HTA Austria
Austrian Institute for
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GmbH

Teplizumab (TEIZEILD®) for stage 2 type 1 diabetes

HTA-Appendix

Final Appendix

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No additional tables and figures.

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No additional tables and figures.

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No additional tables and figures.

2.2 Inclusion criteria

No additional tables and figures.

3 Methods

3.1 Guiding questions [1]

Table 3-1: Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes, is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Table 3-2: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0018	What are the other typical or common alternatives to the current technology?
A0022	Who manufactures the technology?

Table 3-3: Clinical effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect the progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?
D0029	What are the overall benefits and harms of the technology in health outcomes?

Table 3-4: Safety

Element ID	Research question

C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to the dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Table 3-5: Economic aspects

Element ID	Research question
E0001	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
A0002	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated costs of the assessed technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?
E0013	What methodological assumptions were made in relation to the technology and its comparator(s)?

Table 3-6: Organisational, ethical, and social aspects

Element ID	Research question
G0001:	How does the technology affect the current work processes?
G0002	What kind of involvement has to be mobilised for patients/participants and important others and/or caregivers?
G0101	What are the processes ensuring access to the new technology for patients/participants?
H0200	What are the experiences of living with the condition?
H0100	What expectations and wishes do patients have with regard to the technology, and what do they expect to gain from the technology?
H0006	How do patients perceive the technology under assessment?
H0002	What is the burden on caregivers?
H0202	How are treatment choices explained to patients?
F0010	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?
F0011	What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?
F0104	Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?
F0005	Is the technology used for individuals who are especially vulnerable?
H0012	Are there factors that could prevent a group or person from gaining access to the technology?

3.2 Systematic literature search and study selection

3.2.1 Search strategy

Table 3-7: Cochrane

Date of search: 25.11.2025	
ID	**Search**
#1	MeSH descriptor: [Diabetes Mellitus] explode all trees
#2	(diabet*) (Word variations have been searched)
#3	(DMT1):ti,ab,kw
#4	(T1DM):ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	(teplizumab*) (Word variations have been searched)
#7	(TZIELD*) (Word variations have been searched)
#8	(Teizeild*) (Word variations have been searched)
#9	(hOKT3*) (Word variations have been searched)
#10	(alanyl*)
#11	(Ala-Ala)
#12	(PRV-031*) (Word variations have been searched)
#13	(PRV?031*) (Word variations have been searched)
#14	(MGA-031*) (Word variations have been searched)
#15	(MGA?031*) (Word variations have been searched)
#16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	#5 AND #16
#18	(((clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr))):so
#19	#17 NOT #18

Table 3-8: Embase

Date of search: 25.11.2025	
Number	**Search**
#19.	#17 NOT #18
#18.	'clinical trial':dtype
#17.	#16 AND ([english]/lim OR [german]/lim)
#16.	#8 AND #15
#15.	#9 OR #12 OR #13 OR #14
#14.	diabet* NEAR/2 type NEAR/1 (one OR 1 OR i)
#13.	dmt1 OR t1dm
#12.	#10 AND #11
#11.	type NEAR/1 (one OR 1 OR i)
#10.	'diabetes mellitus'/exp OR diabetes$mellitus
#9.	'insulin dependent diabetes mellitus'/exp
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7.	'mga-031*' OR mga$031*
#6.	tzield*
#5.	'prv 031' OR prv?031 OR prv$031
#4.	'ala-ala' OR ala$ala OR alanylalanine
#3.	hokt3*
#2.	telizuma OR telizuma? OR te?lizuma OR te?lizuma?
#1.	'teplizumab'/exp OR 'teplizumab'

Table 3-9: Medline

Date of search: 25.11.2025	
Number	**Search**
1	exp Diabetes Mellitus
2	diabet*.mp.
3	DMT1.ti,ab.
4	T1DM.ti,ab.
5	T1D.ti,ab.
6	1 or 2 or 3 or 4 or 5
7	teplizumab*.mp.
8	tzield*.mp.
9	PRV-031*.mp.
10	PRV?031*.mp.
11	MGA-031*.mp.
12	MGA?031*.mp.
13	alanylalanine*.mp.
14	ala-ala.mp.
15	hOKT3gamma1.mp.
16	hOKT3#1.mp.
17	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	6 and 17
19	limit 18 to (english or german)
20	remove duplicates from 19

Table 3-10:International HTA database

Date of search: 25.11.2025	
Search step	**Search query,"Hits","Searched At"**
11	SAR446681,"0","2025-11-25T16:30:38.000000Z"
10	teizeild*,"0","2025-11-25T16:30:15.000000Z"
9	hOKT3*,"0","2025-11-25T16:29:23.000000Z"
8	ala-ala,"0","2025-11-25T16:28:57.000000Z"
7	alanyl*,"0","2025-11-25T16:28:26.000000Z"
6	MGA031*,"0","2025-11-25T16:27:47.000000Z"
5	MGA-031*,"0","2025-11-25T16:27:39.000000Z"
4	PRV031*,"0","2025-11-25T16:27:07.000000Z"
3	PRV-031*,"0","2025-11-25T16:26:59.000000Z"
2	tzield*,"0","2025-11-25T16:26:26.000000Z"
1	teplizumab*,"0","2025-11-25T16:25:45.000000Z"

3.2.2 Flow chart

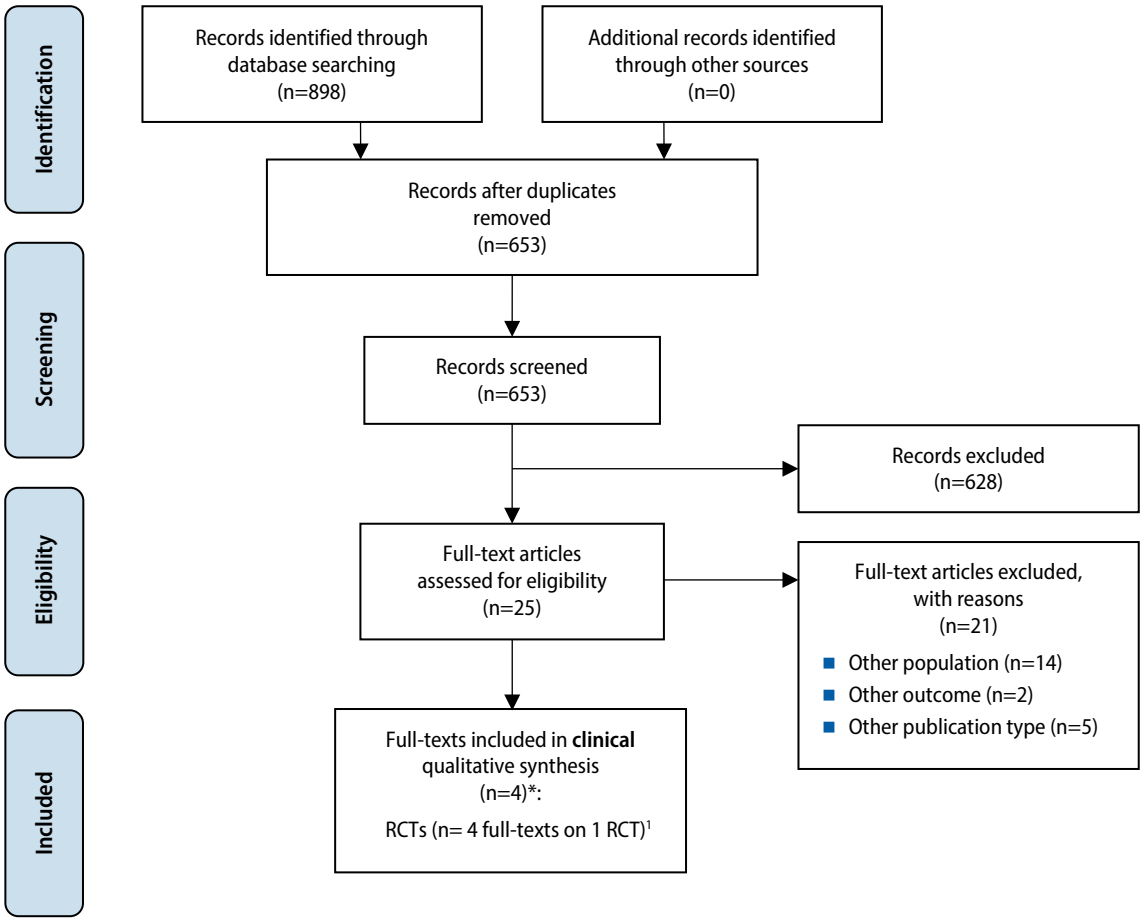

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

Note: 1These full-texts were also included in the dossier from the marketing authorisation holder.

3.3 Economic evaluation methods

No additional tables and figures.

3.4 Organisational, ethical and social assessment

Table 3-11:Questions for patients and relatives of patients diagnosed with T1D

Questions for patients	
Hintergrundinformationen	
1	In welcher Rolle füllen Sie den Fragebogen aus? ■ Einzelne/r Patient:in ■ Angehörige ■ Andere
2	Falls zutreffend, wie sind Sie an Informationen zu den Erfahrungen von Patient:innen gelangt? ■ Persönliche Erfahrungen ■ Erlebnisse von Patient:innen
3	In welchem Land befindet sich Ihr Hauptwohnsitz?
4	Sind Sie Mitglied einer Patient:innenorganisation? Wenn ja: ■ Bei welcher Patient:innenorganisation sind Sie Mitglied? ■ Welche Erkrankung/en wird/werden von der Patient:innenorganisation vertreten? ■ Welche Rolle haben Sie in der Patient:innenorganisation?
5a	Wie lautet die Diagnose?
5b	In welchem Stadium befindet sich die Erkrankung? Wie würden Sie den Schweregrad aktuell einschätzen?
5c	Welche Symptome haben Sie/haben Ihre Angehöriger/Ihr Angehöriger derzeit?
5d	Krankheitsgeschichte: ■ Seit wann leben Sie/Ihre Angehörige/Ihr Angehöriger mit der Erkrankung? ■ Wann wurde sie diagnostiziert? ■ Welche Behandlungen wurden bisher durchgeführt?
5e	Zusätzliche Informationen, die Ihrer Meinung nach für den HTA-Bericht hilfreich wären.
Auswirkungen der Krankheit	
6	Wie beeinflusst die Erkrankung Ihr tägliches Leben (bzw. das Leben einer Patientin/eines Patienten)?
7	Nur für Patient:innen: Wie wirkt sich die Erkrankung auf Ihr familiäres und soziales Umfeld aus?
8	Nur für Angehörige: Wie wirkt sich die Erkrankung auf das familiäre und soziale Umfeld der Patient:innen aus?
Erfahrung mit der derzeit verfügbaren Versorgung und Therapien	
9	Wie würden Sie die aktuelle Versorgungssituation in Österreich für Ihre Erkrankung beschreiben?
10	Wie geht es Ihnen/Ihrer Angehörigen/Ihrem Angehörigen mit der derzeit angewandten Therapie? Falls keine spezifische Therapie zur Verfügung steht, geben Sie das bitte an.
Erwartungen an das zu bewertende neue Arzneimittel	
11	Was würden Sie/Ihre Angehörige/Ihr Angehöriger im Allgemeinen von einer neuen Therapie erwarten?
12	Kennen Sie das Medikament Teizeild®?
13	Welche Gedanken haben Sie zum neuen Arzneimittel?
14	Für Personen, die Erfahrung mit Teilzeild®im Rahmen von klinischen Studien haben: Welche Auswirkungen hatte/hat es auf Ihr Leben (positive und negative Auswirkungen)?
Weitere Angaben	
15	Was ist Ihrer Meinung nach noch wichtig? Gibt es weitere Aspekte, wie z.B. ethische oder soziale Aspekte, die noch nicht besprochen wurden? Bitte erläutern Sie diese.

Abbreviations: HTA...Health Technology Assessment, T1D...type 1 diabetes

Table 3-12:Questions for clinical experts

Questions for the clinical experts addressed during the first meeting	
1	Welche der berichteten klinischen Endpunkte halten Sie für besonders Patient:innen-relevant (kritische Endpunkte)?
2	Welche der in Studien verwendeten PRO-Instrumente (ADDQoL-19, DIDP, Diabetes QoOL-Q) halten Sie am relevantesten und warum?
3	Ist das „Orale Minimal Model" eine geeignete/valide Methode zur Bestimmung der Insulinsekretion?
4	Wird die wesentliche Mehrheit der klinischen T1D-Fälle bei Kindern und Jugendlichen diagnostiziert oder sind auch Erwachsene in erheblichem Ausmaß betroffen? (unterschiedliche Angaben in der Literatur) Falls ja: Wie hoch ist das durchschnittliche Diagnosealter bei Erwachsenen?
5	Liegen Ihnen aktuelle Prävalenz- bzw. Inzidenzdaten zu klinischem T1D für Österreich vor, die uns zur Verfügung gestellt werden könnten? (Die letzten veröffentlichten Daten stammen aus 2021.)
6	Da es in Österreich kein offizielles Screening-Programm gibt, gehen wir davon aus, dass T1D Stadium 2 nur zufällig erkannt werden kann. Wie werden Patient:innen im Stadium 2 in der österreichischen klinischen Praxis typischerweise entdeckt (z.B. gezieltes Screening für Familienangehörige 1. Grades)? Wie viel % aller neuen T1D-Fälle werden jährlich bereits im Stadium 2 entdeckt?
7	Wie werden Patient:innen im Stadium 2 T1D in Österreich derzeit betreut? Gibt es Ausnahmefälle, die schon im Stadium 2 eine T1D-spezifische Behandlung benötigen?
8	Gibt es in Österreich konkrete Überlegungen zur zukünftigen Implementierung eines Screening-Programms für T1D? Falls ja, welche Gestaltung wäre dabei vorgesehen (z.B. regional, für definierte Risikogruppen, altersbezogen)?
9	Sehen Sie derzeit in Österreich gewisse Versorgungslücken für T1D (Stadium 2/3) aus der klinischen Sicht? Könnte Teplizumab diesen Herausforderungen entgegenwirken?
10	Welche relevanten Kostenarten (z.B. Diagnostik, Monitoring, Behandlung und Komplikationen) und welche weiteren wirtschaftlichen Auswirkungen sollten wir im Zusammenhang mit dem T1D-Management bei Stadium 2 berücksichtigen? ■ Szenario OHNE Teplizumab ■ Szenario MIT Teplizumab
11	In welchem Setting würde die Teplizumab-Behandlung erfolgen?
12	Management Stadium 3: Gibt es Schätzungen zur Häufigkeit der automatisierten Insulinabgabe im Vergleich zur herkömmlichen Insulinabgabe?
13	Gibt es zusätzliche relevante Aspekte seitens der klinischen Expert:innen, die im Zuge der HTA-Erstellung berücksichtigt werden sollten?
Questions for the clinical experts addressed during the second meeting	
14	Wie ist die Verzögerung der T1D-Manifestation um ca. 25 Monate im klinischen Kontext und im Hinblick auf einen möglichen Zusatznutzen zu bewerten?
15	Wie ist das Sicherheitsprofil von Teplizumab im Hinblick auf die Häufigkeit unerwünschter Ereignisse zu beurteilen?
16	Zusatznutzen: Teplizumab vs. Watchful Waiting
17	Diskussion möglicher indikationsbezogener Anwendungskriterien
18	Erfassung der Daten zur Anwendung von Teplizumab in Register?
19	Wo sieht die Forschungslage derzeit aus?

Abbreviations: ADDQoL-19…Audit of Diabetes-Dependent Quality of Life (19 items), DIDP…Diabetes Illness and Distress Profile, HTA…health technology assessment, PRO…patient-related outcomes, QoL-Q…Quality of Life Questionnaire, T1D…type 1 diabetes

3.5 Development costs and public contributions

No additional tables and figures.

4 Clinical effectiveness and safety

4.1 Outcomes

No additional tables and figures.

4.2 Characteristics of the included studies

Table 4-1: In- and exclusion criteria of the TN-10-trial [2]

Inclusion criteria	Exclusion criteria
■ Aged between 8 and 45 years of age ■ A relative of a proband with T1D. If the proband is a parent, sibling, or offspring, the study participant must be 8-45 years of age. If the proband is a second or third degree relative (i.e. niece, nephew, aunt, uncle, grandchild, cousin), the study participant must be 8-20 years of age ■ Subject (or parent or legal guardian) is willing to sign the Informed Consent Form. ■ An abnormal glucose tolerance by OGTT confirmed within 7 weeks of baseline (visit 0) (a) Fasting plasma glucose ≥ 110 mg/dL, and < 126 mg/dl or (b) 2-hour plasma glucose ≥ 140 mg/dL, and < 200 mg/dl or (c) 30, 60, or 90-minute value on OGTT ≥ 200 mg/dl ■ At least two diabetes related autoantibodies confirmed to be present on two occasions. The autoantibodies that will be confirmed are anti-GAD65, anti-ICA512, anti-insulin (MIAA), and ICA. Confirmation of 2 positive autoantibodies must occur within the previous six months, but the confirmation does not have to involve the same 2 autoantibodies ■ Weigh at least 26 kg at randomisation ■ If the participant is female with reproductive potential, she must have a negative pregnancy test on Day 0 and be willing to avoid pregnancy for at least one year from randomisation ■ If the participant is male, he must be willing to avoid pregnancy in any partners for at least one year from randomisation ■ Willing and medically acceptable to postpone live vaccine immunisations for one year after treatment ■ Willing to forego other forms of experimental treatment during the study	■ Diabetes, or have a screening OGTT with: (d) Fasting plasma glucose ≥ 126 mg/dL, or (e) 2-hour plasma glucose ≥ 200 mg/dL ■ Lymphopenia (< 1,000 lymphocytes/µL) ■ Neutropenia (< 1,500 PMN/µL) ■ Thrombocytopenia (< 150,000 platelets/µL) ■ Anaemia (Hgb < 10 grams/deciliter [g/dL]) ■ Total bilirubin > 1.5 x upper limit of normal (ULN) ■ AST or ALT > 1.5 x ULN ■ INR > 0.1 above the upper limit of normal at the participating center's laboratory ■ Chronic active infection other than localised skin infections ■ A positive PPD test ■ Vaccination with a live virus within 8 weeks of randomisation ■ Vaccination with a killed virus within 4 weeks or randomisation ■ A history of infectious mononucleosis within the 3 months prior to enrollment ■ Laboratory or clinical evidence of acute infection with EBV or CMV ■ Serological evidence of current or past HIV, Hepatitis B or Hepatitis C infection ■ Be currently pregnant or lactating, or anticipate getting pregnant ■ Chronic use of steroids or other immunosuppressive agents ■ A history of asthma or atopic disease requiring chronic treatment ■ Untreated hypothyroidism or active Graves' disease at randomisation ■ Current use of non-insulin pharmaceuticals that affect glycemic control ■ Prior OKT@3 or other anti-CD3 treatment ■ Administration of a monoclonal antibody within the year before randomisation ■ Participation in any type of therapeutic drug or vaccine clinical trial within the 12 weeks before randomisation ■ Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject

Abbreviations: ALT…alanine aminotransferase, AST… aspartate aminotransferase, CMV…cytomegalovirus, EBV…Epstein-Barr virus, GAD65… glutamic acid decarboxylase 65, Hgb…haemoglobin, HIV…human immune-deficiency virus, ICA…islet cell autoantibody, ICA512…islet antigen 512, INR…international normalized ratio, MIAA…micro insulin autoantibody, OGTT…oral glucose tolerance test, PMN…polymorphonuclear leukocytes (neutrophils), PPD…purified protein derivative, T1D…type 1 diabetes, ULN…upper limit of normal.

Table 4-2: Study endpoints for the study TN-10 trial [2]

Study reference/ID Outcome category	Endpoints as defined in the study protocol
TN-10	
Primary endpoint	■ Time to stage 3 T1D diagnosis
Key secondary efficacy endpoints	■ C-peptide AUC ■ HbA1c ■ T cell phenotypes
Exploratory efficacy endpoints	■ OMM-derived indices ■ Insulin clearance
Safety endpoints	■ Adverse events ■ Serious adverse events

Abbreviations: AUC…area under the curve, OMM…oral minimal model, T1D…type 1 diabetes.

Table 4-3: Study protocol amendments in the TN-10 trial [2]

Version	Date and scope of amendment
TrialNet	
Original protocol	22 June 2010
Version 2	22 June 2010: Addition of language to include Research Ethics Board responsibilities, pursuant to international sites.
Version 3	25 June 2012: Removed section 3.9.1 Staggered Enrollment.
Version 4	17 September 2012: Standardised T1DM acronym throughout protocol for consistency. Section 2.3.4 – Inclusion of updated data on AEs and results from the ABATE trial. Section 2.3.5 – Inclusion of updated information on study results from DELAY trial. Section 2.3.6 – Inclusion of updated information on study results from the Protégé trial. Section 2.3.7 – Inclusion of updated information on study completion of the Protégé Encore trial. Section 3.3.1 – revised age criteria to provide clarification of enrollment of subjects from TN01 who were < 45 years of age, but now may be > 45 years old. Section 3.3.1 – Addition of ZnT8 autoantibodies as one of two Abs required for eligibility. Section 3.3.1 – added statement that T1D clinical history of proband may be reviewed by the eligibility committee to determine study eligibility. Section 5.2 – added IgM and EBNA to reflect current monitoring procedures for possible infections. Section 7.2.1 – added eosinophilia as a possible side effect of drug therapy to be consistent with the new Investigator's Brochure (12/22/2011). Section 7.2.5 – added wording regarding herpes virus infections to be consistent with the new Investigator's Brochure (12/22/2011). Section 8.4 – Modified to reflect revisions to the enrollment period, study duration, and sample size. Appendix 2: Schedule of Assessments – minor wording changes and inclusion of revised EBV monitoring procedures; revision of footnotes to reflect inclusion of revised EBV monitoring procedures.
Version 5	25 June 2014: Section 3.3.1 – modified to reflect revisions to study inclusion criteria related to OGTT requirements. Individuals < 18 years of age must have one abnormal OGTT prior to enrollment, and those 18 years and older must have two consecutive abnormal OGTTs. Section 3.3.2 – modified to reflect revisions to study exclusion criteria mentioned above; Addition of exclusion criteria for AST or ALT > 1.5 ULN; addition of language to allow those with Gilbert's syndrome, in the absence of other causes of hyperbilirubinemia. Section .3.9.1 – modified to provide additional clarification on sample size, actual period, and study duration revisions. Section 4.2 – modified to include further clarification of initial visit procedures related to the OGTT criteria mentioned in point 1. Section 4.3 - modified to include further clarification of initial visit procedures related to the OGTT criteria mentioned in point 1. Section 4.5.1 – modified to provide further clarification of drug administration and dosage calculations. Section 4.5.2 – modified to provide further clarification for drug withholding criteria in subjects with Gilbert's syndrome. Section 4.5.3 – modified to provide further evaluation after withholding infusions for subjects with Gilbert's syndrome. Section 4.6 – modified to provide information related to Gilbert's syndrome and trial cessation. Section 5.2 – Addition of working related to the requirement of liver function testing for subjects with Gilbert's syndrome. Section 7.3 – modified to provide clarification related to pregnancy test requirements, including language that these are only applicable to females of childbearing potential. Section 8.3 – modified to provide clarification related to secondary outcomes and analyses. Section 8.4 – modified to reflect revisions to the study power and sample size. Section 8.5 – modified to reflect revisions to the interim monitoring plan. Section 9.4 – modified to reflect current data sharing, storage, and security procedures. Appendix 2 – revised to reflect modification to entry criteria for subjects < 18 years old, related to removal of requirement for confirmed abnormal OGTT.

Abbreviations: ALT…Alanine Aminotransferase, AST…Aspartate Aminotransferase, EBV…Epstein-Barr-Virus, OGTT…oral glucose tolerance test, T1DM…type 1 diabetes mellitus, ULN…upper limit normal.

4.3 Study population

Table 4-4: Baseline demographics and disease characteristics of participants in the TN-10 trial [2]

Study reference/ID characteristics category	Study intervention	
TN-10	**Teplizumab (n = 44)**	**Placebo (n = 32)**
Age [years], median (IQR)	14 (12-22)	13 (11-16)
Range	8.5-49.5	8.6-45.0
Sex [f/m] (%)	19 (43.2)/ 25 (56.8)	15 (46.9)/ 17 (53.1)
Race, n (%)		
White, n	44 (100)	30 (93.8)
Black, n	0 (0.0)	0 (0.0)
Asian, n	0 (0.0)	2 (6.2)
Other, n	0 (0.0)	0 (0.0)
Autoantibodies titer - median		
Anti-GAD65 (harmonised)	240 (76.8-464)	221 (42.3-520)
Micro Insulin	0.0070 (0.0020-0.028)	0.0040 (0.0020-0.0168)
Anti-IA-2 (harmonised)	52 (0-310)	187 (26-253)
ICA	20 (0-200)	80 (20-160)
Zinc Transporter	0.157 (0.0133-0.496)	0.096 (0.028-0.386)
Autoantibodies – no. of participants positive (%)		
Anti-GAD65, harmonised	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti-IA-2, harmonised	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
C-peptide AUC Mean, OGTT (nmol/L) Median	1.76 (1.47-2.18)	1.73 (1.44-2.36)
HLA alleles present – no. of subjects (%)		
Neither DR3 or DR4	5 (11.6)	3 (9.4)
DR3 only	10 (23.3)	8 (25.0)
DR4 only	17 (39.5)	14 (43.8)

Abbreviations: f...female, GAD65...glutamic acid decarboxylase 65, IA-2...islet antigen 2, ICA...islet-cell auto-antibody, IQR...interquartile range, m...male, n...number of patients, OGTT...oral glucose tolerance test, ZnT8... zinc transporter 8.

Table 4-5: Additional baseline characteristics in Galderisi et al., 2025 [3]

Study reference/ID Characteristics Category	Study intervention				
	Teplizumab (n=39)	Placebo (n=28)	Placebo vs teplizumab		
TN-10	**Slow-progressor n = 28**	**Rapid-progressor n = 11**	**Slow-progressor n = 14**	**Rapid-progressor n = 14**	**p-value**
Age (years)	14.9 (12.0, 35.1)	13.6 (11.4, 18.4)	14.8 (10.4, 17.9)	14.9 (12.2, 16.3)	0.252
Fasting glucose (mmol/l)	5.2 (4.9, 5.4)	5.5 (5.2, 5.8)	5.2 (5.0, 5.8)	5.4 (4.8, 5.9)	0.466
1h glucose (mmol/l)	10.2 (9.0, 11.8)	10.5 (9.8, 12.0)	9.7 (9.0, 11.3)	11 (9.3, 12.1)	0.337
2h glucose (mmol/l)	8.6 (7.8, 9.5)	8.3 (7.8, 9.6)	7.9 (6.8, 9.2)	8.9 (8.0, 9.6)	0.345
Fasting C-peptide (nmol/l)	0.49 (0.36, 0.86)	0.53 (0.46, 0.59)	0.53 (0.40, 0.63)	0.59 (0.46, 0.79)	0.309
1h C-peptide (nmol/l)	1.9 (1.6, 3.3)	1.8 (1.3, 2.0)	2.4 (1.6, 2.9)	1.9 (1.5, 2.4)	0.364
Index 60	0.53 (−0.20, 1.21)	0.59 (0.24, 1.07)	0.07 (−1.07, 0.79)	1.98 (1.48, 2.34)	0.417
DPTRS	9.2 (8.4, 9.8)	9.7 (9.2, 10.0)	9.2 (8.1, 9.4)	9.9 (8.7, 10.5)	0.933
AUC C-peptide (nmol/l x min)	211.9 (176.8, 311.1)	197.1 (168.0, 235.0)	249.5 (171.8, 322.3)	202.0 (185.9, 262.2)	0.441
Insulin secretion (φ total)	113.6 (71.7, 146.7)	80.3 (62.6, 123.9)	130.8 (94.2, 148.8)	82.9 (54.1, 108.1)	0.475
Insulin secretion (φ dynamic)	1001.8 (654.4, 1538.1)	890.6 (388.0, 1379.7)	1396.5 (874.0, 1642.3)	862.4 (676.4, 1396.6)	0.283
Insulin secretion (φ static)	94.9 (56.0, 124.4)	68.3 (54.5, 78.6)	103.7 (73.1, 116.0)	80.3 (45.0, 125.3)	0.252
IS	1.2 (0.6, 2.0)	1.4 (1.1, 2.4)	0.98 (0.6, 2.2)	1.4 (0.6, 3.0)	0.305
DI	101.2 (63.0, 150.7)	106.1 (78.2, 204.4)	125.7 (97.1, 207.2)	113.3 (63.5, 243.0)	0.107
Insulin clearance (AUC $ISR_{C\text{-peptide}}$ / $AUC_{insulin}$	1.3 (0.9, 2.5)	2.0 (1.1, 2.6)	1.8 (1.2, 3.4)	1.2 (0.9, 2.5)	0.326

Abbreviations: AUC…area under the curve, DI…disposition index, DPTRS…Diabetes Prevention Trial Risk Score, f…female, GAD65…glutamic acid decarboxylase 65, h…hour, IA-2…islet antigen 2, ICA…islet-cell autoantibody, IQR…interquartile range, IS…insulin sensitivity, ISR…insulin secretion rate, m…male, min…minute, n…number of patients, OGTT…oral glucose tolerance test, SD…standard deviation, ZnT8…zinc transporter 8, φ…insulin secretion rate.

4.4 Results on relative effectiveness and safety

4.4.1 Clinical efficacy outcomes

Table 4-6: Analysis of insulin secretion to oral glucose in the first 6 months after treatment, Sims et al., 2021 [4]

Measure to be compared between arms	Medians		p-value
	Placebo	Teplizumab	
First hour insulin interval secretion			
Pre-treatment slope	-259.5	-422.7	0.79
Post-treatment slope	-476.2	371.0	0.0003
Paired pre- vs. post-rx p-values* within arms	p = 0.86	p = 0.007	-
Second-hour insulin interval secretion			
Pre-treatment slope	-728.2	-383.6	0.78
Post-treatment slope	-186.8	442.5	0.003
Paired pre- vs. post-rx p-values* within arms	p = 0.38	p = 0.03	-
Insulin interval secretion (2 hr)			
Pre-treatment slope	-1245.0	-1024.0	0.95
Post-treatment slope	-1037.4	1085.8	0.0004
Paired pre- vs. post-rx p-values* within arms	p = 0.80	p = 0.01	-

** p-values based on Wilcoxon signed rank (paired) test comparing the pre- vs. post-rx slopes by subject; evaluation of how much changes in these measures changed pre- vs. post-rx by subject and across those subjects in each treatment arm.*

Table 4-7: Metabolic changes, Galderisi et al. 2025 [3]

Outcome Measure Study reference/ID	Teplizumab (n=39)			Placebo (n=28)			Placebo (n=28) vs teplizumab (n=39)
	Slow-progressor	Rapid-progressor	p-value	Slow-progressor	Rapid-progressor	p-value	p-value
% Change from baseline M3	n = 28	n = 11	-	n = 14	n = 14	-	-
Insulin secretion total, median (25th, 75th centile)	+37.1 (−5.9, +59.2)	+10.0 (−23.3, +68.1)	NS	+17.7 (−15.4, +54.8)	−26.4 (−57.5, +11.7)	0.013	0.021
C-peptide AUC, median (25th, 75th centile)	+6.3 (−9.1, +26.9)	+4.8 (−14.1, +34.3)	NS	+1.1 (−13.0, +13.5)	−12.9 (−18.3, −2.0)	NS	0.033
% Change from baseline M6	n = 28	n = 9	-	n = 14	n = 8	-	-
Insulin secretion total, median (25th, 75th centile)	+17.1 (−10.2, +69.4)	+1.5 (−18.9, +23.7)	NS	+15.8 (−39.4, +66.0)	−33.7 (−57.8, −3.8)	NS	0.043
C-peptide AUC, median (25th, 75th centile)	+6.3 (−9.1, +26.9)	+4.8 (−14.1, +34.3)	NS	−5.8 (−18.3, +11.2)	−12.9 (−18.4, −2.0)	NS	0.002

Outcome Measure Study reference/ID	Teplizumab (n=39)			Placebo (n=28)			Placebo (n=28) vs teplizumab (n=39)
	Slow-progressor	Rapid-progressor	p-value	Slow-progressor	Rapid-progressor	p-value	p-value
% Change from baseline M12	n = 28	n = 8	-	n = 14	n = 6	-	-
Insulin secretion total, median (25th, 75th centile)	+20.3 (−11.4, +61.8)	−5.8 (−31.1, +10.2)	0.039	−10.9 (−28.9, +34.0)	−61.4 (−88.1, −24.3)	NS	0.005
C-peptide AUC, median (25th, 75th centile)	+6.4 (−31.2, +56.2)	−0.7 (−31.6, +74.6)	NS	−28.8 (−52.5, +5.9)	+20.0 (−18.9, +68.5)	NS	NS

Notes: [a]φ total (phi total) represents total insulin secretion during the OGTT, estimated using the Oral Minimal Model (OMM). This model-derived parameter integrates C-peptide and glucose dynamics to quantify beta-cell secretory response. It is expressed as a dimensionless index, with higher values reflecting greater insulin secretory capacity. [b]Slow-progressors - developed stage 3 diabetes >2 years after treatment or remained diabetes-free during follow-up, [c]Rapid-progressors - developed stage 3 diabetes ≤2 years after treatment

Abbreviations: AUC…area under the curve, M3…month 3, M6…month 6, M12…month 12, n…number, NS…not significant, p…p-value.

4.4.2 Safety outcomes

No additional tables.

4.5 Certainty of the evidence

4.5.1 Risk of bias

Table 4-7: Risk of bias of the TN-10 study [2] (RCT at study outcome level: Cochrane RoB 2.0) [5]

Domain	Bias arising from randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall RoB	Comments
Study/ Outcome	Low	Low	Low	Low	Low	Low	-

Abbreviations: RCT…randomised controlled trial, RoB…risk of bias.

4.5.2 Statistical analysis and inconsistencies

Table 4-8: Statistical analysis in the TN-10-trial [2]

Statistical analysis	Description
Primary endpoint	Time to diagnosis of clinical type 1 diabetes
Cumulative incidence	Kaplan-Meier method with Cox proportional-hazards model
Sample size (revised)	≥71 participants; follow until 40 T1D diagnoses; HR 0.4 80% power, α = 0.025
Interim analysis	At 18/40 events
Analysis principle	Intention-to-treat; two-sided tests, α = 0.05
Subgroup analysis	Pre-specified, not adjusted for multiplicity

Statistical analysis	Description
Extended follow-up	Additional analyses at later time points without pre-planned alpha adjustment

Abbreviations: T1D…type 1 diabetes, HR…hazard ratio, α…significance level (alpha).

Table 4-9: Summary table characterising the applicability of the included study [2]

Domain	Description of the applicability of evidence
Population	The TN-10 trial comprised 76 participants (44 teplizumab, 32 placebo) aged 8-49 years (median: 13-14 years) from the United States, Canada, Australia, and Germany. Approximately 92% had a first-degree relative (FDR) with T1D. All participants had stage 2 T1D, defined by the presence of ≥2 islet autoantibodies and dysglycemia on oral glucose tolerance test (OGTT). Participants were predominantly non-Hispanic white (specific percentage not detailed). The majority (72%) were children and adolescents (<18 years).
	Applicability: The TN-10 population represents highly selected patients at high risk for progression to stage 3 T1D, identified primarily through family-based screening. This approach may not reflect the Austrian population for several reasons. First, approximately 90% of individuals who develop T1D in the general population have no family history, yet screening for stage 2 T1D is not established in Austria. Second, the trial population was predominantly from North America with limited European representation, and Austrian patients may differ in genetic risk profiles. Third, the majority of trial participants were under 18 years of age, whereas epidemiological evidence indicates that more than half of new T1D diagnoses occur in adulthood [6]. Taken together, these factors suggest that the trial population does not fully reflect the patient population in Austria. Nevertheless, the Koeger 2025 study demonstrated that progression risk in TN-10 was comparable to that in the European Fr1da population-based screening cohort, including individuals without first-degree relatives with T1D [7]. This finding suggests potential generalisability to broader European populations, partially mitigating concerns about the trial's applicability to Austria.
Intervention	Participants received a single 14-day outpatient course of teplizumab administered intravenously at escalating doses (51 µg/m² on day 0, increasing to 826 µg/m² on days 4-13) or a matching placebo. The median total dose administered was 9.14 mg/m² (IQR: 9.01-9.37). Treatment was administered in specialised clinical research centres with experience in T1D management.
	Applicability: The intervention is a short-course, outpatient immunotherapy requiring specialised administration. Although Austria has established diabetes centres capable of administering intravenous immunotherapy, a 14-day treatment course may not be feasible in the outpatient sector, particularly for children and adolescents, and thus would be administered during a 14-day hospital stay. Moreover, sufficient inpatient capacity to accommodate these stays may not be available. Furthermore, monitoring for adverse events (particularly lymphopenia and rash) requires experienced personnel and laboratory facilities. Importantly, the intervention's feasibility depends on Austria's capacity to implement screening programmes to identify individuals eligible for stage 2 before progression to stage 3.
Comparators	TN-10 was a phase 2, randomised, double-blind, placebo-controlled trial without an active comparator arm.
	Applicability: In Austrian clinical practice, individuals with stage 2 type 1 diabetes (if identified) would typically receive close monitoring with regular metabolic assessments, but no intervention.
Outcomes	<u>Efficacy outcomes:</u> Time to diagnosis of stage 3 T1D: median 48.4 months (teplizumab) vs 24.4 months (placebo); HR: 0.41 (95% CI: 0.22-0.78; P<0.01) C-peptide AUC, pmol/ml: 1.94 (teplizumab) vs 1.72 (placebo) Annualised progression rates: 14.9% (teplizumab) vs 35.9% (placebo) Progression to stage 3: 43% (teplizumab) vs 72% (placebo) Glucose AUC, mg/dl: 164 vs 177 <u>Safety outcomes:</u> Transient lymphopenia: Grade 3 in 75% of teplizumab patients (resolved by day 45 in all but one participant) Rash: 36% of teplizumab-treated participants (spontaneously resolving) Epstein-Barr virus (EBV) reactivation: Quantifiable EBV DNA in 8 seropositive participants (all in the teplizumab group), with viral clearance by a mean of day 77 Cytomegalovirus (CMV) reactivation: 1 participant with detectable CMV DNA (undetectable by day 42)
	Applicability: The outcomes indicate an approximately two-year delay in stage 3 onset, although this was accompanied by an increase in grade 3 adverse events following teplizumab. However, several limitations affect the interpretation and clinical relevance of these findings. First, the study included only 76 patients, which restricts the robustness of the conclusions. Long-term safety data from larger populations are lacking, and quality of life outcomes were not assessed, leaving the patient-relevant impact of delaying diagnosis unclear. Second, the long-term clinical benefit remains uncertain. It is unclear whether the two-year delay in diagnosis translates into meaningful long-term benefits, such as reduced risk of diabetes complications. Third, treatment response was heterogeneous, as not all participants benefited equally, suggesting that predictive biomarkers require further validation to identify those most likely to respond. Collectively, these factors raise questions about the clinical relevance of the observed two-year delay.
Setting	The study was conducted at sites in the United States, Canada, Australia, and Germany. Treatment was administered on an outpatient basis in clinical research centres. Participants required close monitoring during the 14-day treatment course and regular follow-up visits every six months for OGTT assessments.

Domain	Description of the applicability of evidence
	Applicability: Austria has established infrastructure for diabetes care, including specialised pediatric diabetes centres that could potentially accommodate teplizumab administration and post-treatment monitoring. However, several implementation challenges would need to be addressed. The 14-day treatment course requires multiple clinic visits, which may present logistical difficulties for families in rural areas distant from specialised centres. More fundamentally, Austria currently lacks systematic population-based or targeted screening programs necessary to identify individuals at stage 2. Without such a screening infrastructure, most patients remain undiagnosed until stage 3, rendering the intervention inaccessible. Therefore, the practical applicability of teplizumab depends critically on first establishing systematic screening programs to identify eligible patients.

Abbreviations: AUC…area under the curve, CI…confidence interval, CMV…cytomegalovirus, DNA…deoxy-ribonucleic acid, EBV…Epstein-Barr virus, FDR…first-degree relative, HR…hazard ratio, IQR…interquartile range, OGTT…oral glucose tolerance test, T1D…type 1 diabetes, TN-10…TrialNet-10.

5 Price comparisons, treatment costs and budget impact

5.1 Pharmaco economic model(s)

5.1.1 Submitted pharmaco-economic model

The MAH did not submit a pharmaco-economic model for tepluzimab.

5.1.2 Published economic evaluations based on international pharmaco-economic models

Table 5-1: Economic evaluation of teplizumab

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
Mital et al. 2020 [8]	USA	Teplizumab vs no treatment	4 different groups of at-risk individuals: 1. All at-risk relatives of T1D 2. HLA markers (HLA-DR3 or HLA-DR4) 3. HLA-DR3/DR4 combination with highest predicted response 4. Without ZnT8 antibodies1	Threshold analyses: willingness-to-pay threshold of US$100,000 per QALY	Hybrid decision tree (genetic and antibody testing and administration) Markov microsimulation model	Health care system's perspective Cycle length was 1 year and lifetime horizon	Usual care: ■ HLA-DR or ZnT8 tests (if applicable) ■ Annual healthcare costs, depending on diabetes status and existence of diabetes complications Costs of diabetes (without complications) comprised annual costs of insulin treatment (which were dependent on body weight) and cost of two physician visits per year Cost of treatment with teplizumab for 14 outpatient visits (if applicable)	Kaplan Meier (KM) curves that showed time to type 1 diabetes over the trial period (from Herold 2019) - convert these reconstructed raw data to annual risk of developing T1D Effectiveness was measured in terms of quality-adjusted life-years (QALYs) Utility was specific to diabetes status (namely, pre-T1D or diabetes) and was higher for children (age < 18 years) compared with adults (age > 18 years)	Two-way sensitivity analyses: ■ Cost of insulin and cost of managing diabetes complications) along with the price of teplizumab ■ Instead of using a lifetime horizon, we used a 10-year horizon ■ Narrowed the study cohort's age range to 8–17 years Two alternative scenarios instead of extrapolating risks of developing diabetes beyond the 5-year duration: ■ both treated and untreated individuals in the model who are T1D-free at the end of 5 years develop T1D after year 5	Costs and utilities discounted at 3.5% per year	■ All at-risk individuals started in the pre-type-1-diabetes state; in each year, they faced a risk of developing T1D ■ Risk of developing T1D was lower in individuals receiving teplizumab ■ Individual developed T1D face a risk of diabetes-related complications, including microvascular, macrovascular complications and hypoglycemia ■ Probabilities of developing diabetes-related complications and progression through these complications were based on the Sheffield T1D Policy Model

[1] Expected to have the highest response to the drug, likely due to less severe immune-mediated islet cell destruction.

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
			Base-case analysis: average of two individual risks of T1D associated with HLA-DR3 and HLA-DR4 alleles as the risk of T1D onset in individuals with combinations of HLA-DR3 and HLA-DR4 alleles Aged 8–49 years (66% of the cohort was aged below 18 years); were relatives of T1D patients and met the criteria for being at high risk for T1D development (as defined in the phase II clinical trial of teplizumab) 49% of participants were female Mean HbA1c level at baseline was 7.6%						■ Risk of T1D onset becomes zero for individuals treated with teplizumab who do not develop T1D at the end of 5 years, while all individuals who do not receive teplizumab develop T1D at end of 5 years ■ Lower value of the two individual risks of T1D onset, instead, which implies a higher efficacy of the drug for individuals with these alleles Parameter uncertainty: ■ Disutility values for hypoglycemia and diabetic ketoacidosis from alternative sources ■ One-way sensitivity analyses in which we varied key costs and utilities over a reasonably large range of ± 25% of base case; mean price of teplizumab is US$100,000		■ For patients who experienced diabetes-related complications: utility decrements for each complication to the utility value for diabetes ■ As possible diabetes-related complications were several and varied, we used cost of managing ketoacidosis as a proxy for diabetes complications-related health care costs

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
									■ Probabilistic sensitivity analyses (PSA) in which we assigned distributions to input parameters and performed 100 second-order Monte Carlo simulations. In the PSA, we used standard deviations derived from the literature where available. Where unavailable, these were assumed to be 25% of base-case values of parameters; mean price of teplizumab is US$100,000		
Mital et al. 2025 [9]	USA	Three preventive immune therapies: teplizumab, antithymocyte globulin (ATG), or no therapy Two insulin management strategies: automated insulin delivery (AID) systems or conventional insulin management The six strategies were: ■ Teplizumab followed by AID	Target population (base case): Hypothetical cohort of 10,000 individuals at risk of T1D, defined by: Detection of two or more autoantibodies and presence of dysglycemia Age: 8-49 years Sex: 51% male	Cost-utility analysis	Markov microsimulation model adapted from the Sheffield T1D Policy Model. The model tracked movement from pre-T1D to diabetes, diabetes-related complications (microvascular and macrovascular), and death	Perspective: Third-party payer (healthcare system) Time horizon: Lifetime (base case), with sensitivity analyses at 10 and 20 years Each cycle lasted one year	Costs included (in 2024 US dollars): ■ Drug costs: Teplizumab ($194,000), ATG (~$5,000-7,000) ■ Infusion costs (outpatient): $216 per hour ■ AID system device cost: $7,474 (lasting 5 years) ■ AID annual supplies: $8,041 ■ Conventional insulin management equipment: $7,671 annually	Quality-adjusted life years (QALYs) were calculated using: ■ Pre-T1D: 0.91 (age ≤18), 0.90 (age >18) ■ Diabetes with no complications: 0.89 (age ≤18), 0.85 (age >18)	Extensive sensitivity analyses: ■ One-way sensitivity analyses (tornado diagram) ■ Probabilistic sensitivity analysis with 10,000 iterations ■ Threshold analyses for teplizumab price and ATG efficacy ■ Shorter time horizons (10 and 20 years) ■ Varying assumptions about AID effects on HbA1c ■ Different AID uptake rates (30%, 50%, 100%)	3% per year for both costs and effectiveness (QALYs)	Key assumptions: ■ ATG efficacy in preventing T1D was assumed to be half that of teplizumab (base case), as no randomised trials exist for ATG in prevention ■ Beta-cell preserving effects of immune therapies were not sustained after clinical T1D onset ■ AID systems affected glycemic outcomes similarly regardless of prior immune therapy

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
		■ Teplizumab followed by conventional insulin management ■ ATG followed by AID ■ ATG followed by conventional insulin management ■ No immune therapy with AID ■ No immune therapy with conventional insulin management					■ Insulin costs: $47 per kg body weight per year ■ Physician visits: $141 per visit (4 visits/year) ■ Pre-diabetes costs: $419-1,041 depending on age ■ Complications management costs (both initial and annual for various diabetes complications) ■ Treatment of serum sickness with prednisone (for ATG patients)	■ Utility decrements for complications ranging from -0.001 (diabetic ketoacidosis) to -0.208 (blindness)	■ Higher CGM and insulin pump usage rates ■ Alternative scenarios for T1D onset after 5 years ■ Inclusion of time costs for receiving therapy		■ Neither immune therapies nor AID systems affected insulin needs ■ AID systems provided 0.3% improvement in HbA1c and 50% (children) to 95% (adults) reduction in hypoglycemia risk ■ Conventional insulin management breakdown: 30% CGM with pumps, 18% CGM with injections, 10% self-monitoring with pumps, 42% self-monitoring with injections
CDA-AMC 2025 [10][2]	CAN	Teplizumab vs. no intervention	Adult and pediatric patients 8 years of age and older with stage 2 T1D	NI	NI	NI	NI	Clinical efficacy was derived from the TN-10 trial, which compared teplizumab with placebo in adult and pediatric patients 8 years of age and older with stage 2 T1D: ■ Life-years ■ QALYs	NI	NI	NI

[2] Not final, but draft of reimbursement recommendation.

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
NICE 2025 [11][3]	UK	Teplizumab: delivered as a 2 mg per 2 mL clear colourless solution for injection in a single-dose vial; On each day of the 14-day course, the total daily infusion dose is calculated on the basis of BSA as follows: ■ Day 1: 65 mcg/m2 ■ Day 2: 125 mcg/m2 ■ Day 3: 250 mcg/m2 ■ Day 4: 500 mcg/m2 ■ Days 5 through 14: 1,030 mcg/m2 vs established clinical mangement	Adult and pediatric patients 8 years of age and older with stage 2 T1D	Cost-utility analysis with fully incremental analysis	Sanofi model: Markov Model with 3 mutually exclusive health states (stage 2 T1D, stage 3 T1D, death)	Horizon: lifetime (max. 100 years of age) and cycle length of 6 months Costs will be considered from an NHS and Personal Social Services perspective	Costs associated with diagnostic testing for pancreatic islet autoantibodies in people who would not otherwise have been tested Treatment costs include acquisition and administration costs for teplizumab, as well as teplizumab-related resource use (e.g., tests to confirm eligibility for teplizumab, pre-medications, laboratory evaluations and infusions) Costs associated with monitoring people with diagnosed stage 2 T1D *(= established clinical management*) Costs of stage 3 T1D Adverse reaction management costs	Carer disutility was included in the model for children only, with a disutility value of -0.04 relative to the general population (*based on qualitative data from literature*) Impact of stage 3 T1D on quality of life: applying 3 different disutilities to age-dependent utility estimates of the general population: One-off initial disutility during the cycle of onset of stage 3 to reflect the initial negative impact and subsequent adjustment to having symptomatic T1D	■ Sensitivity analysis should be provided without the cost of the diagnostic test ■ Scenario analysis was explored with a 1.5% discount rate ■ An alternative approach to the estimation of mortality in Stage 3 T1D was tested in scenario analyses:	An annual discount rate of 3.5% was applied to both costs and health benefits occurring beyond the first year	■ Baseline characteristics and clinical efficacy data from TN-10 (time to onset of Stage 3 T1D) ■ Transition probabilities from stage 2 - 3 T1D were derived from the individual-level data reported by Sims et al. 2021, where the outcomes of the TN-10 trial with an extended follow-up period (median 923 days) were available

[3] Not final, but first published draft.

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
							The healthcare cost categories included in the model were treatment acquisition and administration, teplizumab-related resource use (test to confirm eligibility, monitoring tests, pre-medications), Stage 2 and Stage 3 T1D, and adverse events. Costs were inflated to 2023 prices using the NHS Cost Inflation Index (NHSCII) pay and price indices	Fixed disutility during all cycles to reflect the impact of having symptomatic T1D compared with the general population or asymptomatic stage 2 T1D An increasing disutility over time since onset of stage 3 T1D to reflect the accumulating impact of T1D health complications			■ Other clinical inputs (risk of DKA at onset of stage 3 T1D and mortality rates) and utility estimates informed by European studies reporting appropriate inputs: Rawshani et al. (2018) was included in the model as a scenario analysis to allow for more granularity in capturing the mortality HR as it reports estimates based on age of onset of stage 3 T1D

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
											■ A 6-month cycle was used in this model. This was appropriate because it allowed the impact of the delay in time to onset of stage 3 T1D associated with teplizumab to be modelled accurately and also reflected data collection in the TN-10 trial which was at 6-month intervals. Furthermore, this cycle length also corresponded more closely to the anticipated frequency of testing for progression to stage 3 T1D for adults and children in the UK following initial diagnosis (every 6 months and every ≥3 months, respectively)

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
											■ No risk groups like in Mital et al. 2020 bc HLA testing is not currently used in routine clinical practice (confirmatory testing for stage 2 T1D prior to initiation of teplizumab is based on autoantibody status only); in addition, the very small sample sizes of the HLA subgroups in the TN-10 trial increases uncertainty of long-term projections for any of the subgroups ■ Inputs for treatment administration and related resource use (e.g., confirmatory tests and premedication) informed by requirements and recommendations for teplizumab use, published literature, and UK cost sources (e.g., NICE British National Formulary [BNF] and National Schedule of NHS Costs)

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
											■ Inputs for AE management and DKA management costs informed by clinical trial experience with teplizumab and the National Schedule of NHS Costs ■ Teplizumab acquisition and administration costs were accrued at the start of the model as one-off costs ■ HCRU costs informed by a previous NICE appraisal and expert opinion for stage 2 T1D, and relevant published literature for stage 3 T1D ■ The inclusion of screening was outside the remit of the evaluation, so did not include screening costs in the model ■ The mortality rate was greater in the stage 3 T1D health state than in stage 2, in which general population mortality was assumed to apply

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Cost categories	Utility values	Uncertainty testing	Discount rate	Model assumptions
											■ The clinical experts explained that complications associated with stage 3 T1D take 10 years to manifest and the disutility in the informing evidence was similar for the first 8 years

Abbreviations: AID Automated insulin delivery (systems), ATG Antithymocyte globulin (low-dose), CAN Canada, CDA-AMC Canada's Drug Agency, NI no information

Table 5-2: Main results of the included economic evaluations of Teplizumab

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
Mital et al. 2020 [8]	USA	■ No teplizumab costs: US$360,904 ■ Teplizumab to all at risk costs: US$418,846 ■ HLA-DR3 negative or HLA-DR4 positive costs: US$399,666 ■ HLA-DR3 negative and HLA-DR4 positive costs: US$373,265 ■ ZnT8 negative costs: US$362,107 <u>Incremental costs at teplizumab price US$100,000:</u> ■ ZnT8 negative: US$1,203 (relative to 'No teplizumab') ■ HLA-DR3 negative and HLA-DR4 positive: US$11,158 ■ HLA-DR3 negative or HLA-DR4 positive: US$26,401 ■ Teplizumab for all pts. at risk: US$19,180	■ No teplizumab QALYs: 18.72 ■ Teplizumab to all at risk QALYs: 19.26 ■ HLA-DR3 negative or HLA-DR4 positive QALYs: 19.19 ■ HLA-DR3 negative and HLA-DR4 positive QALYs: 19.07 ■ ZnT8 negative QALYs: 18.98 <u>Incremental QALYs at teplizumab price US$100,000:</u> ■ ZnT8 negative: 0.26 (relative to 'No teplizumab') ■ HLA-DR3 negative and HLA-DR4 positive: 0.09 ■ HLA-DR3 negative or HLA-DR4 positive: 0.12 ■ Teplizumab for all pts. at risk: 0.07 QALYs	<u>Incremental analysis results (teplizumab price US$100,000):</u> ■ ZnT8 negative: US$4,647 ■ HLA-DR3 negative and HLA-DR4 positive: US$119,702 ■ HLA-DR3 negative or HLA-DR4 positive: US$217,871 ■ Teplizumab for all pts. at risk: US$271,793	Given a WTP threshold of US$100,000/QALY: ■ Teplizumab priced at or below US$19,600: dominant for all individuals at-risk of developing T1D ■ Priced > US$19,600 but < US$48,900: cost-effective for all at-risk individuals (higher costs compared with other patient groups but also maximum QALYs) ■ Priced > US$48,900: no longer be cost-effective to provide teplizumab to all at-risk individuals ■ Priced between US$48,900 and US$58,200: cost-effective only for individuals who are HLA-DR3 negative or HLA-DR4 positive (or both) ■ Priced between US$58,200 and US$88,300: cost-effective only for individuals who are both HLA-DR3 negative and HLA-DR4 positive ■ Priced higher between US$88,300 and US$193,700: cost-effective only for individuals with negative ZnT8 antibody markers ■ No cost-effectiveness with a price of > US$193,700 for any of the 4 patient groups	■ If cost of diabetes management is high (and assuming all other parameters are held constant), it is cost-effective to provide teplizumab to the same patient group at a higher price or to expand treatment access to a broader patient group at the same price ■ For a 10-year time horizon, price thresholds for teplizumab to be cost-effective are substantially lower than those for a lifetime horizon, because the benefits of delayed onset of T1D accrue over a shorter time period ■ Price thresholds that render each patient group cost-effective are also slightly lower for children aged 8–17 years than when the sample also includes adults, as utility losses due to diabetes are lower for children compared with adults ■ Price thresholds are lower relative to the base case under the assumption that all at-risk individuals who have not developed T1D by 5 years will do so after 5 years	■ Results of the trace analysis indicated that, in our model, 76% and 46% of patients in the 'no treatment' and 'teplizumab to all at-risk' groups, respectively, developed T1D at the end of 5 years - similar to those observed in the phase II trial (72% and 43%, respectively) ■ Data on efficacy of teplizumab was only available for a 5-year time period ■ Model did not include teplizumab-induced complications ■ Data on efficacy of the drug among individuals with different combinations of HLA-DR3 and HLA-DR4 alleles were not available: assume that the risk of developing T1D among these individuals was an average of the T1D risks for the patient subsets with each individual marker

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
						■ If the drug could 'completely cure' individuals who do not develop T1D during the first 5 years, it would be cost-effective to treat all at-risk individuals even if priced as high as US$284,500 ■ One-way sensitivity analysis: annual health care costs of diabetes and cost of treating end-stage renal disease as well as utility values for diabetes and pre-T1D health states affect ICER the most ■ PSA also indicate that at the WTP threshold of US$100,000 per QALY gained, giving teplizumab to those with negative ZnT8 antibody is cost effective in the highest number of iterations, namely, 29%	
Mital et al. 2025 [9]	USA	■ ATG-AID: $394,250 (reference strategy - most cost-effective) ■ No Therapy-AID: $402,395 (incremental cost vs ATG-AID: +$8,145) ■ ATG-No AID: $408,380 (incremental cost vs ATG-AID: +$14,130) ■ No Therapy-No AID: $417,192 (incremental cost vs ATG-AID: +$22,942) ■ Teplizumab-AID: $547,923 (incremental cost vs ATG-AID: +$153,673)	■ ATG-AID: 19.13 QALYs (reference strategy) ■ No Therapy-AID: 18.99 QALYs (incremental effect vs ATG-AID: -0.15 QALYs) ■ ATG-No AID: 18.91 QALYs (incremental effect vs ATG-AID: -0.23 QALYs) ■ No Therapy-No AID: 18.75 QALYs (incremental effect vs ATG-AID: -0.39 QALYs)	■ ATG-AID: Most cost-effective strategy **(dominated all strategies except Teplizumab-AID)** ■ Teplizumab-AID vs ATG-AID: $622,771/QALY (main comparison) ■ All other strategies were dominated (more costly and less effective than ATG-AID)	CE-threshold applied (base-case) $100,000 per QALY - This is the willingness-to-pay threshold used throughout the analysis Threshold analyses: ■ Teplizumab price threshold: Would need to decrease from $194,000 to below $65,000 for Teplizumab-AID to become cost-effective at $100,000/QALY threshold ■ ATG efficacy threshold: ATG-AID remains most cost-effective as long as ATG efficacy is at least 17% that of teplizumab (base case assumed 50%)	Sensitivity and scenario analyses 1. Time horizon variations: 20-year horizon: ■ ATG-No AID: $178,445, 12.30 QALYs ■ ATG-AID: $179,339, 12.35 QALYs (ICER vs ATG-No AID: $16,354/QALY) ✓ cost-effective ■ Teplizumab-AID: $341,952, 12.43 QALYs (ICER vs ATG-AID: $1.2 million/QALY) ✗ not cost-effective 10-year horizon: ■ ATG-No AID: $86,075, 7.38 QALYs	■ ATG-AID is the most cost-effective strategy given current prices and assuming ATG has at least 17% of teplizumab's efficacy ■ Preventive ATG therapy followed by AID after T1D onset is "potentially cost-effective" ■ Teplizumab-AID generates additional QALYs but at a cost above the WTP threshold ■ Pairing immune therapies with AID systems enhances their economic value compared to conventional insulin management

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
		■ Teplizumab-No AID: $561,330 (incremental cost vs Teplizumab-AID: +$13,407) *Own calculation (AT comparison):* *Teplizumab-no AID vs no therapy-no AID: +$145.528*	■ Teplizumab-AID: 19.38 QALYs (incremental effect vs ATG-AID: +0.25 QALYs) ■ Teplizumab-No AID: 19.16 QALYs (incremental effect vs Teplizumab-AID: -0.22 QALYs) Own calculation (AT comparison): Teplizumab-no AID vs no therapy-no AID: +0,39	*Own calculation (AT comparison):* *Teplizumab-no AID vs no therapy-no AID: $373.149/QALY*	■ Probabilistic sensitivity analysis: ■ At $100,000/QALY threshold: ATG-AID was cost-effective in 63% of iterations ■ Cost-effectiveness acceptability curves showed ATG-AID had highest probability of being cost-effective across most WTP thresholds up to $100,000/QALY	■ ATG-AID: $89,514, 7.40 QALYs (ICER vs ATG-No AID: $175,463/QALY) ✗ not cost-effective ■ Teplizumab-AID: $260,135, 7.44 QALYs (ICER vs ATG-AID: $3.6 million/QALY) ✗ not cost-effective 2. No effect of AID on HbA1c (only reduces hypoglycemia): ■ ATG-No AID: $408,380, 18.91 QALYs ■ ATG-AID: $412,559, 18.99 QALYs (ICER vs ATG-No AID: $49,031/QALY) ✓ cost-effective ■ Teplizumab-AID: $564,723, 19.24 QALYs (ICER vs ATG-AID: $604,900/QALY) ✗ not cost-effective 3. Imperfect AID uptake: 50% AID uptake: ■ ATG-AID: $400,970, 19.02 QALYs ■ Teplizumab-AID: $554,643, 19.27 QALYs (ICER: $618,536/QALY) ✗ not cost-effective 30% AID uptake: ■ ATG-AID: $404,177, 18.97 QALYs ■ Teplizumab-AID: $557,429, 19.22 QALYs (ICER: $612,659/QALY) ✗ not cost-effective 4. Higher CGM/pump usage (90% CGM, 60% insulin pumps):	■ The optimal prevention-treatment strategy depends on: payers' ability to negotiate lower teplizumab prices; Further evidence on ATG efficacy in the prevention setting Limitations acknowledged by authors: ■ No clinical trials examining combined effects of teplizumab/ATG with AID systems ■ Could not account for interdependencies between immune therapy and AID effects ■ ATG efficacy in prevention is theoretical (no randomised trials) ■ Long-term efficacy of teplizumab beyond 5 years is unknown ■ AID system prices vary across patients and payers ■ Model could not capture all price variation scenarios ■ Heterogeneity in individual treatment responses not fully captured

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
						■ ATG-AID: $394,250, 19.13 QALYs ■ Teplizumab-AID: $547,923, 19.38 QALYs (ICER: $622,771/QALY) ✗ not cost-effective 5. Alternative T1D onset scenarios: All patients develop T1D at 5 years: ■ No therapy-AID: $407,545, 18.93 QALYs ■ ATG-AID: $407,559, 19.01 QALYs (ICER vs No therapy-AID: $179/QALY) ✓ cost-effective ■ Teplizumab-AID: $582,410, 19.10 QALYs (ICER vs ATG-AID: $1.9 million/QALY) ✗ not cost-effective Zero risk of T1D after 5 years (disease-free patients remain so): ■ ATG-AID: $310,979, 19.73 QALYs ■ Teplizumab-AID: $425,333, 20.30 QALYs (ICER: $202,313/QALY) ✗ not cost-effective 6. Accounting for time off work: ■ ATG-AID: $394,710, 19.13 QALYs ■ Teplizumab-AID: $549,533, 19.38 QALYs (ICER: $627,432/QALY) ✗ not cost-effective	

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
						9. Tornado diagram (one-way sensitivity) - most influential parameters (in order): ■ Cost of teplizumab ■ ATG efficacy relative to teplizumab ■ Cost of AID system supplies (annual) ■ Cost of ATG (25mg vial) ■ Cost of insulin ■ AID effect on HbA1c ■ Hypoglycemia risk reduction with AID (children) ■ Cost of AID system device ■ Cost of infusion per hour ■ Hypoglycemia risk reduction with AID (adults) For all parameter variations within ±25% of base case, ICER for Teplizumab-AID vs ATG-AID remained above $100,000/QALY threshold	
CDA-AMC 2025 [10][4]	CAN	■ Teplizumab is available as a sterile solution for IV infusion (1 mg / mL). At the submitted price of $18,410 per 2 mL vial, the cost of teplizumab is expected to be $257,740 per patient for a single course of treatment, based on the Health Canada-recommended dosage	■ Gain of 0.24 life-years (LYs) compared to no intervention ■ Gain of 0.31 QALYs compared to no intervention from the healthcare payer perspective	■ Healthcare payer perspective: ICER of teplizumab compared to no intervention was $747,542 per QALY gained in the CDA-AMC base case	NI	The estimated ICER was highly sensitive to the parametric distribution used to estimate the proportion of patients at risk of developing stage 3 T1D. This finding is accompanied by significant uncertainty, as the long-term benefit of teplizumab remains unknown.	The Canadian Drug Expert Committee (CDEC) recommends that teplizumab not be reimbursed to delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients 8 years of age and older with Stage 2 T1D

[4] Not final, but draft of reimbursement recommendation.

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
		■ Teplizumab will be associated with higher costs to the healthcare system than no intervention (incremental costs =$221,630), primarily driven by increased costs associated with drug acquisition, partly offset by disease management of stage 3 T1D	■ When caregiver benefits are considered in the societal perspective, the incremental benefit is increased (incremental benefit = 0.36 QALYs)	■ Societal perspective: ICER of teplizumab compared to no intervention was $608,736 per QALY gained			■ Although the CDA-AMC base case estimated a gain in QALYs with teplizumab compared to no intervention (incremental: 0.30), approximately 90% of the incremental benefit was gained in the extrapolated period (i.e., after a median 24.5 months of follow-up) - in the absence of long-term evidence, the incremental QALYs for teplizumab predicted in the CDA-AMC base case are highly uncertain and may be overestimated ■ HCRU for stage 3 T1D is associated with significant uncertainty as the mixed regression model used to estimate HCRU costs do not reflect clinical expectations or published literature conducted in Canada ■ Screening is a significant factor that was not adequately considered in the economic evaluation

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
NICE 2025 [11][5]	UK	■ Teplizumab price is confidential! ■ Initial average monthly cost per person of managing stage 3 T1D (£415.22) was taken from literature on direct healthcare costs of diabetes in the UK ■ The clinical experts estimated that the costs of hybrid closed loop systems would add about £5,000 to costs annually ■ Incremental costs: *confidential*	Incremental QALYs: *confidential*	■ Teplizumab was cost-effective when compared with established clinical management, with an incremental QALY gain of (confidential) and an ICER of £29,602 per QALY using a deterministic approach ■ with incremental QALY gain of (confidential) and £28,400, respectively, using a probabilistic approach ■ The committee could not identify a preferred ICER because of uncertainties in the economic model and the need for additional analyses	NICE uses £20,000-30,000/QALY	Probabilistic sensitivity analysis: *confidential* Deterministic sensitivity analysis: ■ Incremental cost for teplizumab vs established clinical management was most sensitive to the disease management cost during Stage 3 T1D, the excess risk of death during Stage 3 T1D, and the administration costs of teplizumab ■ The key drivers for incremental QALYs included: the Stage 3 T1D disutilities based on disease duration; the excess risk of death during Stage 3 T1D; the Stage 3 T1D disutilities vs. the general population, the utilities for the general population; and the carer/parent disutility while tending to individuals with Stage 3 T1D ■ The ICERs were most sensitive to variations in the following: the disease management cost during Stage 3 T1D; the Stage 3 T1D disutilities based on disease duration; the Stage 3 T1D disutilities vs. the general population; and the administration cost of teplizumab	Teplizumab is cost-effective for delaying the onset of stage 3 T1D compared with established clinical management in adults and paediatric individuals aged 8 years and older with stage 2 T1D; however, 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 The committee "could not identify a preferred ICER" due to uncertainties - uncertainties in the model - it is not possible to determine the most likely cost-effectiveness estimates for teplizumab: ■ Population eligible for teplizumab ■ Costs of managing stage 3 T1D ■ Effects of stage 3 T1D on quality of life There are several benefits that are unlikely to be included in the QALY calculation, as no data quantifying these impacts are available: ■ Increased time for people with Stage 2 T1D to prepare for the onset and management of symptomatic Stage 3 T1D ■ Prolonged benefits associated with endogenous C-peptide production

[5] Not final, but first published draft.

Author, year [reference]	Country	(Incremental) costs (base-case)	(Incremental) effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection and limitations
						The scenario with the largest impact on the ICER was the use of a 1.5% discount rate for both costs and health outcomes; this was expected as a lower discount rate increases the impact of long-term outcomes.	■ Improving long-term outcomes in people with lower SES ■ Full impact on carers/parents and siblings ■ Impact on education and employment Key issues identified by the External Assessment Group (EAG): ■ Disagreement with the company's approach of modelling progression to Stage 3 T1D ■ Disagreement with the company's approach of estimating a decline in disutility based on years lived with Stage 3 T1D ■ Disagreement with the company's approach of using prevalent population costs as initial costs and increasing these over time to estimate Stage 3 T1D costs[6]

Abbreviations: AID…Automated insulin delivery (systems), ATG…Antithymocyte globulin (low-dose), CAN…Canada, CDA-AMC…Canada's Drug Agency, NI…no information, NR…not reported, WTP…willingness to pay

[6] Average monthly cost per person from Hex et al. 2024 as the initial cost for individuals transitioning to Stage 3 T1D. However, these costs are based on the prevalent population, including patients who developed Stage 3 T1D many years ago. The EAG considers that using the costs of the prevalent population as initial costs, and then increasing them over time using the regression models developed from the Ou et al. 2016 data,2 is incorrect and substantially overestimates healthcare costs for Stage 3 T1D. The EAG applied the average monthly cost from Hex et al. 2024 as a fixed health state cost of Stage 3 T1D → ICER increases.

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the manufacturer

The MAH did not submit a budget impact analysis of teplizumab for Austria.

5.2.2 Self-calculated budget impact analysis for the Austrian context before negotiation

No additional tables and figures.

6 Extended perspectives

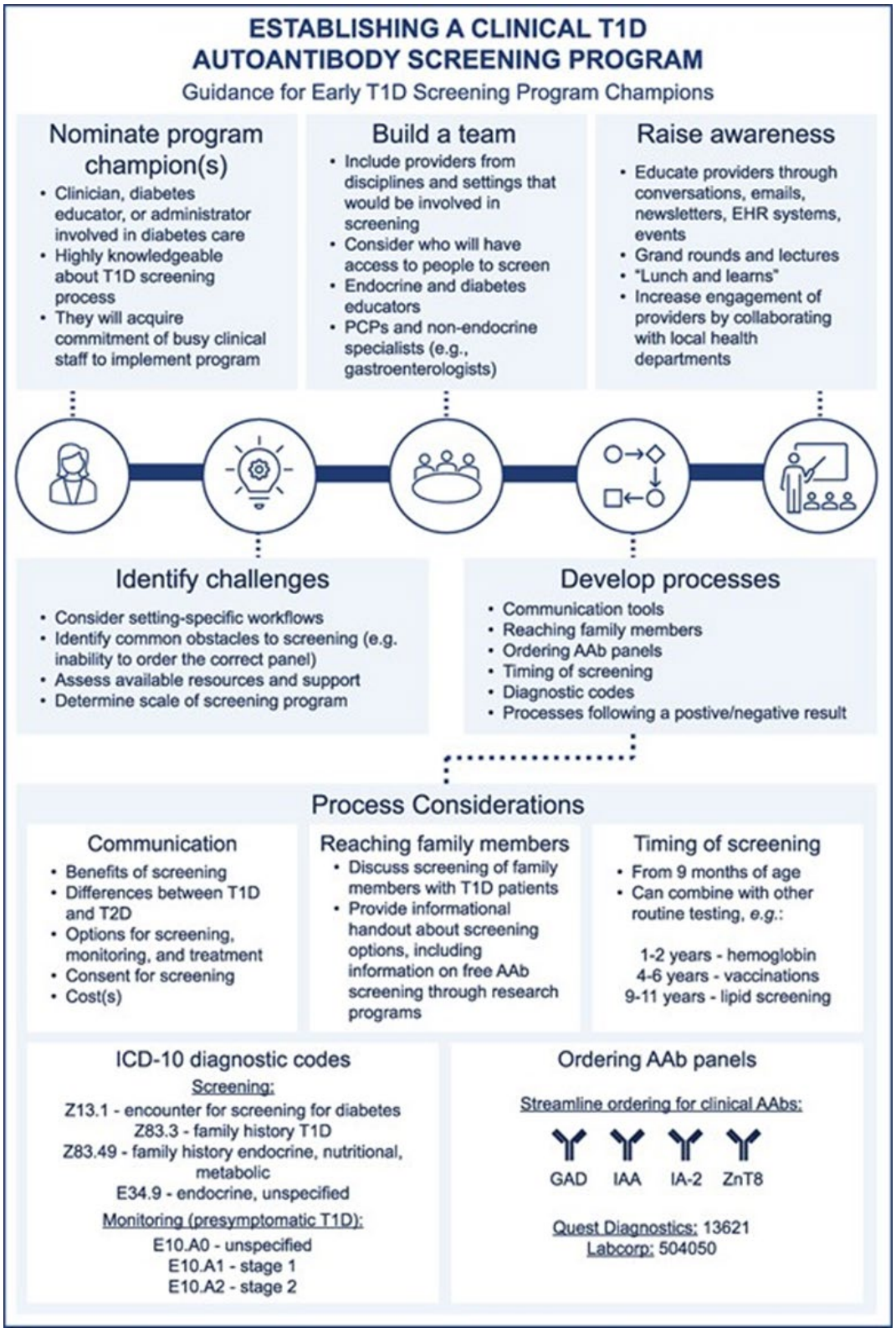

Figure 6-1: Establishing a clinical AAb screening program for early T1D: guidance for endocrinology providers [12]

6.1 Stakeholder perspectives

No additional tables and figures.

6.2 Patient's perspective

No additional tables and figures.

6.3 Further ethical and social aspects

No additional tables and figures.

6.4 Registries and documentation of application

No additional tables and figures.

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licenses

No additional tables and figures.

7.2 Public contributions to drug development

Table 7-1: Financing/patent deals/licensing/funding rounds of all companies involved in the development of Teizeild®

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Yale University					
Basic and clinical development research funding	Modulating pathogenic T cells in Type 1 diabetes Phase I/II Trial Of HOKT3(1(ALA-ALA) In Type 1 Diabetes (PI Herold, K.)	2000- 2025	10,364,066	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	https://reporter.nih.gov/search/V4ge4W3LtEqRnrBsXMv-rQ/project-details/8639227
Basic research funding	Determining the molecular basis for different rates of T1D progression.	2014	1,095,982	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	https://reporter.nih.gov/search/V4ge4W3LtEqRnrBsXMv-rQ/project-details/8837241
Clinical development funding	Phase II trial of extended-release exenatide (Bydureon) and teplizumab in patients with new-onset Type 1 Diabetes (PI Herold, K.)	2016	251,250	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	https://reporter.nih.gov/search/V4ge4W3LtEqRnrBsXMv-rQ/project-details/9143838
Basic research funding	Effects of EBV on autoimmunity and responses to immune therapy (PI Herold, K.)	2021-2022	460,625	National Institute of Allergy and Infectious Diseases (NIAID)	https://reporter.nih.gov/search/V4ge4W3LtEqRnrBsXMv-rQ/project-details/10353823
University of Chicago					
Basic research funding	Immunomodulation Of Transplant Rejection (PI Jeffrey Bluestone)	1990-1998	6,117,725	National Institute of Allergy and Infectious Diseases (NIAID)	https://reporter.nih.gov/search/MkQcUr5cJkCARUT8GyVSw/project-details/2517195
University Of California					
Basic research funding	Immunomodulation of transplant rejection by Anti-CD3 mAb (PI Jeffrey Bluestone)	2000-2015	4,335,305	National Institute of Allergy and Infectious Diseases (NIAID)	https://reporter.nih.gov/search/MkQcUr5cJkCARUT8GyVSw/project-details/8468615
Sanofi					
Acquisition	French pharma Sanofi buys maker of diabetes treatment (Provention Bio) for $2.9 billion	2023	$2.9 billion	Sanofi, Provention Bio	https://www.statnews.com/2023/03/13/french-pharma-sanofi-buys-maker-of-diabetes-treatment-for-2-9-billion/

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Acquisition	Ligand Pharmaceuticals Incorporated acquired Tolerance Therapeutics, Inc. for $20 million in cash. Tolerance Therapeutics is a holding company, owned by the inventors of TZIELD (teplizumab-mzwv), that is owed a royalty of less than 1% on worldwide net sales. The transaction will be immediately accretive to Ligand's royalty revenue.	2023	$20 million	n.a.	https://www.americanpharmaceuticalreview.com/1315-News/608322-Ligand-Acquires-Royalty-on-Sanofi-s-TZIELD-for-20M/
Licensing	DRI Healthcare is paying $100 million for a piece of Provention Bio's drug Tzield, which was approved by the FDA last year. DRI Healthcare Trust, a prolific acquirer of drug royalties, is paying $100 million for a piece of a first-of-its-kind Type 1 diabetes drug. First investigated by MacroGenics, the drug has been in testing for more than a decade and has changed hands multiple times. Eli Lilly struck a deal with MacroGenics in 2007 to test the medicine in patients with recent-onset type 1 diabetes, but sent the drug back to the biotech after it failed in a Phase 3 trial in 2010. DRI could also pay Macrogenics another $100 million in sales and development milestones.	2023	Licensing, royalties, milestones	DRI Healthcare	https://www.biopharmadive.com/news/dri-diabetes-provention-tzield-teplizumab-macrogenics-royalties/644645/
Production	AGC Biologics tapped to produce long-awaited diabetes drug AGC will produce Tzield (teplizumab-mzwv) at its Seattle protein biologics facility, the CDMO said in a Jan. 24 press release. The company was heavily involved with the advancement of the treatment through early manufacture and validation batches, and U.S. regulatory approval.	2023	n.a.	AGC Biologics	https://www.fiercepharma.com/manufacturing/agc-biologics-tapped-produce-long-awaited-diabetes-drug
Licensing/Milestone payments	MacroGenics Earns $60 Million Milestone with U.S. FDA Approval of Teplizumab Teplizumab was acquired by Provention Bio, Inc. in May 2018 pursuant to an asset purchase agreement. Under the agreement, Provention Bio is obligated to pay MacroGenics contingent milestone payments totaling $170 million upon the achievement of certain regulatory approval milestones, including $60 million for the approval of a BLA for a first indication in the United States. In addition, Provention Bio is obligated to make contingent milestone payments to MacroGenics totaling $225 million upon the achievement of certain sales milestones as well as a single-digit royalty on net sales of the product.	2022	$170 million	Provention Bio	https://ir.macrogenics.com/news-releases/news-release-details/macrogenics-earns-60-million-milestone-us-fda-approval
Co-Promotion contract	Sanofi is partnering with Provention Bio on a medicine that could become the first approved treatment to alter the course of Type 1 diabetes.	2022	$20 million	Sanofi	https://www.biopharmadive.com/news/sanofi-provention-diabetes-teplizumab-marketing/633514/

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	The French drugmaker agreed to pay Provention Bio $20 million for a co-promotion contract and the right to negotiate first for a potential license to the drug, known as teplizumab. Sanofi will also make a $35 million equity investment in Provention Bio if teplizumab wins Food and Drug Administration approval. A decision from the FDA is due by Nov. 17.				
Licensing	Eli Lilly is putting down a $41 million payment to acquire exclusive rights to MacroGenics' diabetes drug teplizumab in a deal that could be worth more than a billion dollars in total. MacroGenics also gets a $10 million financing arrangement, up to $200 million in development milestones for diabetes, sales milestones of $250 million and up to $600 million for other approvals of molecules developed by the two companies.	2007	$41 million for exclusive rights	Eli Lilly	https://www.fiercebiotech.com/biotech/eli-lilly-forges-1b-diabetes-deal
Public clinical development funding	Three clinical trials were sponsored by the Immune Tolerance Network (primarily funded by the National Institute of Allergy and Infectious Diseases (NIAID))	n.a.	n.a.	Immune Tolerance Network	https://www.sec.gov/ix?doc=/Archives/edgar/data/1695357/000149315223009516/form10-k.htm
Public clinical development funding	Clinical trial "Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk"" sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	2010-2019	n.a.	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	https://clinicaltrials.gov/study/NCT01030861
Provention Bio					
Equity investment	Provention Bio Completes $35M Equity Investment from Sanofi US	2023	$35 million	Sanofi	https://www.contractpharma.com/breaking-news/provention-bio-completes-35m-equity-investment-from-sanofi-us/
POST-IPO	Provention Bio may be waiting a bit longer for the FDA's decision on its diabetes prevention drug teplizumab, but at least the biotech has $60 million cash in the meantime to work through launch preparations	2022	$60 million	n.a.	https://www.fiercebiotech.com/biotech/provention-sells-60m-stock-private-investors-teplizumabs-future-hangs-balance
IPO	Provention Bio has filed to raise up to $50 million in its Nasdaq IPO, which will bankroll several clinical programs, including a pair of inflammatory bowel disease assets it picked up from Janssen last fall. On Wednesday, it acquired the rights to two clinical-stage candidates from MacroGenics: teplizumab, known as PRV-031, and PRV-3279. Provention launched last June with $28.4 million in seed funding and a goal of intercepting and preventing immune-mediated disease	2018	up to $50 million	Provention Bio	https://www.fiercebiotech.com/biotech/provention-bio-tees-up-for-50m-ipo
Series A	Provention Bio, Inc. Secures $28.4 Million Founding Financing to Fund Development Targeting the Interception and Prevention of Immune-Mediated Disease	2017	$28.4 Million	MDB Capital Group LLC	https://www.prnewswire.com/news-releases/provention-bio-inc-secures-284-million-founding-financing-to-fund-development-targeting-the-interception-and-prevention-of-immune-mediated-disease-300479243.html

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Asset Purchase Agreement	In May 2018, Provention Bio acquired the stake MacroGenics has of teplizumab through an Asset Purchase Agreement. As partial consideration, they issued MacroGenics warrants for 2,162,389 shares at $2.50/share, exercised cashless in July 2019. Provention Bio owes MacroGenics $170M in regulatory milestones, including $60M triggered by FDA's November 2022 approval of TZIELD® for delaying Stage 3 T1D in patients 8+ with Stage 2 T1D, plus $225M in sales milestones. They pay MacroGenics single-digit royalties on net sales and assumed third-party obligations including low single-digit royalties (partially creditable against MacroGenics royalties) and approximately $0.7M in milestone payments. Provention Bio also owes MacroGenics a low double-digit percentage of any future licensing consideration. In November 2022, Provention Bio amended the agreement to pay the $60M FDA approval milestone in four $15M installments.	2018-2022	2,162,389 shares at $2.50/share (warrants issued as partial consideration) $170M (total regulatory milestones), including $60M (FDA approval of TZIELD for Stage 2 T1D) $225M (total sales milestones) Single-digit percentage (royalties to MacroGenics on net sales) Low single-digit percentage (third-party royalties, partially creditable) $0.7M (third-party milestone payments) Low double-digit percentage (share of future licensing consideration to MacroGenics) $15M x 4 installments	MacroGenics	https://www.sec.gov/ix?doc=/Archives/edgar/data/1695357/000149315223009516/form10-k.htm
MacroGenics					
Series D-2	MacroGenics gains $25M in new VC round	2008	$25M in VC funding	Nextech Venture	https://www.fiercebiotech.com/biotech/macrogenics-gains-25m-new-vc-round https://www.fiercebiotech.com/biotech/macrogenics-inc-raises-25m-series-d-2-financing
Public funding	Total Prime Award Amount: $28.6M	2008-2024	$28.6M	HHS/NIH	https://www.usaspending.gov/keyword_search/macrogenics

Type of information	Details on collaboration, financing, and public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Series A	Early financial backing was crucial for MacroGenics. In September 2001, the company closed a Series A financing round, securing $13.5 million. This funding, provided by investors such as InterWest Partners, MPM Capital, and OrbiMed, was essential for establishing the company and supporting its initial research efforts (Read more at: https://swotanalysisexample.com/blogs/brief-history/macrogenics-brief-history)	2001	$13.5 million	InterWest Partners, MPM Capital, and OrbiMed	https://swotanalysisexample.com/blogs/brief-history/macrogenics-brief-history

Abbreviations: HHS…U.S. Department of Health and Human Services, NIH…National Institutes of Health, VC…Venture Capital, NIDDK…National Institute of Diabetes and Digestive and Kidney Disease, PI…Principal Investigator

Table 7-2: Search terms used to identify the development history and public contributions of Teizeild®

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	Teplizumab	n.a.	Yes	Earliest mention – 12/2025	Active substance, Medical speciality, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorization, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorisation issued
https://adisinsight.springer.com/			Yes		Alternative names
https://pubmed.ncbi.nlm.nih.gov/	Teplizumab hOKT3-gamma-1-ala-ala; hOKT3-γ1-ala-ala; MGA-031; PRV 031; PVR031; Teplizumab-mzwv; TZIELD		Yes		Development history
https://clinicaltrials.gov/			Yes		Clinical trials
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://trialsearch.who.int/			Yes		
https://cordis.europa.eu/			Yes		
https://reporter.nih.gov/		TN-10 10-K Macrogenics Provention Bio Jeff Bluestone Kevan Herold Sanofi Type 1 Diabetes Stage 2 T1D	Yes		Basic research. Authors selected based on literature found on PubMed
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm			No		Patent information and associated references
https://competition-cases.ec.europa.eu/search			No		Funding amounts
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		
https://eic.ec.europa.eu/index_en			No		
https://www.eib.org/en/index			No		

https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			No		
https://www.sbir.gov/			No		Project funding for companies involved in the development
https://www.nsf.gov/			No		SME, national, regional, local, international, supranational funding
https://www.ukri.org/			No		
https://foerderportal.bund.de/			No		
https://www.health-holland.com/			No		
https://www.bpifrance.com/					
https://www.inserm.fr/en/home/			No		
https://innovationsfonden.dk/da			No		
https://lundbeckfonden.com/en			No		
https://www.ucc.ie/en/apc/			No		
https://www.amractionfund.com/about			No		
https://www.gatesfoundation.org/			No		
			No		
https://www.google.com/			Yes		Patent information
https://www.forbes.com/			No		n.a.
https://www.reuters.com/			No		
https://www.science.org/			No		
https://www.cafepharma.com/			No		Collaborations, funding, financing, Series A-C funding, patent information, acquisitions
https://www.livescience.com/			No		
https://www.biospace.com/			No		
https://www.bioworld.com/			No		
https://www.biopharmadive.com/			No		
https://pharmaphorum.com/			No		
https://pharmatimes.com/			No		
https://pharmafile.com/			No		
https://www.fiercepharma.com/			Yes		
https://www.fiercebiotech.com			Yes		
https://www.biocentury.com			Yes		
https://www.businesswire.com/			No		
https://www.businessinsider.com/			No		
https://www.statnews.com/			No		
https://finance.yahoo.com			No		
https://www.globenewswire.com			No		
https://www.sec.gov/			Yes		

8 Landscape overview

8.1 Ongoing studies of teplizumab for stage 1/2 T1D

Table 8-1: List of ongoing studies for teplizumab

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
GLP-1Ra Impact on Metabolic Outcomes in Stage 2 T1DM While Receiving Teplizumab (GLP-TEP)	NCT06338553	n.a.	Early Phase 1	Recruiting	2027-03	n.a.
Efficacy and Safety of Teplizumab in Japanese Participants With Stage 2 Type 1 Diabetes (KIBOU-T1D)	NCT06791291	n.a.	Phase 2	Recruiting	2028-03-06	n.a.
Recent-Onset Type 1 Diabetes Extension Study Evaluating the Long-Term Safety of Teplizumab (PROTECT Extension)	NCT04598893	n.a.	Observational	Active, not recruiting	2026-11	n.a.
A Study to Investigate Efficacy and Safety of Teplizumab Compared With Placebo in Participants 1 to 25 Years of Age With Stage 3 Type 1 Diabetes (βETA PRESERVE)	NCT07088068	n.a.	Phase 3	Recruiting	2028-12-12	n.a.
Teplizumab in Pediatric Stage 2 Type 1 Diabetes (PETITE-T1D)	NCT05757713	n.a.	Phase 4	Active, not recruiting	2026-08-27	n.a.
Platform Trial to Delay Stage 3 Diabetes: Comparing Teplizumab With ATG (TN40A)	NCT07216391	n.a.	Phase 2	Not yet recruiting	2029-12-31	n.a.
Effects of Sitagliptin in Relatives of T1D Patients (SITA-one)	NCT05219409	n.a.	Phase 2, 3	Not yet recruiting	2027-12	n.a.

8.2 Treatments in development

Table 8- 1: Landscape overview for stage 1/ stage 2 T1D and recently diagnosed T1D

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
Baricitinib					
Baricitinib monotherapy for treatment of high-risk, Stage 1b or Stage 2 Type 1 diabetes mellitus in infants, toddlers, children, adolescents and adults aged 1 to 35 years	Baricitinib	NCT07222137	Company Eli Lilly	Company Eli Lilly	May 2032

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
Glutamic Acid Decarboxylase (rhugad65)					
Glutamic acid decarboxylase (rhugad65) monotherapy for treatment of stage 1 or stage 2 Type 1 diabetes mellitus in children over 8 years of age and adolescents who carry the HLA DR3-DQ2 haplotype	Glutamic Acid Decarboxylase (rhugad65)	NCT05683990	Diamyd Medical	Diamyd Medical	Nov 2030
Brivekimig					
Brivekimig monotherapy for the treatment of recently diagnosed Type 1 diabetes mellitus in adolescents and adults up to 35 years of age	Brivekimig	NCT06812988	Sanofi	Sanofi	July 2031
Celz-201					
Celz-201 in combination with standard of care for treatment of newly diagnosed, recent-onset Type 1 diabetes mellitus in adults up to 35 years of age	Celz-201	NCT05626712	Creative Medical Technology	Creative Medical Technology	Dec 2030
Ladarixin					
Ladarixin monotherapy for the treatment of recent-onset insulin-dependent Type 1 diabetes mellitus in adolescents and adults between 14-45 years of age who have low residual β-cell function at baseline	ladarixin	NCT04628481 NCT02814838	Dompé Farmaceutici	Dompé Farmaceutici	n.a.
Autologous Cd34+-enriched Hspcs					
Autologous cd34+-enriched hspcs monotherapy for treatment of recent onset Type 1 diabetes mellitus in adults up to 40 years of age with residual β-cell function	Autologous Cd34+-enriched Hspcs	NCT06938334	Altheia Science	Altheia Science	May 2033
Cnp-103					
Cnp-103 monotherapy for add-on treatment of recent onset stage 3 Type 1 diabetes mellitus in adolescents and adults up to 35 years of age	Cnp-103	NCT06783309	COUR Pharmaceuticals	COUR Pharmaceuticals	Nov 2030
Frexalimab					
Frexalimab in combination with insulin for treatment of newly diagnosed Type 1 diabetes mellitus in adolescents and adults up to 35 years of age	Frexalimab	NCT06111586	Sanofi	Sanofi	Mar 2031
Sab-142					
Sab-142 monotherapy for treatment of Stage 3 new onset Type 1 diabetes mellitus in children over 5 years, adolescents and adults up to 40 years of age	Sab-142	NCT07187531	SAB BIO	SAB BIO	Oct 2031

9 References

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10 List of abbreviations

Abs ..... antibodies
ADDQoL-19 ..... Audit of Diabetes-Dependent Quality of Life (19 items)
AID ..... Automated insulin delivery (systems)
ALT ..... alanine aminotransferase
AST ..... aspartate aminotransferase
ATG ..... Antithymocyte globulin (low-dose)
AUC ..... area under the curve
CAN ..... Canada
CDA-AMC ..... Canada's Drug Agency
CGM ..... continuous glucose monitoring
CI ..... confidence interval
CMV ..... cytomegalovirus
DKA ..... diabetic ketoacidosis
DI ..... disposition index
DIDP ..... Diabetes Illness and Distress Profile
DNA ..... deoxyribonucleic acid
DPTRS ..... Diabetes Prevention Trial Risk Score
EBV ..... Epstein-Barr virus
f ..... female
FDR ..... first-degree relative
GAD65 ..... glutamic acid decarboxylase 65
h ..... hour
HbA1c ..... hemoglobin A1c or glycated hemoglobin
Hgb ..... haemoglobin
HHS ..... U.S. Department of Health and Human Services
HIV ..... human immunodeficiency virus
HLA ..... human leukocyte antigen
HR ..... hazard ratio
HSPCs ..... hematopoietic stem and progenitor cells
HTA ..... health technology assessment
IA-2 ..... islet antigen 2
ICA ..... islet cell autoantibody
ICA512 ..... islet antigen 512
INR ..... international normalized ratio
IQR ..... interquartile range
IS ..... insulin sensitivity
ISR ..... insulin secretion rate
m ..... male
M12 ..... month 12
M3 ..... month 3
M6 ..... month 6
MIAA ..... micro insulin autoantibody
min ..... minute
n ..... number
NI ..... no information
NIDDK ..... National Institute of Diabetes and Digestive and Kidney Disease
NIH ..... National Institutes of Health
NR ..... not reported
NS ..... not significant
OGTT ..... oral glucose tolerance test
OMM ..... oral minimal model
p ..... p-value
PI ..... Principal Investigator
PMN ..... polymorphonuclear leukocytes (neutrophils)
PPD ..... purified protein derivative
PRO ..... patient-related outcomes
QoL-Q ..... Quality of Life Questionnaire
RCT ..... randomised controlled trial
RoB ..... risk of bias
SD ..... standard deviation
T1D ..... type 1 diabetes
T1DM ..... type 1 diabetes mellitus
TN-10 ..... TrialNet-10
ULN ..... upper limit normal
VC ..... Venture Capital
WTP ..... willingness to pay
ZnT8 ..... zinc transporter 8
α ..... significance level (alpha)
φ ..... insulin secretion rate

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH