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

Confidential information redacted

Technology appraisal committee A [07 October 2025]

Chair: James Fotheringham

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Emma McCarthy, Caron Jones, Ian Watson

Company: Sanofi

Teplizumab (Tzield, Sanofi)

Marketing authorisation	Tzield is indicated to delay the onset of Stage 3 type 1 diabetes in adult and paediatric patients 8 years of age and older with Stage 2 type 1 diabetes (T1D). Granted August 2025
Mechanism of action	Binds to CD3, may involve deactivation of pancreatic beta-cell autoreactive T lymphocytes. Also increases regulatory T cells.
Administration	IV infusion, once daily for 14 consecutive days based on BSA: • Day 1: 65 mcg/m^2 • Day 2: 125 mcg/m^2 • Day 3: 250 mcg/m^2 • Day 4: 500 mcg/m^2 • Days 5 to 14: 1,030 mcg/m^2
Price	• List price - [redacted] per 14-vial treatment course • A simple patient access scheme discount applies for teplizumab

NICE

CD3, cluster of differentiation 3; BSA, body surface area-based dosing

Clinical trial results – TN-10

In primary and extended follow up analysis, teplizumab increases the median time to Stage 3 T1D onset compared with placebo

Outcome	Teplizumab (n=44)	Placebo (n=32)
Primary analysis (median follow up = 745 days)		
Median time from randomisation to Stage 3 T1D onset, months (95% CI)	49.5 (32.2, NE)	24.9 (9.5, 48.6)
Median difference in between arms, months (95% CI)	24.6 (NE, NE)	
Hazard ratio (95% CI); p-value	HR 0.41 (0.22 to 0.78); p=0.0066	
Extended follow up analysis (median follow up = 923 days)		
Median time from randomisation to Stage 3 T1D onset, months (95% CI)	59.6 [redacted]	27.1 [redacted]
Median difference between arms, months (95% CI)	32.5 [redacted]	
Hazard ratio (95% CI); p-value	0.457 (NR); p=0.01	

KM curve showing delayed onset of T1D

CI = confidence interval; HR = hazard ratio; NE = not estimable; NR = not reported; T1D = type 1 diabetes; KM, Kaplan-Meier

Draft guidance consultation

Preliminary recommendation: Teplizumab should not be used for delaying the onset of stage 3 type 1 diabetes in people 8 years and over with stage 2 type 1 diabetes.

Key uncertainties:

- Population eligible for teplizumab
- Costs of managing stage 3 T1D
- Effects of stage 3 type 1 diabetes on quality of life

Consultation responses received from:

- Sanofi (company)
- NHS England
- West Yorkshire ICB and West Yorkshire Association of Acute Trusts
- British Society for Paediatric Endocrinology and Diabetes
- Breakthrough T1D
- Diabetes UK
- Web comments (n=10)

ICB, Integrated Care Body; T1D, type 1 diabetes

Committee discussion at ACM1 – issues for discussion

Issues discussed	Committee conclusion at ACM1
Identifying people with stage 2 T1D and defining eligible population	More information needed on number and proportions of populations potentially eligible for teplizumab, and who would be offered testing
Modelling progression to stage 3 T1D	Log-normal distribution for teplizumab and gamma distribution for ECM plausible, but further exploration of hazard functions and curve fitting requested
Approach to estimating decline in utility	Further analyses requested exploring rate of disutility over time in stage 3 T1D, and how this interacts with one-off disutility and constant disutility values
Carer disutility	Scenarios requested in which carer disutility is halved or absent, and where carer disutility ends at age 25
Stage 3 T1D costs	New estimates of stage 3 T1D costs requested, based on more recent data source including costs and benefits of hybrid closed loop systems
Adverse events	Costs of CRS should be included in the teplizumab arm of model at incidence of 5.8%

T1D, type 1 diabetes; ECM, established clinical management; CRS, cytokine release syndrome

Other issues from ACM1

Consultation comment themes

Unmet need and impact on quality of life (BTT1D, Diabetes UK, West Yorkshire ICB, web comments)

- Managing glucose levels and living with T1D is challenging and impacts psychological well being/quality of life – as evidenced by surveys of people living with T1D and their caregivers
- Concern that effects of stage 3 T1D on QoL of people with T1D and their carers is not fully accounted for
- Specific impacts on health include disruption to employment, sleep, and complications such as DKA, cardiovascular problems, and kidney disease

Identifying populations and care pathway (Sanofi, BSPED, West Yorkshire ICB, NHSE, web comments)

- Ongoing research studies are the main route to identifying Stage 2 T1D without formal screening programme
- Information provided from ELSA study on proportions of screened participants with autoantibodies (Quinn 2025)
  - Proposal submitted (based on ELSA findings) on potential plan for rollout of screening and follow up of early T1D in children (specifically FDRs) - see appendix
- Uplift in screening for FDRs not expected to be significant without structured screening programme – and FDRs only account for a small proportion of T1D population
- There is now a nationally recognised pathway for follow up of children and young people identified with positive islet autoantibodies (Besser et al, 2025) – but commissioning of pathway and prior autoantibody testing would be the responsibility of ICBs

Costs in economic model (BSPED, West Yorkshire ICB, NHSE, Diabetes UK, web comments)

- Appropriate to capture cost of hybrid closed loops in modelling since this is now part of standard treatment, but uptake not linear over time due to limitations in funding
- Costs of managing stage 3 T1D for 3 years with no treatment could be compared with costs of managing stage 2 T1D over the same period with teplizumab
- Overall costs to the health service of increased screening should be considered

BSPED, British Society for Paediatric Endocrinology and Diabetes; BTT1D, Breakthrough Type 1 Diabetes; ICB, Integrated care board; QoL, quality of life; FDR, first degree relatives

Equality considerations

Additional potential equalities issues raised in consultation responses

Consultation comments

- Caregivers may have to reduce working hours or leave employment which may cause additional financial strain within households.
    - Uneven split between parents that may impact mother
- Separate consideration may be needed for visually impaired people (who may struggle to independently manage insulin), people with learning difficulties or children residing in care settings
- Access to insulin supplies and storage, and access to consistent healthcare, can be problematic for travelling communities and other nomadic groups

Are there any additional equality issues that need to be considered?

Key issues

Key issue	ICER impact
Identifying people with Stage 2 T1D and defining population eligible for teplizumab	Unknown
Modelling progression to Stage 3 T1D	Large
Approach to estimating decline in stage 3 utility	Large
Carer disutility	Moderate
Stage 2 disutility	Large
Estimation of stage 3 T1D costs	Large
Adverse events	Small

T1D, type 1 diabetes; ICER, incremental cost effectiveness ratio

Key issue: Identifying people with Stage 2 T1D and defining population eligible for teplizumab

Key populations that may be tested, identified at ACM1:

1. People identified in research studies (e.g. ELSA)
2. People tested because of clinical suspicions
3. First degree relatives of people with T1D
4. All-comers (i.e. people requesting antibody testing)

Committee considerations and conclusions at ACM1

- If teplizumab was recommended, more people would need autoantibody tests – but expected increase overall and in each population is unknown, which is a significant uncertainty
- The potential increase in demand for ad-hoc autoantibody testing and the associated costs, if teplizumab were recommended, should be captured in the economic model
- Further information requested on number and proportions of populations potentially eligible for teplizumab and who would be tested → essential for understanding size, composition and characteristics of population potentially accessing teplizumab
- Implementation issues regarding testing (see slide 11) also discussed at ACM1

Treatment pathway and population eligible for teplizumab

Company positions teplizumab for people already diagnosed with stage 2 T1D – but no routine testing available in current practice

Stage 2 T1D:

Asymptomatic and not usually identified in routine practice – diagnosis mostly from research studies

Teplizumab

Established clinical management following diagnosis:

- monitoring blood glucose
- psychosocial support
- education

Stage 3 T1D:

Most people with T1D diagnosed at stage 3 following symptom onset and enter treatment pathway here

Stage 3 management includes:

- insulin
- blood glucose monitoring
- carbohydrate counting
- exercise

- **Key issue** – for teplizumab to be introduced into pathway, eligible population needs to be identified. But there is no national screening programme or standard pathway of care for pre-symptomatic T1D
- Some people with stage 2 T1D already identified through research studies or because of clinical suspicion of T1D, but no currently available treatment for delaying stage 3 T1D so demand for testing is low

Other considerations: implementation issues

Implementation issues discussed at ACM1

- New pathway of care would need to be established – including standardised methods of testing, administering teplizumab in secondary care and appropriate follow up
  - Committee acknowledged the need for infrastructure in the NHS to support any potential recommendation (and that there may need to be further service design work)

Company and stakeholder comments

- New guidance from BSPED on best practice recommendations for children and young people (<18 years) with pre-stage 3 T1D (Besser et al, 2025) outlines pathway for follow up following positive autoantibody testing
  - Commissioning of care pathway and prior autoantibody testing would be the responsibility of ICBs
- Company: 14-day teplizumab administration will place limited additional demand on the NHS → important to distinguish resources needed for this from resources need for setting up wider management of pre-symptomatic T1D
- Web comment: proposed 5-year plan for screening of children starting with FDRs based on ELSA study findings (see appendix)
- ICB: NHS not ready for use of treatment without an available screening programme – overall costs to the health service would need to be considered.

What is the committee's view on implementation issues including screening and treatment pathway?

T1D; type 1 diabetes: ICB, integrated care board; BSPED,

Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Company

- Maintains cost of autoantibody testing related to identifying patients should not be included in modelling – base case includes confirmatory autoantibody testing in teplizumab arm only
  - Additional benefits from testing not directly related to teplizumab may bias results if testing included
  - Modelled budget impact scenarios estimating costs of mild to moderate increase in FDR testing (uptake from [redacted])
- Company advisory boards discussing autoantibody testing anticipated approval of teplizumab would lead to "mild to moderate" increase in FDR testing, a "modest increase" in research study population testing, and no testing increase due to clinical concerns (since this population is diagnosed incidentally)
  - For population requesting testing – most expected to be FDRs
- Ongoing study with between company and NHS trust (UHMBT) found [redacted]
  - [redacted]

EAG comments

- Agrees largest increase in testing uptake would be in FDRs, but also potential for substantial increase in uptake from research studies or those requesting testing without an FDR
- Size of increase will depend on proportion of those tested who would have stage 2 T1D (ranging from 1 in 10 to 1 in 20 in FDRs with any stage T1D, to 1 in 300 to 1 in 400 in general population with any stage T1D)

FDR, first degree relatives; T1D, type 1 diabetes; UHMBT, University Hospitals of Morecambe Bay Trust (UHMBT)

Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Anticipated testing numbers and total costs from company based on increased uptake in FDRs

Scenario	Total individuals tested	Incremental tests vs. baseline	Total testing cost*	Incremental cost vs. baseline
Current [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing uptake [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing uptake [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] testing uptake [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Calculated by multiplying cost of single autoantibody test (£29.04) by number of tests

Company

- Additional testing costs and uptake is modest in context of managing Stage 3 T1D costs
- Approach assumes 2 FDRs for every person with T1D – in practice this may be lower

FDR, first degree relatives; T1D, type 1 diabetes

Testing numbers and costs split by incident and prevalent population

Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Input from NHSE

Submitted estimates of numbers in each population that may present for autoantibody testing, including:

1. FDRs (either 2 or 5 FDRs tested plus central estimate of 2.5 FDRs): ~775,000 tests needed (3.2x capacity increase)
2. FDR population plus 1% uplift to account for ad hoc testing requests or clinical concerns (including people identified from research studies): ~1.3m tests needed (13.6x capacity increase)

Cost of testing includes autoantibody testing, but also phlebotomy appointments, blood tests, oral glucose tolerance test and diabetes service costs (cost per patient [FDR]: £668.53 for children, £212.73 for adults; cost per patient [ad hoc]: £637.35 for children, £193.26 for adults)

NHSE anticipated numbers eligible for testing (1 autoantibody test per person):

Population	2 FDRs	2.5 FDRs	5 FDRs
FDRs	620,374	775,468	1,550,935
FDR + ad hoc testing	1,146,692	1,301,786	2,077,253

Should testing costs be included in modelling? If so, how?

EAG comments

- NHSE calculations do not explicitly exclude 9% of T1D population under 8 years (ineligible for teplizumab)
- Assumes greater uptake of testing so company estimates likely conservative
- Basis for NHSE assumption of FDR% plus additional 1% for ad hoc uplift is unclear

FDR, first degree relatives; T1D, type 1 diabetes

Anticipated testing numbers (systematic population) and costs of screening, NHSE figures

Key issue: Modelling of progression to Stage 3 T1D

Company = log-normal for teplizumab, gamma for ECM, EAG = gamma for both arms

Committee conclusion at ACM1

Log-normal distribution for teplizumab and gamma distribution for ECM plausible, but further exploration of hazard functions and curve fitting requested

Company

- Scenario analysis explored flexible spline models fitted with hazard, odds, and normal scales and 0-3 knots
- Base case maintains log-normal distribution for teplizumab arm, based on best goodness of fit statistics
- Revised base case assumes gamma distribution for ECM based on long term projections from this model aligning with that of best fit model (normal spline with 3 knots)

EAG comments

- Long term projections for teplizumab arm still uncertain since additional data or expert opinion not provided – EAG maintains gamma distribution for both treatment arms based on good fit to data and more conservative long-term projections of progression in teplizumab arm
  - Also maintains use of same type of parametric model for both arms since PH assumption does not hold
- Differences in goodness of fit between log-normal and some other extrapolations in teplizumab arm are extremely minor
- Choice of modelling for additional analysis (including selection of number of knots) is unclear

ECM; established clinical management; AIC; Akaike information criterion; BIC, Bayesian information criterion; T1D, type 1 diabetes; DSU, Decision Support Unit; PH, proportional hazards

Key issue: Modelling of progression to Stage 3 T1D

Company = log-normal for teplizumab, gamma for ECM, EAG = gamma for both arms

Time to Stage 3 T1D, parametric and flexible base case projections

Projected proportions of people still in stage 2 T1D (teplizumab)

Time (years)	Normal spline, 3 knots	Log normal	Gamma
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

Projected proportions of people still in stage 2 T1D (placebo)

Time (years)	Normal spline, 3 knots	Gamma
5	[redacted]	[redacted]
10	[redacted]	[redacted]
15	[redacted]	[redacted]

What approach to extrapolating progression to stage 3 T1D should be used?

T1D, type 1 diabetes

ACM1 recap of projections

Key issue: Approach to estimating decline in stage 3 utility

Updated company base case uses piece-wise approach for stage 3 decline with 10-year inflexion point

Committee conclusion at ACM1

- Further analyses requested exploring rate of disutility over time in stage 3 T1D, and how this interacts with one-off disutility and constant disutility values applied.

Company

- Retains time-dependent disutility as in original source of disutility estimates (Sparring 2013) but adapted rate of decline in model to use piece-wise approach
- Adjusted rates of decline and inflexion point of 10 years informed by additional simulation analysis using patient level model (Core Diabetes Model, version 10)
  - New time-dependent disutility estimates also account for impact of hybrid closed loops on long term QoL trajectory (additional utility of 0.005 for first 10 years and 0.03 after 10 years used to inform slope)
- 10-year inflexion point in line with clinical expert opinion from draft guidance stating complications associated with stage 3 T1D take 10 years to manifest
- Scenarios explored with change to utility declines

T1D, type 1 diabetes; QoL, quality of life

Key issue: Approach to estimating decline in stage 3 utility

Updated company base case uses piece-wise approach for stage 3 decline with 10-year inflexion point – EAG uses same values in base case

	ACM1 company base case	Revised company and EAG base case	Company scenario
One off disutility on cycle of stage 3 onset	-0.025	-0.025	-0.025
Constant disutility	-0.0621	-0.0621	-0.0621
Time-dependent disutility – absolute decline	8 years: -0.023 15 years: -0.055 24 years: -0.074	≤10 years: -0.0026 11+ years: -0.0028	≤10 years: -0.0028 11+ years: -0.0030
Time-dependent disutility – relative decline (baseline utility = 0.93)	-	<10 years: -0.28% 11+ years: -0.30%	<10 years: -0.25% 11+ years: -0.23%

EAG comments

- EAG approach (with removal of time-dependent disutility and one-off disutility at ACM1) has been revised to include one-off disutility, constant disutility and time-dependent disutility in line with company base case
- Updated approach is more flexible, but unclear exactly how utility decline rates were calculated
- Changes to inflexion point from time points other than 10 years has minimal impact on results

How should decline in utility at stage 3 of T1D be modelled?

Key issue: Carer disutility

Company has increased age at which disutility for carers ends from 18 to 25 years

Committee conclusion at ACM1

- Approach to modelling carer disutility likely reasonable, but uncertain. Scenarios requested in which carer disutility is halved or absent, and where carer disutility ends at age 25.

Company

- Revised base case maintains carer disutility of -0.04 but upper age limit increased from 18 to 25 years
- Additional scenarios include disutility of -0.04 applied until age 18 (as in original base case), -0.02 applied until age 18 and -0.02 applied until age 25 – scenario with no disutility also explored, but company views this implausible
- Committee concern at ACM1 regarding carer disutility being overestimated due to capturing effects of carer having T1D themselves is not applicable to wider appraisal population → around 90% of people with T1D do not have FDR with condition

EAG comments

- If caregiving burden is higher for younger children with T1D, a disutility of -0.04 may be too high as population in model ages since the model starting age is 13.6 years
- Considers that caregiver burden in families with 2 parents should be similar to that of single parent family (and split if applying to both)
  - Applying disutility to 1 caregiver only increased ICER by 11.2%
- Acknowledges uncertainty around carer disutility and considers age threshold arbitrary - does not specify a preferred alternative age threshold

At which age should carer disutility no longer apply?
What size of carer disutility is appropriate? What number of caregivers should be used?

T1D, type 1 diabetes; ICER, incremental cost effectiveness ratio; FDR, first degree relative

Key issue: Stage 2 disutility

Company includes treatment-specific disutility at stage 2, EAG prefers no stage 2 disutility

Background

- Company has revised base case to include a disutility associated with stage 2 T1D which differs by model arm (-0.049 in teplizumab and -0.124 in ECM)
- Values based on additional data from company (Guenther et al. 2025, conference abstract) assessing HRQoL perceptions of T1D progression in UK cross sectional study (n=300 adults)

Company

- Findings show HRQoL is lower with pre-symptomatic T1D compared to general population
- Results also show statistically significant difference in hypothetical HRQoL decline when disease modifying therapy is available compared with natural progression (p=0.004)

EAG comments

- Conference abstract only – EAG unable to properly assess validity or applicability of study
- Size of disutility for stage 2 lacks face validity, particularly relative to stage 3 values used in model
  - ECM stage 2 disutility larger than constant stage 3 disutility applied in company base case
- Utility values estimated in stage 3 of study (0.553 with disease modifying therapy vs 0.527 without) are low and comparable to utility values used in progressed cancers
- Prefers no disutility applied at stage 2 as in original submission

Should a disutility associated with stage 2 T1D be applied in the model?
If yes, is applying a treatment-specific disutility appropriate? What size of disutility should be applied?

T1D, type 1 diabetes; HRQoL, health related quality of life; ECM, established clinical management

Key issue: Estimation of stage 3 T1D costs

ACM2 company submission uses Danish data with linear regression along with additional HCL cost data

Committee conclusion at ACM1

- Request for plausible estimates for the cost of managing stage 3 T1D based on more recent data source that includes costs and benefits of hybrid closed loop systems.

Company

- Updated costs of managing stage 3 T1D → used Danish case control data with 19 year follow up
  - Linear regression model with quadratic term applied to data from 5-19 years to extrapolate long term costs past 19 years
  - Stage 3 costs calculated by subtracting costs in the control group from costs in T1D group
- Additional factor of 0.95 reflecting increased Danish healthcare spending relative to UK applied
- Used Core Diabetes Model to simulate additional impact of HCL systems in line with model baseline characteristics
  - Assumed a 10% price discount on average annual reported price of £5,684 in NICE guidance on hybrid closed loop systems for managing blood glucose levels in type 1 diabetes (TA943) to account for confidential discount in NHS
  - Reduction in HbA1c of 0.5% for HCLs compared with non-HCL systems – assumed constant over 50 -year time period (TA943 assumes 0.23% to 0.59% depending on HCL system)
- Company base case assumes 100% eligibility and uptake of HCLs

T1D, type 1 diabetes; HCL, hybrid closed loops

Average annual total healthcare costs from Danish data and cost projection

Key issue: Estimation of stage 3 T1D costs

Company and EAG estimated stage 3 T1D monthly costs over time:

EAG comments

- Approach to extrapolation of costs using Danish data is reasonable during observed period, but extrapolation beyond 19 year follow up overestimates long term costs
  - Average estimated monthly costs of stage 3 T1D in company base case are [redacted] (increased from £415.22 from data source used at ACM1)
  - Costs of stage 3 T1D from Core Diabetes Model substantially below company estimates
- Prefer to adapt linear regression model to exclude quadratic term
- Adding costs of HCL systems is appropriate but uptake of 100% does not align with NHS practice - EAG base case assumes 54% uptake based on NHSE numbers

Stakeholder comments on HCL uptake figures

- NHSE submitted numbers show uptake of 27% in people 19 and over with weighted higher uptake in other age groups - but uptake constrained by phased implementation leading and limitations in funding availability
- Diabetes UK – NPDA data show 62% uptake of HCLs in children and young people across England and Wales

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How should stage 3 T1D costs be modelled?
What percentage of HCL uptake should be assumed?

T1D, type 1 diabetes; NPDA, National Paediatric Diabetes Audit; HCL, hybrid closed loops; ACM1, appraisal committee meeting 1

NHSE uptake figures for hybrid closed loops

Key issue: Adverse events

Updated company approach includes CRS incidence at 4.6% in teplizumab arm – EAG thinks this is reasonable

Committee conclusion at ACM1

- Costs of cytokine release syndrome should be included in teplizumab arm of model at incidence rate of 5.8% (in line with teplizumab arm of integrated safety analysis)
- Not a key driver of cost effectiveness estimates

Company

- CRS reported in 1.2% of people in control arm of integrated safety analysis – since model captures excess risk of AEs, an incidence rate of 4.6% was assumed for teplizumab arm
- Duration of 2.5 days assumed and sex-weighted disutility value of -0.028 applied, based on literature

EAG comments

- Agrees with company approach
- Model results not sensitive to changes in CRS – related changes in % CRS, duration, costs or utility decrements lead to minimal changes in cost effectiveness results.

What rate of CRS incidence should be assumed in the model?

T1D, type 1 diabetes; CRS, cytokine release syndrome

Summary of company and EAG base case assumptions at ACM2

Assumption	Company base case ACM1	Revised company base case	Revised EAG base case
Testing costs	Excluded	Excluded	Excluded
Modelling stage 3 progression	Teplizumab: log-normal ECM: gamma	Teplizumab: log-normal ECM: gamma	Teplizumab: gamma ECM: gamma
Time dependent disutility at stage 3	Linear decline with values from literature, increasing disutility at 8, 15, and 24 years after onset	Piece wise approach with 10-year inflexion point, values from CDM simulation	Piece wise approach with 10-year inflexion point, values from CDM simulation
Stage 2 disutility	None	Treatment-specific disutility	None
Costs of Stage 3 T1D	Values from UK data and Taiwanese regression model, No HCL costs included	Values from Danish study, linear regression with quadratic term applied HCL costs included, assumed 100% uptake	Values from Danish study, linear regression without quadratic term applied. HCL costs included, assumed 54% uptake
Carer disutility	Based on 1.76 carers, up to age 18	Based on 1.76 carers, up to age 25	Based on 1.76 carers, up to age 25
AEs in teplizumab arm	Excluded	CRS included at rate of 4.6%	CRS included at rate of 4.6%

NICE

= Company and EAG base case differ

T1D, type 1 diabetes; ECM, established clinical management; HCL, hybrid closed loops: CRS, cytokine release syndrome; CDM, Core Diabetes Model

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts for hybrid closed loops

- Company base case results between £20,000 and £30,000 per QALY
- EAG base case significantly above £30,000 per QALY

In Part 2, the committee will also consider:

- EAG exploratory analysis applying testing costs (£29.04 – antibody test as per company submission):
  - to 1 in 10, 1 in 15, 1 in 20 people – to represent the expected risk of having T1D at any stage (that is, people having autoantibodies) for people with a first degree relative with T1D
  - to 1 in 300 to 400 people – to represent the expected risk of having T1D at any stage in the general population

Key issues

Key issue	ICER impact	Slide
Identification of people with Stage 2 T1D and defining population eligible for teplizumab	Unknown	9-14
Modelling progression to Stage 3 T1D	Large	15-16
Approach to estimating decline in stage 3 utility	Large	17-18
Carer disutility	Moderate	19
Stage 2 disutility	Large	20
Estimation of stage 3 T1D costs	Large	21-22
Adverse events	Small	23

T1D, type 1 diabetes

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

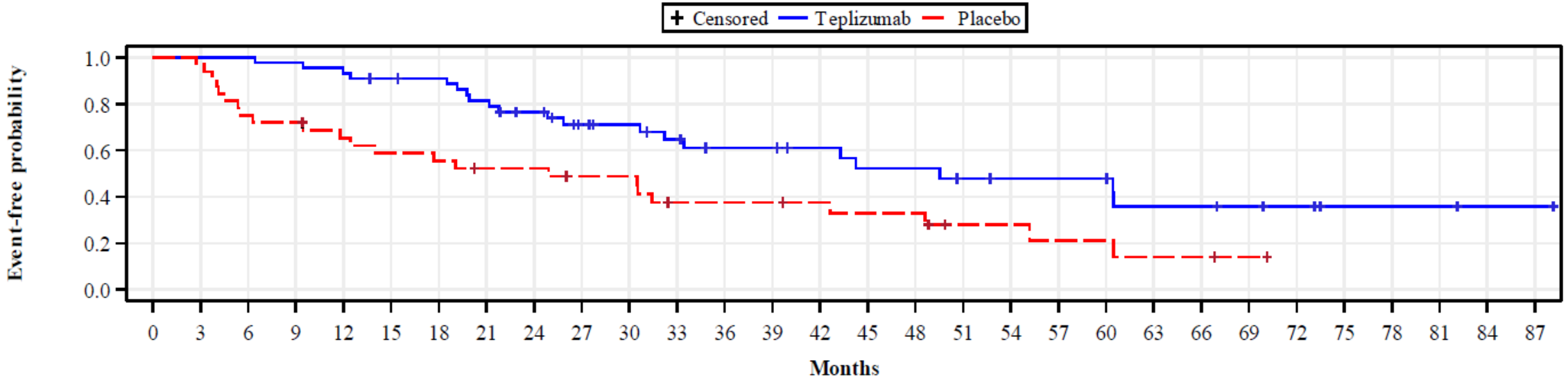
Supplementary appendix

NICE National Institute for Health and Care Excellence

Clinical trial results –TN-10

In primary and extended follow up analysis, teplizumab increases the median time to Stage 3 T1D onset compared with placebo

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



Number of Patients at Risk

Teplizumab	44	44	44	43	41	39	38	34	30	24	22	19	16	16	14	12	12	10	9	9	9	6	6	5	4	2	2	2	1	1
Placebo	32	31	24	23	20	18	17	15	15	13	13	9	9	9	8	7	7	4	4	3	3	2	2	1	0					

Number of Events

Teplizumab	0	0	0	1	3	4	4	8	10	12	12	14	15	15	15	17	17	18	18	18	18	20	20	20	20	20	20	20	20	20
Placebo	0	1	8	9	11	13	14	15	15	16	16	19	19	19	19	20	20	21	21	22	22	23	23	23	23					

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

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Committee discussion at ACM1 – issues not for discussion

Issues discussed	Committee conclusion at ACM1 – not for discussion
ECM as comparator	ECM is an appropriate comparator
Generalisability of teplizumab TN-10 trial population	Data from TN-10 suitable for decision making
General population mortality	Use 2017-18 life tables

T1D, type 1 diabetes; ECM, established clinical management; CRS, cytokine release syndrome;

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Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Anticipated testing numbers from company based on increased uptake in FDRs

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

FDR, first degree relatives; T1D, type 1 diabetes

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Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Anticipated testing numbers, systematic population:

Population	Low	Central	High
Age range-systematic population	8-11 years	8-16 years	8-29 years
Number of tests with systematic population	2,765,437	6,270,405	15,523,130

Anticipated costs of testing only (excluding patient identification, follow up and ongoing treatment):

Population	Low	Central	High
FDRs	£330 million	£412 million	£825 million
FDR + ad hoc testing	£578 million	£656 million	£1 billion
Systematic population	£1.6 billion	£3.6 billion	£7.1 billion

NHSE – with systematic general population testing (including those identified in research studies), a 66x capacity increase would be needed, assuming ~6,270,000 tests needed (1 autoantibody test per person)

NICE

FDR, first degree relatives; T1D, type 1 diabetes: FDR, first degree relatives

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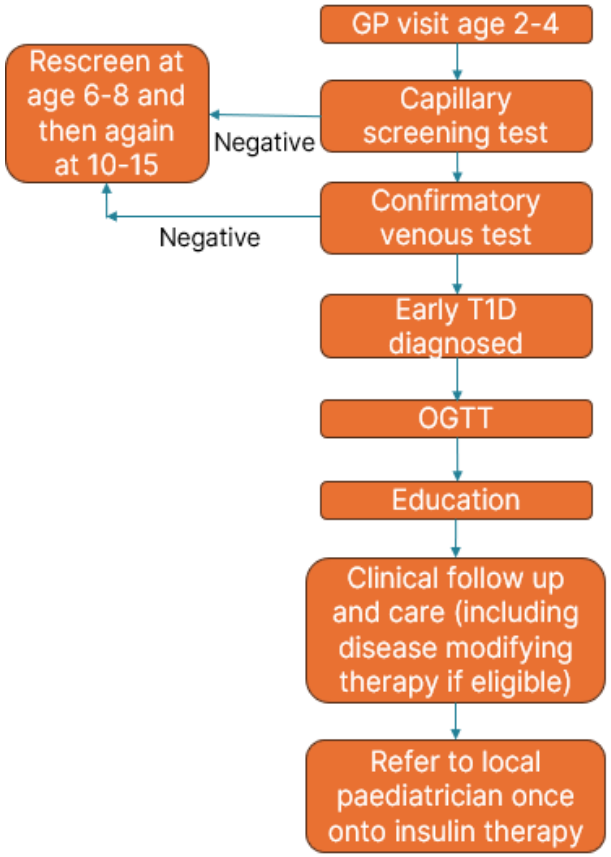
Proposed plan for screening, follow up and treatment of early T1D

Comments from ELSA study investigator

Proposed screening and treatment pathway:



Comments regarding treatment and monitoring pathway

- Screening limited to FDRs would identify ~15% of population before wider rollout
- Screening at ages 2-4, 6-8 and 10-15 years
- Regional centres would provide follow up for those diagnosed with early T1D – these pathways are already published
- People eligible for teplizumab treated in regional centres until insulin needed – then transferred back to local secondary care T1D teams for long-term management

Comments regarding testing numbers and costs over 5 years

- If testing 2 FDRs per index case – and half are under 16 (so eligible for children's services), then 24,500 children tested
- Based on ELSA study results, approx. 680 identified with stage 1 T1D and stage 2 T1D, with 102 moving from stage 1 to stage 2 annually
- Assuming 50% are over 8 years (so eligible for teplizumab) and 50% uptake following costs expected over 5 years:
  - Screening FDRs (including rescreening of those testing negative): £1.7M
  - Monitoring those with early T1D: £4M
  - Treating those identified at stage 2 (including progression from stage 1): £78M

NICE

FDR, first degree relatives; T1D, type 1 diabetes: FDR, first degree relatives; OGTT, oral glucose tolerance test

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Key issue: Estimation of stage 3 T1D costs

Company uses Danish data with linear regression along with additional HCL cost data

Average annual total healthcare costs (DKK) per person

Stage 3 T1D cost projection

T1D, type 1 diabetes: FDR, first degree relatives: HCL, hybrid closed loops; DKK, Danish krone

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Key issue: Identification of people with Stage 2 T1D and defining population eligible for teplizumab

Background

- Population in final scope and CS = people aged 8 and over with Stage 2 T1D
- People with Stage 2 T1D are asymptomatic → no screening programme in NHS practice to identify people with Stage 2 T1D (screening programmes currently only available via research trials)

Company

- Costs of screening not included in cost effectiveness estimates
- Eligible individuals are already confirmed as having Stage 2 T1D (i.e. have been diagnosed)
- Considers inclusion of screening outside scope of evaluation → responsibility of the NSC
- Evidence from BSPED shows children and young people identified with Stage 2 T1D in both the NHS (53%) and research settings (47%) (based on n=111 reported as being managed across the UK)

EAG comments

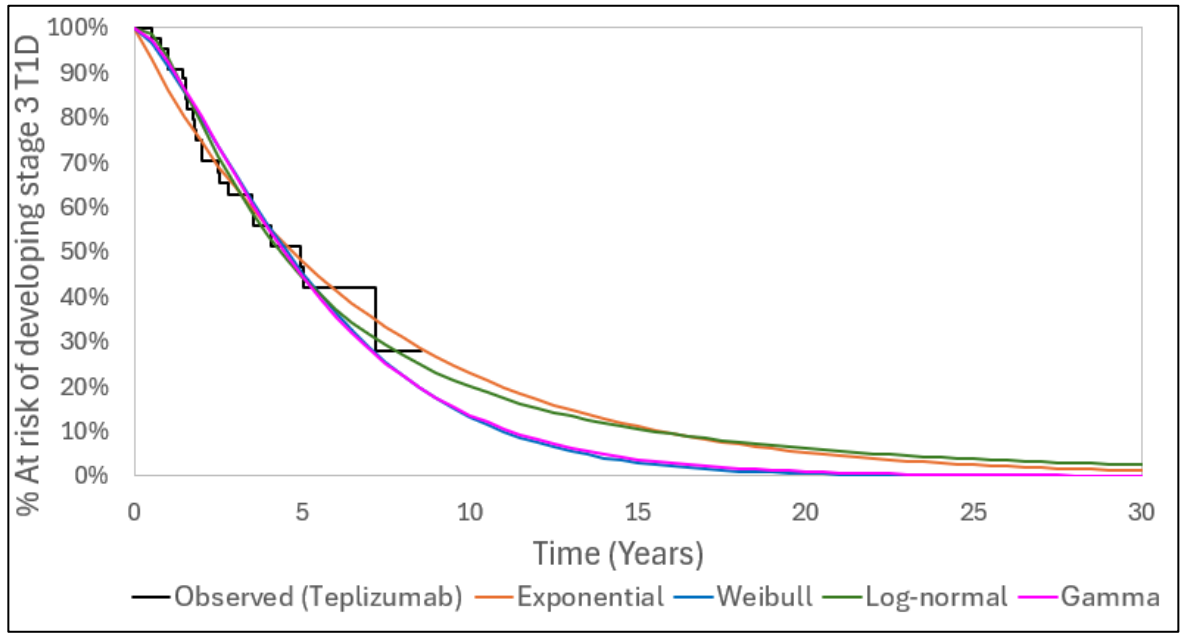
- Method of identifying patients eligible for treatment could significantly impact prognosis and expected treatment effect – important to identify selection criteria for diagnostic testing
  - TN-10 clinical trial identified people with Stage 2 T1D by testing relatives of people with Stage 3 T1D – but unclear if testing based on familial relationship would also be done in NHS practice

CS; company submission; T1D, type 1 diabetes; BSPED, British Society for Paediatric Endocrinology and Diabetes

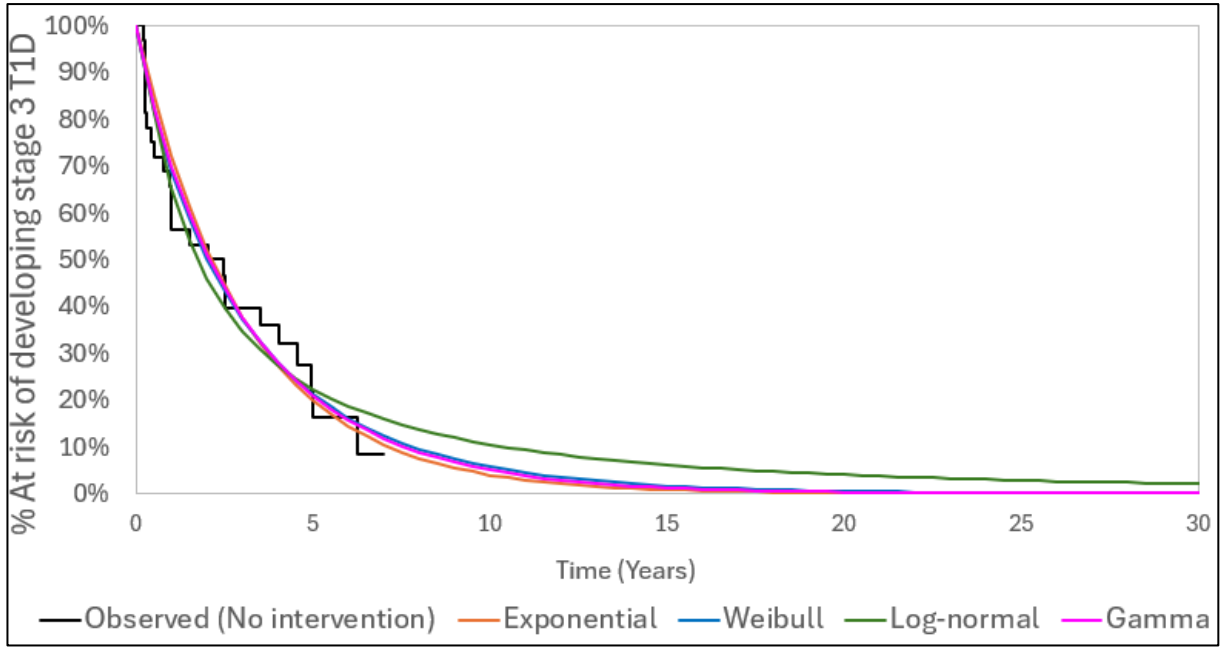
Key issue: Modelling of progression to Stage 3 T1D

Company = log-normal for teplizumab, exponential for ECM, EAG = gamma for both arms

Time to Stage 3 T1D, teplizumab arm (ITT population)



Time to Stage 3 T1D, placebo arm (ITT population)



Projected proportions of people still in stage 2 T1D (teplizumab)

Time (years)	Log-normal	Gamma
0	[redacted]	[redacted]
5	[redacted]	[redacted]
10	[redacted]	[redacted]
15	[redacted]	[redacted]

Projected proportions of people still in stage 2 T1D (placebo)

Time (years)	Exponential	Gamma
0	[redacted]	[redacted]
5	[redacted]	[redacted]
10	[redacted]	[redacted]
15	[redacted]	[redacted]

ECM; established clinical management; T1D, type 1 diabetes; ITT, intention to treat

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Key issue: Estimation of stage 3 T1D costs

Company prefers to increase costs of stage 3 T1D over time, EAG believes this approach overestimates costs

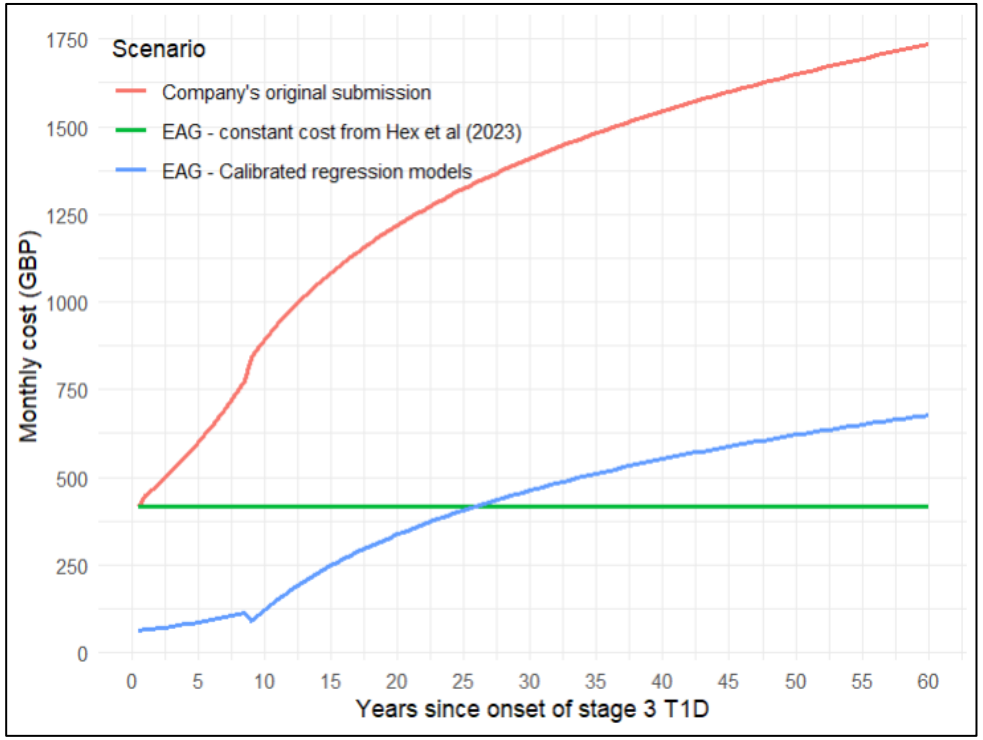
Company

- Initial cost of transitioning to Stage 3 T1D in model derived from literature on direct health costs of diabetes in the UK (Hex et al. 2024) - based on prevalent population
  - Company assumes increase over time starting from £415.22
- Projected costs of Stage 3 T1D estimated using piece-wise regression model based on data from literature – leads to annual cost per person of [redacted] over 60 years

EAG comments

- Company's approach significantly overestimates costs in Stage 3 T1D - annual cost per person significantly higher than the cost in prevalent population from literature (£4,982)
- EAG base case applies monthly cost of stage 3 T1D from Hex (£415.22) as a fixed value regardless of time in Stage 3 state
  - Also based on prevalent population - EAG acknowledges that fixed approach overestimates costs in newly diagnosed people and underestimates costs later on
  - Alternative approach – recalibration of regression models so average monthly cost over 60 years = £415.22 (but initial cost estimates not possible to validate)

Company versus EAG estimates of Stage 3 T1D healthcare costs



How should stage 3 T1D costs be modelled?

T1D, type 1 diabetes

Key issue: Estimation of stage 3 T1D costs

NHSE current and expected uptake data on hybrid closed loop systems by age group

	0-12 years	13-18 years	19-25 years	26-40 years	41-60 years	61-80 years	>80 years	All ages
HCL % uptake, 2024/25	68.0%	59.0%	18.1%	12.9%	9.0%	4.8%	0.9%	15.5%
Estimated annual diagnoses of T1D per year	2,300	1,340	985	1,735	1,130	355	30	7,870
Proportion of new patients eligible for HCLs	100%	100%	69%	72%	73%	73%	70%	85%
Assumed HCL% uptake	90%	75%	50%	25%	20%	1%	1%	54%
Assumed annual volume starting HCLs	2,070	1,005	341	311	165	2	0	3,894

T1D, type 1 diabetes; HCL, hybrid closed loop

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