolute rate: up to 10 years -0.0026 (-0.28%), 11+ years: -0.0028 (-0.30%)

The remaining uncertainties following ACM2 are addressed in this document.

6.1.5 Threshold change

Recently proposals have been put forward to increase the cost-effectiveness threshold from £20k - £30k/QALY to £25k - £35k/QALY. It is our understanding that this new threshold will be implemented soon and apply to ongoing appraisals with the goal to improve access to advanced treatment innovations.

Teplizumab addresses unmet need, equality and innovation alongside the reduction in uncertainty achieved though the NICE process. Even if the formal implementation of the increased threshold is not in place at the time of the final decision making for

teplizumab we urge the committee to consider the most appropriate WTP in the context of the update to the methods and the important step change that teplizumab represents.

6.1.6 Conclusion

Taken together, the potential for teplizumab to decrease inequality in T1D, the resolution of key uncertainties identified during the NICE process and consideration of the threshold change point towards a plausible WTP considerably higher than the midpoint of the current threshold of £25k/QALY, particularly as this is the lower bound of the new WTP envelope.

6.2 Discount Rate

Type 1 Diabetes (T1D) is an autoimmune condition characterised by chronic high blood sugar (glucose) levels which progressively worsens over time. Once a person is diagnosed with Stage 3 T1D they face a permanently greater risk of death from hypoglycaemia, serious complications such as DKA,[40,41] and chronic complications and comorbidities such as kidney disease and cardiovascular disease.[42-44] Diagnosis is usually made in childhood and from this point forward patients must carefully manage their insulin, carbohydrate and exercise levels for the rest of their life. This lifelong impact of T1D means that it is important to fully recognise long-term future health gains and costs within the economic modelling framework, not least to ensure intergenerational equity.

The methods guide states that '*Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis*' and places the reference case discount rate at 3.5%. However, in specific circumstances alternative analyses using rates of 1.5% for both costs and health effects may be presented. The updated NICE manual confirms that non-reference case analyses can be considered particularly for technologies which can deliver long-term benefits.[45]

The population in the economic analyses is 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. The mean age in the TN-10 study (and implemented in the model) is 13.58 years and the expectation for the use of teplizumab in the real world is in younger people (the peak age of T1D diagnosis in England and Wales is 12 years (based on National Diabetes Audit [NDA] data from 2019-2020).[24] Teplizumab has been shown to delay the onset of Stage 3 T1D by 2.7 years (median time to onset 5.0 vs. 2.3 years; difference: 2.7 years; p=0.01) while also preserving the C-peptide response.[46,47] Importantly, this delay is likely to occur in childhood, a period

when early exposure to hyperglycaemia has a profound and lasting impact on long-term health outcomes.

The clinical experts at committee explained that short-term control of T1D can reduce the risk of complications in the long term despite diabetes progression. The TN10 study ran for over 7 years including follow-up but the primary end point was onset of Stage 3 T1D and not the investigation of long-term complications. However, much longer-term evidence from longitudinal studies does demonstrate that even short-term reductions in cumulative glycaemic exposure significantly reduces the risk of microvascular and macrovascular complications and can improve outcomes and survival over decades.

- **Early-Onset Risk:** Children diagnosed with T1D face the longest exposure to hyperglycaemia, increasing lifetime risk of nephropathy, retinopathy, and cardiovascular disease.

- **DCCT/EDIC Legacy Effect:** The Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that early glycaemic control has a lasting impact on reducing complications and mortality, even decades later.[48] A key finding was that people who had intensive glucose control early in the disease continued to experience lower rates of complications and mortality many years later, even when glycaemic control became similar to the conventional group. This 'legacy effect' shows short-term improvements in glycaemic exposure translate into long-term health gains.

6.2.1 Conclusion

TN-10 was a relatively long study which ran from July 2011 through to March 2020 (primary cut-off: November 2018; extended follow-up: March 2020). This follow-up was not designed to investigate the complications of diabetes which, in any case, manifest after many decades. By year 7.5 in TN-10, all individuals in the placebo group had progressed to Stage 3 T1D, and 5 teplizumab-treated individuals had not progressed to Stage 3 T1D.

Delaying Stage 3 T1D onset and preserving β-cell function in children and young people during key formative years (a critical developmental window early in life, and notably in adolescents when Stage 3 T1D is often less well managed), means that teplizumab is expected to alter the lifetime trajectory of disease burden well beyond the observed 2.7 year delay to onset. This meets the spirit of the NICE criteria for the application of the non-reference case and plausibly supports the case for 1.5% discounting.

Applying a 1.5% discount rate results in a 78.3% reduction in the ICER vs. the 3.5% rate illustrating the significant and lasting effect of delayed onset of Stage 3 T1D. 1.5% is justified to ensure the full value of these future health gains is appropriately captured

and avoids undervaluing an important preventive intervention with enduring impact.

7. Revised Base Case & Scenario Analysis

7.1 Base case results

In line with Topics 1-5 above, we have revised our base case. Assumptions related to the topics in the additional call for evidence are summarised below (Table 9).

Table 9. Revised base case assumptions (assumptions relevant to call for additional evidence)

Parameter	Description	Justification	Tested in sensitivity analysis?
Testing costs	Blended cost estimate of £224.15 (blended estimate 13% NHS and 87% not NHS) applied to both arms of the model.	• Recent UK publication • Expert clinical validation	Yes
Caregivers	1.76 caregivers maintained for individuals aged < 25 years old. (disutility applied: -0.04)	• Recent publication • Patient testimony	Yes
Stage 2 disutility	Teplizumab: -0.049 vs ECM: -0.124	• Statistically significant evidence • Expert clinical validation	No (onset of Stage 3 T1D disutility is tested)
Stage 3 costs	Quadratic approach adjusted for expected HCL acquisition and impact on long-term costs aligned with 85% uptake.	• Expert clinical validation • Statistical, visual and clinical validity	Yes

The incremental cost-effectiveness results including the deterministic and probabilistic ICER are presented in Table 10 below. The disaggregated results for the base case are provided in Appendix 5.

Table 10. Revised base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£27,720
Teplizumab	[redacted]	[redacted]	[redacted]					
Probabilistic results								
ECM	[redacted]	[redacted]	[redacted]					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	£26,342

ECM: established clinical management

The convergence plot (convergence was achieved after ~200 iterations), scatter plot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 8, Figure 9 and Figure 10 respectively.

Figure 8. Convergence plot.

Figure 9. Scatter plot for incremental cost-effectiveness results (400 iterations)

Figure 10. Cost-effectiveness acceptability curve (400 iterations)

The probability of being cost effective at £20,000/QALY is [redacted] and at £30,000/QALY it is [redacted].

7.2 Scenario analysis

Scenario analyses and associated ICER impact are presented in Table 11.

Table 11. Scenario analysis

	Scenario description	Justification	Analysis	Incremental Cost	Incremental QALYs	ICER	ICER % change vs. base case
0	Base case	See Table 10	Deterministic	[redacted]	[redacted]	£27,720	NA
			Probabilistic	[redacted]	[redacted]	£26,342	NA
1	£224.15 patient identification cost applied to teplizumab only (blended estimate 13% NHS and 87% not NHS) *Base case = applied to both arms*	Committee request	Deterministic	[redacted]	[redacted]	£28,091	1.3%
			Probabilistic	[redacted]	[redacted]	£26,922	-2.9%
3	HCL uptake = 100% *Base case = 85%*	Present "world with" HCL (ie expected maximum benefit from the technology)	Deterministic	[redacted]	[redacted]	£25,195	-9.1%
			Probabilistic	[redacted]	[redacted]	£23,862	-13.9%
4	Stage 3 T1D cost projections truncated after 65 years. *Base case uses projected series as per regression (quadratic) models.*	Removal of longer-term costs of which there is greatest uncertainty	Deterministic	[redacted]	[redacted]	£28,081	1.3%
			Probabilistic	[redacted]	[redacted]	£26,889	-3.0%
5	Stage 2 disutility applied, but no Stage 3 T1D onset disutility *Base case = -0.025.*	Abate concerns of double counting adjustment to T1D	Deterministic	[redacted]	[redacted]	£27,774	0.2%
			Probabilistic	[redacted]	[redacted]	£26,553	-4.2%
6	Number of caregivers = [redacted] *Base case = 1.76.*	Aligned to new caregiving survey output	Deterministic	[redacted]	[redacted]	£29,672	7.0%
			Probabilistic	[redacted]	[redacted]	£28,498	2.8%
7	Discount rates set to 1.5%. *Base case = 3.5%.*	See section 6.2	Deterministic	[redacted]	[redacted]	£6,005	-78.3%
			Probabilistic	[redacted]	[redacted]	£4,076	-85.3%

Conclusion

Teplizumab is a cost-effective innovation that addresses significant unmet need and represents good value for money to the NHS. It is the first disease-modifying therapy to delay Stage 3 T1D onset while preserving β-cell function, representing a step-change in the treatment pathway.

In line with committee asks, we have resolved the four remaining areas of uncertainty, and revised our base case appropriately:

- Patient identification costs that represent the full testing and diagnosis pathway (at a realistic blend of cost attributable and not attributable to the NHS) are included across both treatment arms.
- The multi-caregiver burden in managing a child or young person with T1D, validated through real-world survey data, is included.
- Stage 2 diagnosis disutility, and the benefit associated with a disease-modifying treatment like teplizumab, is included; again, validated by expert clinical opinion.
- Long-term Stage 3 T1D management costs are projected using quadratic extrapolation, which clinical experts confirm better reflects the accumulation of complications over time compared to the linear approach (EAG preferred assumption).

The probabilistic base case ICER is £26,342 / QALY which is well within the range generally considered to be cost effective to the NHS. All the parameters and assumptions above have been tested in sensitivity analysis and in no case does the ICER rise above £30,000 / QALY indicating that the updated base case is robust and credible.

The value of teplizumab extends beyond clinical efficacy. The intervention has potential to improve health equity for disadvantaged populations with worse T1D outcomes and deliver long-term benefits. This is doubly important for children and young people who often receive a diagnosis in key formative years which are a critical developmental window early in life when T1D is often poorly managed.

Given the clinical profile of teplizumab, potential equity impact and resolution of the key areas of uncertainty, flexibility in decision making should be available to the committee. The willingness-to-pay threshold should reflect the higher end of the current range which is highly likely to be extended soon, and a 1.5% discount rate should be considered to appropriately capture the lifetime value of delaying Stage 3 T1D progression and ensure intergenerational equity.

Appendices

Appendix 1. Exploration of Testing Costs in Other NICE Appraisals

Diagnosis of Early-T1D tends to follow three key steps (Besser et al., 2025):[5]

1. **Exploratory testing:** the initial autoantibody (AAB) test to determine if an individual could have Early-Type 1 Diabetes (T1D).
2. **Confirmatory testing:** for those positive at the exploratory phase, a venous capillary test & HbA1c test to confirm Early-T1D.
3. **Staging:** for those positive at the confirmatory phase, an Oral Glucose Tolerance Test (OGTT), or equivalent, to confirm which stage of Early-T1D the individual is in.

This flow is not dissimilar to the pathway observed in lung cancers (e.g. non-small cell lung cancer (NSCLC)) where early stages of the disease are also asymptomatic, rarely identified as incidental findings and patient awareness/willingness to present early may be influenced by availability of new treatments:

1. **Exploratory testing:** imaging diagnostics to confirm if an abnormality is present.
2. **Confirmatory testing:** for those confirmed at the exploratory phase, a biopsy to confirm if cancerous.
3. **Staging:** for those positive at the confirmatory phase, biomarker testing and staging.

In our analysis of relevant lung cancer NICE appraisals (durvalumab for NSCLC (TA1030); pembrolizumab for NSCLC (TA1037) and osimertinib for NSCLC 1b-3a (TA1043)), in all CEMs patients entered upon diagnosis and in the disease/event-free health state. This is the same as the agreed model structure for teplizumab. However, a critical difference is that **there is no evidence of upstream exploratory and/or confirmatory testing costs being considered in those CEMs**.

Therefore, if the committee considers it important that all pathway costs are considered in the model despite previous precedent, then our base case considers the additional testing costs due to teplizumab availability on both arms of the model.

Appendix 2. Secondary Caregiver

A2.1 Secondary caregiver survey flow

Respondent type	Sample size
- Parents/carers of children and young people (25 years or under) with T1 Diabetes Target quota = at least 50% of sample to have /care for a child with T1 Diabetes who is aged 8 or over	n = 100

Introduction

Thank you for your interest in this study being conducted by Red Leaf Research.

The study is being conducted on behalf of a pharmaceutical company. The purpose of this research is to understand more about the impact having a child, adolescent or young adult with type 1 diabetes places on parents, caregivers and families. The survey will take approximately 5 minutes to complete.

Red Leaf is an independent market research agency working within the codes of conduct of the Market Research Society (MRS) and British Healthcare Business Intelligence Association (BHBIA) and complying with Data Protection legislation.

- You have the right to withdraw from the survey at any time and to withhold information as you see fit. For more information about your rights please see our privacy notice, available at https://www.redleafresearch.co.uk/Privacy-Policy-v2.pdf

- We will not be collecting any personal data as a part of this survey but all the information we do collect will be treated confidentially and only used for the purposes of market research. It may be stored beyond the end of this market research study, for up to 12 months. Please contact our data protection representative at [redacted] if you have any queries regarding the research

- We would prefer not to reveal the name of the commissioning pharmaceutical company until the end of the survey in case knowing this influences any responses

Adverse events

Different patients sometimes respond in different ways to the same medicine, and some side effects may not be discovered until many people have used a medicine over a period of time. For this reason, we are now required to pass on to our client, who is a manufacturer of medicines, details of

any side effects related to their own products that are mentioned during the course of market research.

Should you mention in any of your answers a side effect when you, or someone you know, became ill after taking one of our client's medicines, we will need to report this, so that they can learn more about the safety of their medicines

Please confirm that you have read, understood and accept the points above and are happy to proceed with the market research survey on this basis.

SINGLE CODE

Yes	1	
No	2	CLOSE IMMEDIATELY

SCREENING QUESTION

TERMINATE RESPONDENT UPON FIRST CLOSE IN SECTION

S1. Are you a parent or caregiver of a child OR a young person aged 25 or younger with type 1 diabetes?

Yes	1	
No	2	CLOSE IMMEDIATELY

*Please note, if you have - or care for - more than one child or young person aged 25 or younger with type 1 diabetes, you should complete this survey **only once, for the oldest child or young person**.*

MAIN QUESTIONNAIRE

Q1. What is the age of this child or young person with type 1 diabetes?

Please note, if you have or care for more than one child or young person aged 25 or younger with type 1 diabetes, you should enter the age of the oldest child or young person here.

Dropdown menu	CLOSE IMMEDIATELY IF ENTER AGE OVER 25

Q2a. Within the household/family, would you describe yourself as the main person providing care for this child or young person with type 1 diabetes or not? PLEASE CHOOSE THE OPTION WHICH BEST MATCHES YOUR SITUATION

Yes, I am the main person	1	GO TO Q2b
No, I am not the main carer, but I am involved in their care	2	GO TO Q3

Q2b. Is anybody else within the household/family involved in the care of this child or young person with type 1 diabetes?

Yes	1	GO TO Q3
No	2	CLOSE

Q3. Which of the following aspects of caring for a child or young person with type 1 diabetes do you - or another caregiver within the household/family - get involved with? (SELECT ALL THAT APPLY)

Getting up in the night with the child or young person as a result of their diabetes (checking glucose, treating hypos, alarms, bolus/correction doses)	1
Checking child or young person's glucose levels during the daytime	2
Calculating insulin dose and administering insulin to the child or young person, including technology maintenance such as injection and pump site changes.	3
Ordering diabetes-related supplies for the child or young person (e.g CGM/pump supplies, test strips, insulin, ketone strips etc)	4
Attending diabetes-related appointments with the child or young person (e.g. appointments with GP, diabetes specialist team, eye screening etc)	5
Speaking to child or young person's school/educational/work setting about their diabetes (also e.g. recreational settings such as afterschool/sports clubs, friends' parents etc.)	6
Taking time off work to care for the child or young person due to their diabetes	7
Diabetes education/learning about managing Type 1 Diabetes	8
Other (please specify) _____	9

Q4. Thinking about the total time spent each week on all the different things listed at the previous question that have to be done to support the child or young person specifically with their type 1 diabetes…

…what % of that time do YOU spend doing these things and what % of that time does another caregiver spend doing them?

% of the total time providing care/support I am responsible for	___%
% of the total time providing care/support another caregiver is responsible for	___%

MUST ADD TO 100%

Q5. Are there any other ways that caring for a child or young person with type 1 diabetes impacts on your life, or the lives of others who support in their care (this could be physically, financially, emotionally, or anything else you would like to share).

OPEN TEXT

Q6. Can you share any insights about the mental burden that caring for a child or young person places on you or other caregivers?

OPEN TEXT

Q7. Not including healthcare professionals, from which organisations or sources outside of the household, if any, do you or other caregivers seek support in relation to your child or young person's type 1 diabetes? (SELECT ALL THAT APPLY)?

Breakthrough T1D

Carbs & Cals

Diabetes 101

Diabetes UK

DigiBete

Education programs e.g. DAFNE, BERTIE

Facebook groups

NHS website

T1resources.uk

TikTok

YouTube channels

Other social media e.g. X

Other (please specify)_____

THANK AND CLOSE; NAME SANOFI AS DATA CONTROLLER

A2.2 Calculation of the carer burden

There were [redacted] respondents to the survey.

Of the [redacted] respondents who answered Question 2b:

> *Is anybody else within the household/family involved in the care of this child or young person with type 1 diabetes?*

- [redacted] of respondents answered yes, indicating that there was a secondary caregiver within the household.
- [redacted] answered 'No' indicating they were the sole carer.
- [redacted] skipped this question

The ratio of carer giver burden for primary vs secondary caregiver was calculated taking into account the respondents who answered 'No' to Question1 and according to the answer to Question 4 which was:

> *Thinking about the total time spent each week on all the different things listed at the previous question that have to be done to support the child or young person specifically with their type 1 diabetes…*
>
> *…what % of that time do YOU spend doing these things and what % of that time does another caregiver spend doing them*

Question 4 was directed to the respondents who answered 'YES' to Question 2b (n = [redacted] answered this question) and asks about the proportions of the total time spent care giving. It was phrased in this way to make the concept easy to understand for respondents. Necessarily the proportions will sum to 1 across both caregivers but this does not mean that the caregiver burden is only 1.0 per patient. This cannot be the case when 2 people are involved. On the contrary, it allows for a ratio of burden to be assessed for the secondary carer vs the primary caregiver who represents 1. The secondary caregiver is in addition to this.

The calculation of the ratio of caregivers : patients was based on all [redacted] respondents : [redacted] who answered Question 4 and the [redacted] who were not included because they had already indicated that they were the sole caregiver. (There is no relevant data from the remaining [redacted] respondents who entered the survey).

For example, in the case where there is 1 carer the burden is 100% for that person and 0% for another person and the ratio is 1:1 carer : patient. For the hypothetical split of 66% : 33% the secondary carer represents 50% (33%/66% = 50%) and the ratio of caregivers to patients is 1.5 : 1.0. In the case where the caregiving is split equally between people the percentage are 50% and 50%. This means that the caregivers each shoulder the same burden and the number of carers is 2 per patient.

The full dataset is shown in Table 12 overleaf.

Table 12 Proportion of time spent caring for the dependent T1D patient.

Respondents who were the sole caregiver			**Respondents who indicated an additional caregiver**		
Anonymised Respondent (Convenience numbering)	**% of the total time I spend providing this care/support**	**% of the total time another caregiver spends providing this care/support**	**Anonymised Respondent (Convenience numbering)**	**% of the total time I spend providing this care/support**	**% of the total time another caregiver spends providing this care/support**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
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			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]

Respondents who were the sole caregiver			Respondents who indicated an additional caregiver		
Anonymised Respondent (Convenience numbering)	% of the total time I spend providing this care/support	% of the total time another caregiver spends providing this care/support	Anonymised Respondent (Convenience numbering)	% of the total time I spend providing this care/support	% of the total time another caregiver spends providing this care/support
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]

Respondents [redacted] to [redacted] (convenience numbering) indicated that the primary carer spent less than 50% of the total time providing support to the patient. (For example, Respondent [redacted]: [redacted] vs [redacted]). This suggests that in terms of burden the secondary carer shoulders more. It may be the case that these respondents did not fully understand the survey and the person answering the questionnaire felt that they were the primary caregiver for reasons other than the general burden of day-today caring. Nonetheless any ratio in which the primary carer is less than 50% under the assumptions above results in a nonsensical calculation (eg [redacted] suggests a ratio of [redacted]). Therefore, we have assumed that the carer in these cases with the larger proportion is the primary carer. This results in an adjusted calculation for the ratio (Table 13).

Table 13. Adjusted ratio of primary to secondary carer.

	PRIMARY carer (Adjusted sum of proportions in Table 12)	SECONDARY carer (Adjusted sum of proportions in Table 12)
Total Proportions	[redacted]	[redacted]
Ratio	[redacted]	[redacted]

Therefore, we have implemented [redacted] carers to one patient in sensitivity analysis.

Appendix 3. Stage 3 Costs: Calculation of Weighted Averages

Table 14 shows the calculation of the monthly weighted average cost for managing an individual with Stage 3 T1D without HCL according to the quadratic projection shown in Figure 3.

Stage 3 T1D duration (years)	% of individuals with Stage 3 T1D duration	Monthly cost
4	[redacted]	[redacted]
10	[redacted]	[redacted]
20	[redacted]	[redacted]
30	[redacted]	[redacted]
40	[redacted]	[redacted]
50	[redacted]	[redacted]
Weighted average		**£368.80**

Table 14. Weighted average cost based on Sanofi's projection without HCL

Table 15 shows the calculation of the monthly weighted average cost for managing an individual with Stage 3 T1D including HCL (85% uptake) according to the quadratic projection shown in Figure 3.

Stage 3 T1D duration (years)	% of individuals with Stage 3 T1D duration	Monthly cost
4	[redacted]	[redacted]
10	[redacted]	[redacted]
20	[redacted]	[redacted]
30	[redacted]	[redacted]
40	[redacted]	[redacted]
50	[redacted]	[redacted]
Weighted average		**£666.90**

Table 15. Weighted average cost based on Sanofi's projection assuming an 85% uptake in HCL

Table 16 shows the calculation of the monthly weighted average cost for managing an individual with Stage 3 T1D without HCL according to the linear projection shown in Figure 3.

Stage 3 T1D duration (years)	% of individuals with Stage 3 T1D duration	Monthly cost
4	[redacted]	[redacted]
10	[redacted]	[redacted]
20	[redacted]	[redacted]
30	[redacted]	[redacted]
40	[redacted]	[redacted]
50	[redacted]	[redacted]
Weighted average		**£280.76**

Table 16. Weighted average cost based on EAG's projection without HCL

Table 17 shows the calculation of the monthly weighted average cost for managing an individual with Stage 3 T1D with HCL (54% uptake) according to the linear projection shown in Figure 3.

Stage 3 T1D duration (years)	% of individuals with Stage 3 T1D duration	Monthly cost
4	[redacted]	[redacted]
10	[redacted]	[redacted]
20	[redacted]	[redacted]
30	[redacted]	[redacted]
40	[redacted]	[redacted]
50	[redacted]	[redacted]
Weighted average		**£595.50**

Table 17. Weighted average cost based on EAG's projection including HCL at 54% uptake

Appendix 4. Summary of long-term Stage 3 T1D complications

Complication	Prevalence	Prevalence by severity	Onset (years since Stage 3 T1D diagnosis)	Treatment	Approx. Cost
Retinopathy	34%[49] (increasing to >60% over 40 years disease duration) [50]	Diabetic macular oedema 11.1% of all T1D[51,52]	5 yrs [51]	• Laser surgery • Vitrectomy surgery • Anti-VEGF injections	• £131[53] • £1,701[54] • £550-800[55]
		Severe proliferative diabetic retinopathy 6.96% of all T1D[56]	24–33 yrs[50]		
Nephropathy	21 -40%[57-59]	Severe albuminuria 26.7%, within CKD population[57,58] 10.8% severe kidney disease within CKD population[57,58] 5.3% treated for kidney failure within CKD population[57,58]	5–25 yrs [60] >30 years[61]	• Dialysis (13% with in CKD population) [58] • Kidney transplant (6.9% within CKD population [58]	£16K[62] £34K/year[63]
Neuropathy	43.1%[64]	Foot ulcer 6.3% of all T1D[65]	25% at 5 yrs to 60% lifetime risk[66]	Wound care	£2.8K[67]–£7.3K/yr[68]
		Amputation: 3.2/1000 pt-yrs[69]	43 years[69]	Amputation	£4-8k[67]
Macrovascular	CHD: 15%;[70] Stroke: 2%;[70] PAD: 1.7%[70]	• Major CAD event: 1%[71] • 16% event rate over 10 yrs[71]	20–30 yrs[71]	Coronary angioplasty and stent Stroke NHS costs (first year)	£1782[72] £13,269[73]

Appendix 5. Disaggregated Results

Clinical outcomes	Teplizumab	Est. Clin. Mgmt.	Incremental
Life years (LYs)	[redacted]	[redacted]	[redacted]
Undiscounted life years (LYs)	[redacted]	[redacted]	[redacted]
LYs at risk (stage 2)	[redacted]	[redacted]	[redacted]
LYs after clinical T1D onset (stage 3)	[redacted]	[redacted]	[redacted]
Quality adjusted life years (QALYs)	[redacted]	[redacted]	[redacted]
QALYs at risk (stage 2)	[redacted]	[redacted]	[redacted]
QALYs after clinical T1D onset (stage 3)	[redacted]	[redacted]	[redacted]
Carer disutility	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]
Cost outcomes	**Teplizumab**	**Est. Clin. Mgmt.**	**Incremental**
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse event management	[redacted]	[redacted]	[redacted]
Treatment related HRU	[redacted]	[redacted]	[redacted]
Testing	[redacted]	[redacted]	[redacted]
Disease management at risk (stage 2)	[redacted]	[redacted]	[redacted]
Disease management after clinical T1D onset (stage 3)	[redacted]	[redacted]	[redacted]
Indirect (productivity loss) – Patients	[redacted]	[redacted]	[redacted]
Indirect (productivity loss) – Carers	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]

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Addendum following receipt of updated hybrid closed loop uptake data.

Updated Economic Analysis for HCL Uptake

We have noted in our Factual Accuracy Check (FAC) form submitted on 28th January 2026, that updated clinical insight on the current and future level of hybrid closed loop (HCL) uptake was provided by [redacted] on 28th January 2026. HCL uptake is currently 80% in the relevant age group and is expected to plateau at 84% **by March 2026**. Prior to this updated information, current uptake was estimated at 72% (preferred by the EAG) with a plateau of 80% to 85%. This is no longer correct.

It is important that the most recent information is reflected in analyses placed before the committee on the 10th February 2026.

Therefore, we have provided two scenarios below; please note, all other inputs remain the same as the revised ACM3 company base case submitted in response to the Call for Additional evidence. In Scenario 1 the current HCL uptake of 80% is modelled. In Scenario 2, 84% is modelled. According to the clinical expert, by the time that the NICE recommendation is extant following the conclusion of this appraisal, HCL uptake is likely to be steady at this proportion (note this is slightly less than previously expected). Therefore 84% uptake should be the base case assumption preferred by the committee.

Scenario 1. Updated Economic Analysis with **80%** HCL uptake

The incremental cost-effectiveness results including the deterministic and probabilistic ICER with 80% HCL uptake are presented in Table 1 below.

Table 1. Incremental cost-effectiveness results with 80% HCL uptake

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£28,562
Teplizumab	[redacted]	[redacted]	[redacted]					
Probabilistic results								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	£27,313
Teplizumab	[redacted]	[redacted]	[redacted]					

The convergence plot, scatter plot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 1, Figure 2 and Figure 3 respectively.

Figure 1. Convergence plot with 80% HCL uptake

Figure 2. Scatter plot for incremental cost-effectiveness results with 80% HCL uptake (400 iterations)

Figure 3. Cost-effectiveness acceptability curves with 80% HCL uptake (400 iterations)

The probability of being cost effective at £20,000/QALY is [redacted] and at £30,000/QALY it is [redacted].

Scenario 2. Updated Economic Analysis with **84%** HCL uptake

The incremental cost-effectiveness results including the deterministic and probabilistic ICER with 84% HCL uptake are presented in Table 2 below.

Table 2. Incremental cost-effectiveness results with 84% HCL uptake

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	ICER incremental (£/QALY)
Deterministic results								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	£27,888
Teplizumab	[redacted]	[redacted]	[redacted]					
Probabilistic results								
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	£26,788
Teplizumab	[redacted]	[redacted]	[redacted]					

The convergence plot, scatter plot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 4, Figure 5 and Figure 6 respectively.

Figure 4. Convergence plot with 84% HCL uptake

Figure 5. Scatter plot for incremental cost-effectiveness results with 84% HCL uptake (400 iterations)

Figure 6. Cost-effectiveness acceptability curves with 84% HCL uptake (400 iterations)

The probability of being cost effective at £20,000/QALY is [redacted] and at £30,000/QALY it is [redacted].

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]

Call for additional evidence EAG critique

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. EAG critique of company response to call for additional evidence

The following is the EAG critique of the company response to the Call for additional evidence, which was requested by the committee.[1, 2]

1.1 Topic 1. Identification and Testing

EAG comment:

The company argue that what they refer to as *"exploratory"* and *"confirmatory"* testing should not be included in the economic model because this was not the case in previous lung cancer appraisals where diagnosis precedes economic model entry. However, this fails to address the point that if the diagnostic pathway for those forms of lung cancer are already in place, then there will be no additional cost due to the introduction of the intervention. However, in this appraisal it is the EAG's understanding that where there is no established diagnostic pathway to identify Stage 2 type 1 diabetes patients, the additional cost due to the introduction of the intervention in order to identify those patients needs to be included.

The company also argue that the cost of any additional testing should apply to both arms of the model, including established clinical management (ECM). However, the EAG would argue that this does not make sense given that the basis of the additional testing is the introduction of teplizumab i.e. ECM, which is pre-teplizumab introduction, does not include this additional testing.

The company assume that: *"Any increase in demand for additional testing will be in the FDRs* [first-degree relatives] *sub-population"*, as opposed to those in three other populations, which are those identified in research studies, tested because of concerns for hyperglycaemia or on request by the patient/relative.[1] However, the EAG notes that, although the committee recognised that: *"...most additional NHS-funded tests would be for first-degree relatives"*, they still also requested: *"Blended cost-effectiveness estimates for the full population based on differing proportions of each of the 4 subpopulations eligible for teplizumab"*.[2] This was addressed by assuming that: *"13% of additional testing costs are attributable to the NHS and 87% will be carried out in research studies and testing due to clinical concern, based on recent evidence"*.[1] The figure of 13% was attributed to: *"...recent evidence[3] and expert clinical opinion"*. The EAG notes that this recent evidence is a survey of UK paediatric diabetes units (PDUs) in 2024, which showed that the reasons for autoantibody (AAB) testing included: *"...family screening in secondary care (13%),"*.[3] If this is the source of the 13% then it is unclear to the EAG how this, which is the percentage of current testing, can be used to inform the percentage of additional testing that would be that of FDRs. As the EAG understands, this implies that only 13% of testing to identify patients eligible for teplizumab would be of FDRs, but this seems to contradict the assertion by the company that it is only in the FDR population where there will be an increased need for testing. Also note that, according to this split, the additional cost of testing, which is borne by the NHS, is 13%. On this basis, the final cost of testing used in the model base case is only 13% of the FDR test cost estimate (see below), and the maximum percentage in a scenario is 25%.

- ***Estimating the FDR test cost per teplizumab recipient***

For the FDR population, an assumption of 30 tested to 1 treated is made, which the company attribute to a figure of *"3.4% of the original population*", from a *"personal communication*" from a clinical expert. The company then state that the pathway for testing in FDRs was agreed with clinical experts. Within this pathway, the company state that 3.7% of those tested will be ≥2 AAB positive, based on the ELSA study, and that it is only after a confirmatory venous test and HbA1c test that 0.3% are excluded.

1 in 30 is also the figure that was recommended for calculating the cost of testing in the Call for additional evidence.[2] The EAG note, however, that the *"personal communication"* appears to be an Excel file,[4] which shows that the reduction from 3.7% to 3.4% is based on excluding 8.1% of those ≥2 AAB positive, and that those excluded include false positives and those with stage 3 T1D. Also, according to this Excel file, the 3.4% (approximately 1 in 30) is those identified as "early T1D", and of the 3.4%, only 20% are categorised as stage 2, 75% being categorised as stage 1, these figures being attributed to ELSA. In addition, the Excel file states that only [redacted]% are at least 8 years old, but these would not be included for testing to identify patients eligible for teplizumab. However, only [redacted]% uptake is assumed. Therefore, according to these figures, it can be calculated that testing one person would result in [redacted]% of 20% of 0.034 = [redacted] patients to be treated with teplizumab i.e. 1/[redacted] = [redacted] would need to be tested to find one person who would actually be diagnosed with stage 2 Type 1 DM and who would be treated with teplizumab. Of course, the EAG acknowledge that there is movement from stage 1 to stage 2, which is also included in the Excel file at a rate of [redacted]% per year. In the Excel file the cost of monitoring those patients until progression to stage 2 is also included, but this does not seem to be included in the company calculations.

Therefore, although the figure of 1 in 30 would appear to be conservative for the FDR population because it is higher than the 1 in 10 to 1 in 20 figure mentioned in the draft guidance (DG),[5] it might still be an underestimate of the number needed to test to identify a patient who would receive teplizumab. As a result, the cost of testing estimated by the company could also be an underestimate, by an amount that depends on the proportion of those who are AAB2+ who are at stage 2 (as opposed to stage 1), and the proportion of those who then accept the offer of treatment with teplizumab. In fact, the cost to identify one teplizumab patient is £1,724.26, according to the company's response to the Call for additional evidence.[1] This contrasts with the Excel file referred to above, which calculates an estimate of £[redacted] (after changing the % aged at least 8+ from [redacted]% to [redacted]%).[4] This figure would be £[redacted] if the unit costs for AAB and confirmatory testing were the same as in the company response (£46.20 and £140.24 instead of £[redacted] and [redacted] respectively). However, the cost would be much lower if one assumes that all of those with stage 1 convert to stage 2, and are detected by monitoring. In the Excel file, it is assumed that there is [redacted]% uptake of stage 1 monitoring, which means that the number of patients with stage 2 detected is increased from [redacted] ([redacted]% of 20% of 2AAB+) by adding [redacted]% of [redacted] ([redacted]% of 75% of 2AAB+) to give [redacted]. This is equivalent to needing to test 1/[redacted], which is about [redacted] people to detect 1 patient who receives teplizumab. The testing cost would also increase a little by the amount required to monitor those with stage 1 disease: according to the monitoring costs in the Excel file, this would lead to a cost of £[redacted] per person treated with teplizumab. Note that this figure would decrease if there was greater uptake of stage 1 monitoring. On the other hand, it would probably be higher in the first years after the introduction of testing, if only [redacted]% convert to stage 2 per year.

1.2 Topic 2. Carer Disutility (Number of Caregivers)

EAG comment:

The EAG considers it plausible that in general more than one caregiver is involved in the care of a child or young person with T1D. Based on the evidence presented by the company in Appendix 2 of the Call for additional evidence,[1] the EAG prefers assuming [redacted] carers to one patient instead of 1.76. Alternative values were explored in sensitivity analyses by the EAG.

1.3 Topic 3. Stage 2 Disutility

EAG comment:

Although accepted in previous NICE appraisals, PMG36 classifies vignettes studies as the least preferred HRQoL method.[6] Guenther et al. 2025 is an internal vignettes study commissioned by the company.[7] To the best of the EAG's knowledge it has not been published in any peer reviewed journal. Therefore, the EAG would recommend interpreting the results from this study with caution. The EAG conducted a critical assessment of the vignettes study as reported in "Stage 2 Disutility Report_BOD0249_version1_0.pdf" using the GROVE checklist,[8] which can be found at the end of this section. The main concerns identified by the EAG are the following:

- Framing and instructions of the vignettes were non-neutral, conflating health-state valuation with emotional responses to treatment availability.
- The study is likely to be conceptually biased: it does not measure health-state utility; instead, it measures perceived severity shaped by prognosis, treatment availability, and emotional framing.
- No manipulation or realism checks were performed, and data-quality controls were not reported.
- Results show low external validity and seem unsuitable for reference-case HRQoL inputs.

In addition, based on the information provided by the company in Section 3 of the Call for Additional Evidence document,[1] the EAG considers it plausible that there is a disutility associated with Stage 2 T1D and that the availability of a DMT to delay the onset of Stage 3 disease can be perceived to mitigate the decrease in HRQoL observed in the presymptomatic stage. However, the EAG is concerned about 1) how long the Stage 2 disutility should be applied and 2) the magnitude of such disutility.

Regarding how long the disutility should be applied, the EAG would like to note the following:

- The company indicated that the resulting disutility values used in the cost-effectiveness model are only those associated with the *diagnosis* of Stage 2 and not the *transition* to Stage 3 T1D. Also, the company mentioned that, whilst Stage 2 T1D is asymptomatic, the new evidence indicates that there is an *initial* psychological burden with the diagnosis and regular follow-up in Stage 2 T1D. The company concluded that this analysis (the vignettes study) captures the more important impact of a *shock* Stage 2 diagnosis for an apparently healthy individual vs. the transition from Stage 2 to 3 T1D for patients already carrying a Stage 2 diagnosis. The EAG would like to emphasise that the company's overall narrative seems to refer to a short-term shock effect associated with the diagnosis of Stage 2, but in the economic model this disutility is *continuously* applied as long as patients are in the Stage 2 T1D health state.
- The company also referred to one clinician describing that the disutility in Stage 2 T1D may in fact be greater than in the *onset* of Stage 3 T1D, as the '*shock*' of diagnosis comes at Stage 2 T1D rather than Stage 3 T1D. By the time the individual reaches Stage 3 T1D, they are more accepting. The EAG considers a '*shock*' effect plausible, but this should only be temporary then, because it seems equally plausible that the more time patients spend in Stage 2, the more accepting they would also become. It should be noted that Stage 2 is still asymptomatic and a 'shock' effect when moving to Stage 3 (implemented as a one-off disutility at onset) seems plausible as well.

Based on these points above, the EAG agrees with the company that it seems inappropriate to disregard the impact of Stage 2 *diagnosis* and not to apply a disutility. However, the EAG considers that

"diagnosis" or "shock" refers to a temporary (likely short-term) situation and questions whether a disutility should be continuously applied for being at the Stage 2 T1D health state as the company have assumed. It seems more appropriate to apply such disutility for a shorter period of time, possibly as a one-off disutility, very much like the one used in the economic model for the transition from Stage 2 to Stage 3.

Regarding the magnitude of the estimated disutilities, the EAG still considers that these lack face validity if these are going to be applied as a continuous health-state-related disutility, since those for Stage 2 are higher than for Stage 3.

In conclusion, the EAG is willing to accept the disutility associated to Stage 2 T1D estimated from the vignettes study – despite the limitations discussed above – only if this is implemented as a one-off disutility reflecting the '*shock*' of diagnosis at Stage 2 T1D.

Checklist form - Guideline for RepOrting Vignette Experiments (GROVE)*

Criterion	Description	Location in manuscript where item is reported	Details on methodological approach**
1. Rationale	Provide a rationale for the use of an experimental vignette-based design, including an explanation why the study could not be conducted in a non-simulated setting.	4.2	The study does not include an explanation why it could not be conducted in a non-simulated setting.
2. Vignette content	Describe in detail how the vignette content was developed and refined, and explain any choices made.		Report all relevant information below (sub-criteria 2.1-2.5)
2.1. Clinical scenario	Describe and explain in detail how the healthcare scenario was developed and what it entailed. Include information about the sources used to inform vignette content, key characteristics of the portrayed characters, and the setting described in the vignette.	Not in the report but in Call for Additional Evidence document[1]	A literature review was conducted to understand clinical differences, symptoms, and treatments for Stage 2 and Stage 3 T1D. Two T1D patients reviewed the draft vignettes, focusing on the most impacted HRQoL domains at each stage. A final medical review ensured symptoms and acute complications were accurate and appropriately emphasised, confirming alignment with current medical classifications and clinical practice guidelines. A native speaker revised both vignettes to ensure clarity and neutral language. A pilot study was conducted. Participants read and summarised the vignettes to confirm understanding of the health status and differences between Stage 2 and

			Stage 3 T1D. The entire survey was piloted to ensure clarity and reasonable completion time. Minor linguistic changes were made, and vignette presentation was adjusted to ensure visibility throughout the online survey. The accuracy of the disease health states was validated by three UK clinical experts, who agreed with the descriptions.
2.2. Manipulation & standardization	Describe what the experimental manipulations are (i.e., operationalization of the phenomenon under study), detailing which elements of the scenario were varied and how. Also report how other elements in the vignette were kept constant and provide information on vignette duration or length.	5.2 & 11.7	The only experimental manipulation was treatment availability at Stage 2; all other scenario elements were kept constant, and total vignette exposure occurred within a single 20-minute online survey.
2.3. Mode of delivery	Describe and explain the delivery modality and provide any information necessary for replication. Explain choices regarding narrative perspective and amount of detail described. Describe how participants were introduced to the vignette and in which setting data were collected.	5.2 & 11.7	**Narrative perspective and level of detail**: Vignettes were written in second-person perspective, placing the respondent as patient interacting with their doctor. The text contained clinical and procedural detail, describing symptoms, biochemical explanations, treatment steps, and emotional reactions. This perspective was likely chosen to enhance immersion and facilitate empathy, but it also increased the risk of emotional and framing bias, limiting replicability and neutrality. No rationale was reported for the chosen narrative voice or length. **Introduction and setting**: Participants were first introduced through a contextual narrative: attending a doctor's appointment after screening for type 1 diabetes and learning their stage and risk of progression.

			Each participant then proceeded to read the Stage 2 vignette (and later Stage 3), followed by EQ-5D valuation tasks. All participation occurred remotely, online, and apparently unsupervised, with no laboratory or interview setting.
2.4. Expert involvement	Explain who were involved in developing the vignettes, highlighting their particular expertise and contributions.	Not in the report but in Call for Additional Evidence document[1]	Please refer to 2.1 Clinical scenario.
2.5. Pilot testing	Describe if, how, and when pilot testing was used in the vignette development process. Explain whether and how this affected the vignette content and format.	Not in the report but in Call for Additional Evidence document[1]	Please refer to 2.1 Clinical scenario.
3. Outcomes & participant instructions	Explain the selected study outcome(s) for the vignette study, particularly how these outcome(s) relate to real-world outcomes of interest.	5.1	The study outcomes were EQ-5D-based utilities intended to approximate HRQoL decrements across disease stages, but they represent perceived, not experienced, health impacts—making their external validity for NICE-relevant modelling limited.
4. Vignette validity & realism	Report how manipulation success of the independent variable(s) of interest was evaluated (i.e., manipulation check). Also describe if and how realism and aspects of participant engagement with the scenario were assessed.	Not reported	Based on the available information, no manipulation checks or realism assessments were reported in the study. There is no indication that participants were asked to confirm their understanding of the treatment framing (e.g., whether they realised they were assigned to a "treatment available" or "no treatment" scenario). The study does not describe any post-task questions assessing perceived realism, credibility of the vignettes, or ease of imagination. No measures of engagement were included (e.g., completion time monitoring, attention checks, or comprehension questions). As a result, it is unclear whether the experimental manipulation (treatment framing) was consistently

			understood or whether differences in interpretation occurred between participants.
5. Participants	Provide a rationale for the choice of study participants (e.g., analogue patients), both in relation to the target population and to the characters portrayed in the vignettes.	8	The study recruited members of the UK general population, consistent with NICE's reference-case requirement that health-state valuations reflect public, not patient, preferences. **Relation to target population**: The target population for the health states (people at risk of or newly diagnosed with type 1 diabetes) is difficult to recruit because stage 2 disease is typically asymptomatic and rarely identified outside trials. Therefore, general-population "analogue patients" were used to provide societal valuations of hypothetical disease stages. **Relation to vignette characters**: The vignettes placed respondents directly in the patient role ("you have stage 2/3 T1D"). This aligns with standard utility-elicitation methods where members of the public are asked to imagine themselves in the described state.
6. Accessibility	Include information on the availability of the final vignettes and pilot data for research, teaching, or commercial purposes. Detail any restrictions to access and (re)use of the vignettes and data.	6	The final vignettes and study results were presented at ISPOR Europe 2025. The full study is not publicly available yet and appears to be subject to sponsor ownership and confidentiality restrictions. No mechanisms for external access, reuse, or replication have been reported, except that all records should be kept and made available for review in the event of audits, or inspections and must be safely archived for at least 10 years after the completion of the study.
*The order of reporting these criteria is intended to be flexible. Information can be combined or reorganized and information may be placed in any manuscript section, figure, table and or supplementary material, depending on the study content and journal requirements. **Authors may report additional methodological details in this column beyond the information included in their main manuscript.			

1.4 Topic 4. Managing Stage 3 Costs

EAG comment:

The company has retained the methodology used in ACM2 for estimating stage 3 T1D costs over time, with the only substantive modification being an updated assumption regarding uptake of hybrid closed-loop (HCL) systems. In summary, the company's approach comprises three steps:

1. Estimation of stage 3 T1D management costs for up to 19 years based on a case–control analysis using national Danish registry data. Although limited detail is provided on the design of this study, the data source and overall approach appear broadly reasonable.

2. Extrapolation beyond 19 years through fitting separate quadratic models to case and control cost data from years 5 to 19 (see below for discussion).

3. Adjustment for HCL adoption, incorporating both the incremental cost of HCL devices and potential cost offsets from improved disease management.

The approach to including HCL costs is appropriate. In the ACM2 the company assumed 100% uptake while the EAG assumed 54% based on NHS England projections. In the updated submission, the company assumes 85% uptake, citing clinical opinion that current uptake in the relevant age group is approximately 72% and is likely to plateau at 80–85% in 2025. Subject to validation by other clinicians or NHS England, this appears reasonable. For the revised EAG base-case, the current estimated uptake in the relevant group based on expert clinical opinion of 72% was used.[1]

The primary concern remains the plausibility of the extrapolated stage 3 T1D costs beyond 19 years. The company defends the use of the quadratic extrapolation on three grounds:

(1) Better statistical fit versus a linear model when assessed using R^2;

(2) The observation that high costs occur only among survivors, implying that population-level average costs do not rise at the same rate once mortality is accounted for. We do not consider this further here since the argument is about costs conditional on surviving.

(3) Expert opinion suggesting a quadratic trajectory is more plausible than a linear one.

With respect to model fit, reliance on R^2 to justify long-term cost trajectories is of limited value. As shown in Figure 1.1, observed costs for both T1D cases and controls are relatively stable, with modest increases over years 5-19. The slightly steeper increase among T1D cases drives large long-term differences between the extrapolated curves. However, the shape of the control cost curve would be expected to be more similar to that of the T1D population, given that the control cohort includes individuals with a wide range of comorbidities (e.g., type 2 diabetes, cardiovascular disease, cancer, dementia). Since the model uses the difference in costs between cases and controls, small discrepancies in fitted slopes over the observed period generate substantial divergence in the extrapolated period.

Figure 1.1: Projections of Stage 3T1D annual costs in the company base case analysis

The extrapolation should not be justified based on internal fit to limited observed data but primarily on clinical plausibility and supported, where possible, by external evidence. The company identifies few relevant sources. Hex et al. 2014 provides an estimate of the average healthcare costs for patients type 1 diabetes based on the prevalent population in the UK at £4,982.64 per year.[9] Stedman et al. 2020 hospital episode statistics and estimated average total annual secondary care costs for people with type 1 diabetes at £3,280 compared to £560 for people without diabetes.[10] Neither source provides us with the trajectory of type-1 diabetes related healthcare costs with age or time in stage 3 T1D but they provide an indication of reasonable annual cost estimates, which are far below those implied by the company's extrapolation.

The company also presents estimates of weighted average monthly costs based on the cross-sectional distribution of individuals at different durations of T1D, arguing that these appear lower than those reported by Hex et al. 2014.[9] However, insufficient information is provided to validate this comparison. For reference, total undiscounted stage 3 T1D costs for ECM in the model were £[redacted], with an average [redacted] years spent in stage 3, equating to £[redacted] per year in Stage 3 (or £[redacted] per month). These are substantially higher than the numbers provided by the company.

The EAG agrees that a purely linear extrapolation of costs is unlikely to represent the true evolution of Stage 3 T1D costs and that a non-linear increase over time in state is most plausible. However, the assumptions used in the company's current extrapolation remain implausible as discussed above and as noted by the NICE committee and clinical experts. The company includes a scenario in which monthly costs are capped after 65 years in stage 3 T1D. In the absence of more robust data, introducing such a cap is a reasonable way to explore sensitivity to long-term assumptions. The appropriate level of the

cap remains uncertain. For the revised EAG base-case we apply the cap after 40 years with stage 3 T1D and explore other values in scenario analyses.

Previous cost-effectiveness analyses of type-1 diabetes for NICE have used economic models to estimate lifetime costs based on complication event rates and event costs. In fact, the company used the IQVIA Core Diabetes Model to estimate potential cost reductions from the use of hybrid closed loop systems. These proportional cost reductions were then applied to the Stage 3 T1D costs estimated through extrapolation. The company did not provide rationale for not using the IQVIA Core Diabetes Model for direct estimation of stage 3 T1D costs..[11]

1.5 Topic 5. Committee Other Considerations and Preferred Assumptions

EAG comment:

The EAG agrees with the company's approach regarding the following issues/assumptions following ACM2 which have been included in the company's revised base case:

1. Using an incidence rate of 4.6% for cytokine release syndrome (CRS) in the teplizumab arm of the economic model.
2. Using the log-normal distribution for time to onset of Stage 3 T1D in the teplizumab arm.
3. Using the gamma distribution for time to onset of Stage 3 T1D in the teplizumab arm.
4. Using the company's revised approach to Stage 3 disutility in the model presented at ACM2

1.6 Topic 6. Willingness to Pay and Discounting

EAG comment:

Since new WTP thresholds are not yet in place, the EAG will not comment on this point.

It is also the EAG's understanding that any inequality concerns should be discussed at the scoping phase of the appraisal. Therefore, at this point, the EAG will not comment on this point either.

Regarding using an alternative discount rate, PMG36 establishes that "*Alternative analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis, in specific circumstances*".[6] These specific circumstances indicate that "*all of the following criteria are met*":

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

The EAG considers that not all these criteria are met, but it is ultimately up to the Appraisal Committee to decide whether this is the case or not.

1.7 Topic 7. Revised Base Case & Scenario Analysis

EAG comment:

Based on the EAG comments related to the topics above, the EAG has a revised base-case. The EAG's and company's preferred assumptions are summarised in Table 1.1.

Table 1.1: Revised base-case assumptions (assumptions relevant to call for additional evidence)

Parameter	Company assumption	EAG assumption	EAG rationale for change
Testing costs	Blended cost estimate of £224.15 (13% NHS and 87% not NHS) applied to both arms of the model.	Blended cost estimate of £224.15 (13% NHS and 87% not NHS) applied to teplizumab arm of the model.	Appraisal Committee request.
Caregivers	1.76 caregivers maintained for individuals aged < 25 years old (disutility applied: -0.04).	[redacted] caregivers maintained for individuals aged < 25 years old (disutility applied: -0.04).	In line with caregiving company's survey.
Stage 2 disutility	Teplizumab: -0.049 ECM: -0.124 Applied continuously	Teplizumab: -0.049 ECM: -0.124 Applied as one-off	EAG's interpretation of new evidence submitted by the company.
Stage 3 costs	Quadratic approach adjusted for expected HCL acquisition and impact on long-term costs aligned with 85% uptake.	Quadratic approach capped at 40 years in Stage 3 T1D adjusted for expected HCL acquisition and impact on long-term costs aligned with 72% uptake.	The company's extrapolation is based on limited data and provides unrealistic estimates of long-term Stage 3 T1D costs. In the request for additional evidence the company capped stage 3 costs after 65 years in state in a scenario analysis. Most patients have left the model at this stage and the estimates remain very high. A lower cap is therefore considered. The company provide expert opinion that uptake of HCL systems is higher among children than the general eligible population. Uptake is currently estimated at 72% and anticipated to increase to 80-85%. We have chosen to use the current uptake as the EAG base-case.

The step-by-step changes made by the EAG to derive its revised base-case, using the company's revised base-case, can be seen in Table 1.2. The change with the largest impact on the results was capping Stage 3 T1D at 40 years. Including 13% testing costs for the NHS in the teplizumab arm had a minimal impact on the model results. Each one of the other changes increased the ICER between £2,000 - £3,000 per QALY gained. Overall, the EAG's revised ICER was £14,119 higher than the company's revised ICER.

Table 1.2: Cumulative impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's revised base-case					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	27,720
ECM	[redacted]	[redacted]			
EAG change 1 – Testing costs: blended estimate (13% NHS, 87% not NHS) of £224.15 to teplizumab arm only					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	28,091
ECM	[redacted]	[redacted]			
EAG change 1 + 2 – Number of caregivers: [redacted] caregivers for individuals aged < 25 years old (disutility applied: -0.04)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	30,070
ECM	[redacted]	[redacted]			
EAG change 1-2 + 3 – Stage 2 disutility: teplizumab -0.049, ECM -0.124, applied as one-off					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	33,123
ECM	[redacted]	[redacted]			
EAG change 1-3 + 4 – Stage 3 costs: quadratic approach capped at 40 years in Stage 3 T1D					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	39,138
ECM	[redacted]	[redacted]			
EAG change 1-4 + 5 (base-case) – Stage 3 costs: 72% HCL uptake					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	41,839
ECM	[redacted]	[redacted]			
Based on the model submitted following the Call for Additional Evidence. CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

Table 1.3 shows the results of the probabilistic EAG's revised base-case (discounted, assuming teplizumab PAS price), which are comparable with the EAG base-case results. The CE-plane presented in Figure 1.2 shows that [redacted] This indicates that in general teplizumab is expected to be [redacted] than ECM. Based on the derived CEAC (Figure 1.3), the probability that teplizumab is cost effective at £20,000 and £30,000 per QALY gained was [redacted] and [redacted], respectively.

Table 1.3: EAG revised PSA results (teplizumab PAS price, discounted)

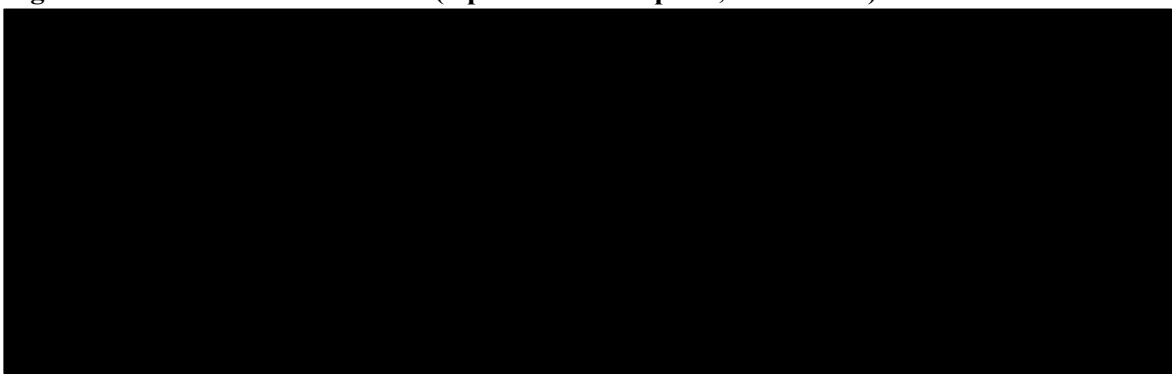
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	40,588
ECM	[redacted]	[redacted]			
Based on the model submitted following the Call for Additional Evidence.					

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
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 1.2: EAG probabilistic CE-plane (teplizumab PAS price, discounted)

Based on the model submitted following the Call for Additional Evidence.
CE = cost effectiveness; EAG = External Assessment Group; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

Figure 1.3: EAG base-case CEAC (teplizumab PAS price, discounted)



Based on the model submitted following the Call for Additional Evidence.
CEAC = cost effectiveness acceptability curve; EAG = External Assessment Group; PAS = patient access scheme; QALY = quality-adjusted life year

The following scenario analyses were explored by the EAG:

- Testing costs: Assuming an estimate of £1,724.26 (100% NHS costs) to teplizumab arm only, a blended estimate of £404.33 (1 in 60 detection rate) assuming 13% NHS costs to teplizumab

arm only, and a blended estimate of £1,845.77 (1 in 300 detection rate) assuming 13% NHS costs to teplizumab arm only

- Number of caregivers equals 1 (lower end scenario) and 1.76 (company's base-case).
- Stage 2 disutility applied for 0, 1, 2 and 5 years, and for as long as patients are in Stage 2 T1D.
- Stage 3 costs capped at 20, 30, 50, 60 years, and no cap.
- HCL uptake: assume 50% and 85%

The results of the scenario analyses are provided in Table 1.4. These results are all conditional on the EAG revised base-case settings. The scenario analyses conducted by the EAG indicated that the results were relatively sensitive to all the assumptions explored.

Table 1.4: 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			[redacted]	[redacted]	**41,839**
Testing costs	Blended estimate (13% NHS, 87% not NHS) of £224.15 to teplizumab arm only	Estimate of £1,724.26 assuming 100% NHS costs to teplizumab arm only	[redacted]	[redacted]	44,768
		Blended estimate of £404.33 (1 in 60 detection rate) assuming 13% NHS costs to teplizumab arm only	[redacted]	[redacted]	42,191
		Blended estimate of £656.59 ([redacted] detection rate) assuming 13% NHS costs to teplizumab arm only	[redacted]	[redacted]	42,683
		Blended estimate of £1,845.77 (1 in 300 detection rate) assuming 13% NHS costs to teplizumab arm only	[redacted]	[redacted]	45,005
Number of caregivers	[redacted]	1.76	[redacted]	[redacted]	38,827
		1	[redacted]	[redacted]	43,619
Stage 2 T1D disutility duration over time	6 months	0 years	[redacted]	[redacted]	44,649
		1 year	[redacted]	[redacted]	38,719
		2 years	[redacted]	[redacted]	37,112
		5 years	[redacted]	[redacted]	35,555

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
		As long as patients are in Stage 2 T1D	[redacted]	[redacted]	37,982
Stage 3 T1D costs capped time	40 years	20 years	[redacted]	[redacted]	48,202
		30 years	[redacted]	[redacted]	45,396
		50 years	[redacted]	[redacted]	38,683
		60 years	[redacted]	[redacted]	36,699
		No cap	[redacted]	[redacted]	35,703
HCL uptake	72%	50%	[redacted]	[redacted]	46,410
		85%	[redacted]	[redacted]	39,138

Based on the model submitted following the Call for Additional Evidence.
EAG = External Assessment Group; ECM = established clinical management; HCL = hybrid closed-loop; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; Inc. = incremental; NHS = National Health Service; PAS = Patient Access Scheme; QALY = quality-adjusted life year; QoL =quality of life; T1D = type 1 diabetes

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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]

Additional EAG analyses pre-ACM 3

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. EAG additional analyses

1.1 Stage 3 T1D costs

The PMB slide describing the key issue "Estimation of stage 3 T1D costs" shows a table comparing the company's and EAG's annual cost projections, assuming HCL uptake = 85% in company base case, 54% in EAG (based on ACM2 EAG base case). The EAG considers that previous EAG estimates based on 54% HCL uptake are no longer relevant as the updated data on HCL update has been accepted. Note also that assumptions about HCL uptake do not have a direct impact on the costs extrapolation, which is the main concern. The EAG considers then that the most relevant scenarios are the following:

- Company updated base case (quadratic extrapolation; HCL 84%)
- Company scenario analysis (quadratic extrapolation; HCL 84%; costs capped at 65 years in stage 3)
- EAG updated base case (quadratic extrapolation; HCL 72%; costs capped at 40 years in stage 3)
- EAG linear model (linear extrapolation; HCL 72%)
- EAG ACM1 base case (calibrated regression using Hex et al. Not including HCL costs)
- Current EAG scenarios above but with HCL at 84% uptake

The results of these scenarios on both the company's and EAG's base-case are summarised in Table 1.1 and Table 1.2, respectively.

Table 1.1: Additional scenario analyses on company's base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base-case pre-ACM 3 (HCL uptake 85%, no cost cap in Stage 3)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	27,720
ECM	[redacted]	[redacted]			
Company's updated base-case (HCL uptake 84%, no cost cap in Stage 3)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	27,888
ECM	[redacted]	[redacted]			
Company's scenario (HCL uptake 84%, cost cap in Stage 3 at 65 years)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	28,250
ECM	[redacted]	[redacted]			

Based on the model submitted following the Call for Additional Evidence.
CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 1.2: Additional scenario analyses on EAG's base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG's base-case pre ACM 3 (HCL uptake 72%, cost cap in Stage 3 at 40 years)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	41,839

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]			
EAG's scenario (Stage 3 costs – linear extrapolation, no cap)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	48,169
ECM	[redacted]	[redacted]			
EAG's scenario (Stage 3 costs – calibrated regression using Hex et al. HCL costs not included, no cap)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	62,751
ECM	[redacted]	[redacted]			
EAG's scenario (HCL uptake 84%, cost cap in Stage 3 at 40 years)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	39,346
ECM	[redacted]	[redacted]			
EAG's scenario (HCL uptake 84%, Stage 3 costs – linear extrapolation, no cap)					
Teplizumab	[redacted]	[redacted]	[redacted]	[redacted]	45,440
ECM	[redacted]	[redacted]			

Based on the model submitted following the Call for Additional Evidence.
CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

1.2 Results, subgroups and blended ICER

In addition, the current ICER is for first degree relatives subgroup. Note this ICER assumes 13% of testing costs to NHS. If possible, ICERs for the other subgroups (tested in research, clinical suspicion and all comers) are also needed in order to calculate a blended ICER. The following assumptions hold:

- Tested in research (ELSA) subgroup assumes no cost of testing.
- Clinical suspicion subgroup also assumes no cost of testing.
- All comers assumes 100% testing costs to NHS.

To calculate a blended ICER we need to know the proportion of patients in each subgroup. Since this is unknown at this moment, the results per subgroup are presented separately in Table 1.3. Note that these results are based on the EAG's base-case only since in the company's approach the ICER does not change per subgroup since testing costs are applied to both teplizumab and ECM arms.

Table 1.3: Results of subgroup analyses on EAG's base-case (teplizumab PAS price, discounted)

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base-case	**First degree relatives subgroup**	**--**	[redacted]	[redacted]	**41,839**
Testing costs	Estimate of £224.15 (13% NHS, 87% not	Estimate of £1,724.26 assuming 100% NHS costs to teplizumab arm	[redacted]	[redacted]	44,768

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
	NHS) to teplizumab arm only	only ("all comers" subgroup)			
		Estimate of £1,724.26 assuming 0% NHS costs to teplizumab arm only (tested in research and clinical suspicion subgroups)	[redacted]	[redacted]	41,401
HCL uptake	72%	"All comers" subgroup with 84% HCL uptake	[redacted]	[redacted]	42,275
		Tested in research and clinical suspicion subgroups with 84% HCL uptake	[redacted]	[redacted]	39,908

Based on the model submitted following the Call for Additional Evidence.
EAG = External Assessment Group; ECM = established clinical management; HCL = hybrid closed-loop; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; Inc. = incremental; NHS = National Health Service; PAS = Patient Access Scheme; QALY = quality-adjusted life year; QoL =quality of life; T1D = type 1 diabetes

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]

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 ensure there are no factual inaccuracies or errors in the marking of confidential information contained within the documents. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

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 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Topic 1. Identification and Testing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg. 3, 1.1, para 3: "As the EAG understands, this implies that only 13% of testing to identify patients eligible for teplizumab would be of FDRs, but this seems to contradict the assertion by the company that it is only in the FDR population where there will be an increased need for testing"	The statement should be corrected to accurately reflect the company approach. **Proposed text:** "The company approach states that any increase in testing where a cost will be borne to the NHS is in the FDR population. However as is the case now, the FDR population will continue to be tested within **both** NHS and research settings. Increases to FDR testing are expected to be absorbed in research with NHS-funded FDR testing remaining somewhat constant"	The EAG have made an incorrect interpretation of the company approach. The 13% refers to the additional testing costs that will be attributable to the NHS, not that 13% of those tested will be FDRs. Figure 2 of the company response indicates that FDR testing currently accounts for 13% of testing in children and young people in the NHS. This is not expected to significantly change with the availability of teplizumab, with clinicians preferring to use the established research studies. Whilst the FDR population is where there will be an increased need for testing, the majority of that testing is expected to take place in research, not in the NHS.	Not a factual inaccuracy. Given that FDR testing was separated from that identification through research studies, the implication is that any additional FDR testing will not be funded through research. If the company are now assuming that most of the additional FDR testing is funded through research studies, then that was not clear in the additional evidence. It also does not seem to justify the figure of 13% NHS funded, which is based on the percentage of those currently identified via the FDR route. This percentage also seems to lack plausibility given the potentially large number of those with T1D who could be a FDR of those to be tested.

Pg. 3, 1.1, para 4: “an assumption of 30 tested to 1 treated is made…”	“treated” should be corrected to “identified with ≥2 autoantibodies (AAB)”.	The company took the approach directly requested by the NICE Committee (cost based on having T1D in the FDR cohort at a population risk rate of 1 in 30).	The EAG believe that this is not a factual inaccuracy given that the company make no mention of teplizumab uptake from those identified with ≥2 autoantibodies (AAB) i.e. all are treated.
Pg. 3, 1.1, para 4: “an assumption of 30 tested to 1 treated is made which the company attribute to a figure of “3.4% of the original population”, from a “personal communication” from a clinical expert.””	Clarification should be provided upfront alongside this statement that this was not an assumption by the company, but in response to a direct request by the NICE Committee (Call for Additional Evidence, pg 2). Whilst it is true that these numbers were provided in “personal communication” to the company, context recognising the unique expertise of the clinician providing the values should be provided in order not to dimmish their veracity through the language used in the text. **Proposed text:** “The company approach was in line with the NICE Committee request to estimate testing costs using a 1 in 30 population risk rate. 1 in	The statement as it currently stands is misleading and indicates this is an assumption made by the company, when in fact the use of a 1 in 30 population risk rate was due to a direct request from the NICE Committee as specified in the Call for Additional Evidence. It is also important to note that [redacted] is the clinician in question. [redacted]. Whilst we acknowledge that published data is preferred, there is limited published data on the diagnosis pathway of Early-T1D and the associated costs. We felt it important to discuss the pathway with an experienced clinician in order to accurately capture the	Not a factual inaccuracy: the EAG acknowledge that this was the figure mentioned in the Call of Additional Evidence, but the company cite this “personal communication” as a source, and the Call for Additional Evidence stated that it was the company who informed the committee of this figure.

	30 is approximately 3.4%, which the company states is the percentage of the FDR population who are positive for ≥2 autoantibodies following confirmatory testing. The 3.4% value was informed through discussion with [redacted] who is a [redacted]	expected patient pathway and costs. The pathway, and associated patient numbers and costs were subsequently validated with another two leading clinicians: • [redacted] • [redacted]	
Pg 4, 1.1, para 4: "In fact, the cost to identify one teplizumab patient is £1,724.26, according to the company's response to the Call for additional evidence"	"teplizumab patient" should be changed to "Early-T1D individual".	Factual inaccuracy: in the company response £1,724.26 is the cost to identify one individual with Early-T1D at a 1 in 30 population risk rate (in line with the NICE Committee request).	The EAG believe that this is not a factual inaccuracy, presuming that the company have not assumed a percentage uptake of teplizumab that is less than 100%.

Issue 2 Topic 3. Stage 2 Disutility

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg. 5, 1.3, para 4: "The EAG would like to emphasise that the company's overall narrative seems to refer to a short-term shock effect associated with the diagnosis of Stage 2, but in the economic model this disutility is continuously applied as long as patients are in the Stage 2 T1D health state."	**Proposed wording:** "The EAG notes that the company's submission discusses the HRQoL impact associated with diagnosis of Stage 2 T1D. The company maintains that the duration and persistence of any HRQoL impact may extend beyond the initial period after Stage 2 diagnosis and so they have modelled this disutility for as long as patients are in the Stage 2 T1D health state. The EAG have suggested an alternative scenario in which the disutility is curtailed"	It is a factual inaccuracy that the company has suggested "a short-term shock effect" in this context. The characterisation of the Stage 2 disutility as a short-term "shock" by the EAG is overly narrow and risks presenting a one-sided interpretation of the evidence. While an initial psychological impact at diagnosis is clearly important, it is also likely that the HRQoL impact of a Stage 2 diagnosis is not necessarily confined to an instant short-term adjustment period. Being diagnosed with a chronic, progressive condition despite being asymptomatic can give rise to sustained uncertainty, anticipatory anxiety, and ongoing burden associated with regular monitoring and follow-up, which may persist beyond the initial period of a Stage 2 diagnosis. As highlighted in the company	Not a factual inaccuracy. This is the EAG's interpretation of the evidence submitted by the company. It is up to the Appraisal Committee to decide whether this is correct or not. The EAG would like to point out that in case the Appraisal Committee agrees with the company's view and the stage 2 disutility should be applied continuously, the EAG is concerned about the validity of the estimated disutilities since these are larger than those applied at Stege 3. This concerned was already highlighted by the EAG but has not been addressed by the company.

		response to the Call for Additional Evidence, Guenther et al (2025) indicated that a disease-modifying therapy (DMT) such as teplizumab is likely to provide a statistically significant relative improvement to the HRQoL associated with Stage 2 T1D (-0.049 vs. -0.124 (p=0.004)). This is clinically plausible, illustrating that whilst individuals still carry the diagnosis the hope in slowing and managing the disease derived from treatment with a DMT is very important to them. Therefore, framing the effect solely as a transient shock implicitly assumes full adaptation thereafter, which is not directly supported by the evidence. This interpretation therefore risks understating the potential duration of impact experienced by individuals living with Stage 2 T1D.	
Pg. 10, Checklist form, Row 6 Accessibility: "The final vignettes and	**Proposed wording**: "The final vignettes and underlying data were made	The final vignettes are publicly available having been presented at ISPOR Europe in November	Amended as follows: "The final vignettes and study results were presented at ISPOR Europe 2025.The full study is not publicly

underlying data are not publicly available”	available at ISPOR Europe, November 2025”	2025: ISPOR - Valuing Health States When Transitioning From Stage 2 to Stage 3 Type 1 Diabetes in a Sample of the General Population in the United Kingdom	available yet and appears to be subject to sponsor ownership and confidentiality restrictions. No mechanisms for external access, reuse, or replication have been reported, except that all records should be kept and made available for review in the event of audits, or inspections and must be safely archived for at least 10 years after the completion of the study."

Issue 3 Topic 4. Managing Stage 3 Costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg. 11, 1.4, para 3: “…current uptake in the relevant age group is approximately 72% and is likely to plateau at 80–85% in 2025”	**Proposed wording:** “…current uptake in the relevant age group is 80% and is likely to plateau at 84% in March 2026”	We were unable to specify a precise timing for when uptake of hybrid closed loop systems would reach a plateau in previous evidence submissions. However, updated clinical insight provided by [redacted] on 28th January 2026 indicates that uptake in the relevant age group is currently 80% and is expected to plateau at 84% by March 2026. This means that by the time any NICE	Not a factual inaccuracy. The figures quoted by the EAG are those provided by the company, which they stated were: “…based on personal communication with [redacted]”

		guidance is published for teplizumab, following the conclusion of this appraisal, referencing a plateau of 80-85% or current uptake in the relevant age group as approximately 72% is no longer accurate. This amendment reflects the most up-to-date expert clinical evidence and represents a marginal reduction of the plateau compared with the previously stated assumption of 85%. We have provided updated economic analysis with 80% and 84% estimates for HCL uptake in a separate submission. It is very important that these data are reflected at committee given the critical impact of the HCL uptake estimates on the ICER.	
Pg. 12, 1.4, para 1-2: "Hex et al. 2014"	"2014" should be corrected to "2024".	Corrected as per publication date.	
Pg 12, 1.4, para 1: "Neither source provides us with the trajectory of type-1 diabetes related healthcare costs with	**Proposed wording: "**Neither source provides us with the trajectory of type-1 diabetes related healthcare costs with	*We assume that when referring to "the numbers provided by the company", the EAG are referring to the weighted averages calculated for the quadratic extrapolation (pg. 31 of the company response).*	Not a factual inaccuracy. The average annual cost of stage 3 disease management is £[redacted] for Teplizumab and £[redacted] for ECM based on the

age or time in stage 3 T1D but they provide an indication of reasonable annual cost estimates, which are far below those implied by the company's extrapolation."	age or time in stage 3 T1D but Hex et al (2024) provides an approximate cross-sectional average of the cost of a Stage 3 T1D population in one year. If the **same** methodology is applied to the company approach, the annual figures are comparable £4,982.64 per year (Hex et al, 2024) vs £4,425.60 per year (company approach)."	It is factually inaccurate for the EAG to state that Hex et al (2024) provides a figure that is far below the company extrapolations. As explained in section 4.3.3 of the company response (pg. 31), £4,982.64 per year (Hex et al, 2024) represents a weighted average across the entire prevalent population (all ages and duration of diagnosis). If the **same calculation** is applied to the Company's unadjusted quadratic extrapolation, this is £368.80 per month, or £4,425.60 per year. This illustrates that our unadjusted approach (the quadratic extrapolation before HCL adjustment is applied) is in line with the published literature. The EAG also do not state whether the company projections in Figure 1.1 account for HCL adjustments or not. This is important when making comparisons against as Hex et al. (2024) does not account for present-day HCL availability. As the EAG state, "Neither source provides us with the trajectory of type-1 diabetes related healthcare costs with age or time in stage 3 T1D" therefore it is speculative and potentially misleading for the EAG to compare the Hex et al figure with the extrapolation in Figure 1.1. As explained above, the like-for-like figures in our	model results. This is calculated from the average total per person costs of state membership divided by the average duration in stage 3.

		unadjusted approach are in line with those in Hex et al (2024).	
Pg. 12, 1.4, para 2: "However, insufficient information is provided to validate this comparison."	The statement should be removed, or revised to state that calculations for these estimates were provided as part of the company response. **Proposed wording:** "Calculations for these estimates were provided as part of the company response"	It is factually incorrect to say insufficient information was provided. Calculations were provided in Appendix 3 of the Company Response to the Call for Additional Evidence. It is unclear what additional information is required by the EAG.	Not a factual inaccuracy. The methodology used to describe these calculations is not fully described. In addition, these estimates do not appear consistent with the model results. The average annual cost of stage 3 disease management is £10,879 for Teplizumab and £11,226 for ECM based on the model results. This is calculated from the average total per person costs of state membership divided by the average duration in stage 3.
Pg. 12, 1.1, para 3: "the assumptions used in the company's current extrapolation remain implausible"	**Proposed wording:** "the assumptions used in the company's current extrapolation remain plausible"	It is factually inaccurate for the EAG to state that the company's long-term costs are implausible. As explained above and in the company response to the call for additional evidence, we have validated the approach with clinical experts (section 4.3.1), against published data regarding long-term complications (section 4.3.2) and against published estimates (section 4.3.3), all of	Not a factual inaccuracy. The EAG provided a detailed critique in its review of the company's submission. In short, the EAG agrees, in line with clinical expert opinion, that a quadratic relationship with costs over time was more realistic than a linear

		which indicate the clinical plausibility of the Company approach.	extrapolation, as agreed by the EAG. The issue is however with the specific quadratic model used which implies implausibly additional high costs of T1D management in later years. The estimates were not formally validated against long-term complication rates.
Pg 13, 1.4, para 1: "For the revised EAG base-case we apply the cap after 40 years with stage 3 T1D and explore other values in scenario analyses"	Please provide justification for the choice of 40 years as the cap with Stage 3 T1D selected as the base case.	The EAG does not provide a clear clinical or methodological justification for selecting a cap at 40 years in Stage 3 T1D as its base case assumption. Given that this assumption is a key driver of the ICER, it is important that the choice of cap is supported by a clinically plausible rationale. In the absence of such justification, additional explanation is required to support the appropriateness of the EAG's selected figure.	Not a factual inaccuracy. There is limited data to select an appropriate cap. As described above the extrapolated cost estimates appear implausible even when applying the company's 60-year cap. This suggests a lower cap would be appropriate.
Pg 13, 1.4, para 2: "The EAG previously asked the company to justify why the IQVIA Core Diabetes Model was appropriate for this purpose but not for direct estimation of	**Proposed wording:** "The EAG previously asked the company to justify why the IQVIA Core Diabetes Model was appropriate for this purpose but not for direct estimation of Stage 3 T1D costs.	It is factually incorrect to state no response was provided. This states that the company declined or failed to provide a response. This point was raised within the EAG critique of the Company's response to Draft Guidance (ID6259 DG Company comments form Sanofi 080925 v1.0_EAG critique_final_021025 [CON]) rather than as a direct question to the company.	The following change was made: "The company did not provide rationale for not using the IQVIA Core Diabetes Model for direct estimation of stage 3 T1D costs."

Stage 3 T1D costs but no response was provided”	This point was raised within the EAG critique of the Company’s response to Draft Guidance, and therefore the Company has not yet had an opportunity to provide a further response at this stage”	We are committed to providing as much information as possible to ensure the EAG and committee are in full possession of all the evidence. In this case the company had no opportunity within the appraisal process to comment. The text should be amended to accurately reflect the appraisal process rather than suggesting non-response.	

Issue 4 Topic 7. Revised Base Case & Scenario Analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.1, Stage 3 costs: “The company’s extrapolation … provides unrealistic estimates of long-term Stage 3 T1D costs”	**Proposed wording:** Removal of “ provides unrealistic estimates of long-term Stage 3 T1D costs”	It is factually inaccurate for the EAG to state that long term costs are unrealistic. As explained above and in the company response to the call for additional evidence, we have validated the approach with clinical experts (section 4.3.1), against published data regarding long-term complications (section 4.3.2) and against published estimates (section 4.3.3), all of which	Not a factual inaccuracy. See EAG response to Issue 3.

		support the clinical plausibility of the Company approach.	
Table 1.1, Stage 3 costs: “The company accepted this in the request for additional evidence and considered a cap after 65 years in state”	**Proposed wording:** “In the call for additional evidence, the company provided a scenario with a cap after 65 years in Stage 3 T1D to illustrate the impact of the longest-term costs being attenuated.”	It is factually incorrect to state that the company “accepted” that any extrapolations were based on “limited data” or provided “unrealistic estimates”. The truncation after 65 years was provided as a scenario analysis to illustrate the impact of the longest-term costs being attenuated.	Change to: "In the request for additional evidence the company capped stage 3 costs after 65 years in state in a scenario analysis."
Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	
Pg. 12, para 2	The figures in the following text should be marked confidential, as they refer to costs and QALYs in the cost-effectiveness model: “For reference, total undiscounted stage 3 T1D costs for ECM in the model were [redacted], with an average were [redacted], years spent in stage 3, equating to were [redacted], per year in Stage 3 (or were	For reference, total undiscounted stage 3 T1D costs for ECM in the model were [redacted], with an average [redacted] years spent in stage 3, equating to [redacted] per year in Stage 3 (or [redacted] per month). These are substantially higher than the numbers provided by the company.	Corrected.

	[redacted], per month). These are substantially higher than the numbers provided by the company."		
Pg. 12, Figure 1.1	Figure 1.1 should be marked as commercial in confidence.	Mark the figure as commercial in confidence.	Corrected
Pg. 4, para 1	Some of the inputs and outputs from the calculations of the Excel file should be marked as commercial in confidence, as they refer to assumptions of a commercially sensitive nature.	In addition, the Excel file states that only [redacted] are at least 8 years old, but these would not be included for testing to identify patients eligible for teplizumab. However, only [redacted] uptake is assumed. Therefore, according to these figures, it can be calculated that testing one person would result in [redacted] of 20% of 0.034 = [redacted] patients to be treated with teplizumab i.e. 1[redacted]=[redacted] […] Of course, the EAG acknowledge that there is movement from stage 1 to stage 2, which is also included in the Excel file at a rate of [redacted] per year	Corrected
Pg. 4, para 2	Some of the inputs and outputs from the calculations	This contrasts with the Excel file referred to above, which	Corrected

	of the Excel file should be marked as commercial in confidence, as they refer to assumptions of a commercially sensitive nature.	calculates an estimate of [redacted] (after changing the % aged at least 8+ from [redacted] to [redacted]).[4] This figure would be [redacted] if the unit costs for AAB and confirmatory testing were the same as in the company response (£46.20 and £140.24 instead of [redacted] and [redacted] respectively). However, the cost would be much lower if one assumes that all of those with stage 1 convert to stage 2, and are detected by monitoring. In the Excel file, it is assumed that there is [redacted] uptake of stage 1 monitoring, which means that the number of patients with stage 2 detected is increased from [redacted] ([redacted] of 20% of 2AAB+) by adding [redacted] of [redacted] ([redacted] of 75% of 2AAB+) to give [redacted]. This is equivalent to needing to test 1/[redacted], which is about [redacted] people to detect 1 patient who receives teplizumab. The testing cost would also increase a little by the amount required to monitor those with stage 1 disease: according to the monitoring costs in the Excel file, this would lead to a cost of	

		[redacted] per person treated with teplizumab. Note that this figure would decrease if there was greater uptake of stage 1 monitoring. On the other hand, it would probably be higher in the first years after the introduction of testing, if only [redacted] convert to stage 2 per year.	
Pg. 4, 1.2, para 1	1.76 does not need to be redacted.	Based on the evidence presented by the company in Appendix 2 of the Call for additional evidence,[1] the EAG prefers assuming [redacted] carers to one patient instead of 1.76. Alternative values were explored in sensitivity analyses by the EAG.	Corrected
Pg. 14, Table 1.1, Caregivers	1.76 does not need to be redacted.	1.76 caregivers maintained for individuals aged < 25 years old (disutility applied: -0.04).	Corrected
Pg. 17, para 1, bullet 2	1.76 does not need to be redacted.	Number of caregivers equals 1 (lower end scenario) and 1.76 (company's base-case).	Corrected
Pg. 18, Table 1.4, number of caregivers	1.76 does not need to be redacted.	1.76	Corrected