5.14 TEPLIZUMAB, Solution for injection 2 mg in 2 mL, Tzield®, SANOFI-AVENTIS AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested Section 100 (Highly Specialised Drugs Program), Authority Required listing for teplizumab for the treatment of Stage 2 type 1 diabetes (T1D) in patients aged 8 years or older in order to delay the onset of Stage 3 T1D.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult and paediatric patients 8 years of age and older with Stage 2 T1D
Intervention	Teplizumab by intravenous infusion (over a minimum of 30 minutes), using a BSA-based dosing, once daily for 14 consecutive days as follows: • Day 1: 65 microgram/m^2 • Day 2: 125 microgram/m^2 • Day 3: 250 microgram/m^2 • Day 4: 500 microgram/m^2 • Days 5 through 14: 1030 microgram/m^2
Comparator	Placebo, representing best supportive care (BSC; referred to as established clinical management [ECM] in the economic evaluation).
Outcomes	Key efficacy outcomes: progression from Stage 2 to Stage 3 T1D (specifically time to progression and rate of progression) and levels of stimulated C-peptide Safety outcomes
Clinical claim	Teplizumab is superior to placebo in terms of efficacy in delaying the onset of Stage 3 TID, with an inferior but manageable safety profile.

Source: Table 1-1, p4 of the submission.
BSA = body surface area; T1D = type 1 diabetes.

2 Background

Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA)/ Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. Teplizumab was registered on the ARTG on 21 May 2026.

2.2 The approved TGA indication is "to delay the onset of Stage 3 type 1 diabetes mellitus in adult and paediatric patients aged 8 years and older with Stage 2 type 1 diabetes mellitus."

2.3 The ACM minutes indicate that the ACM was satisfied that available efficacy results from the TN-10 study were clinically significant. However, the data evaluated by the TGA were derived from a relatively small number of clinical studies including one study in Stage 2 T1D (TN-10), and six studies in Stage 3 T1D. The ACM highlighted the need

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for further confirmatory/replicatory clinical trials and comprehensive long-term clinical studies. The ACM recommended an ongoing pharmacovigilance program given teplizumab's immunomodulatory mechanism of action. The currently ongoing clinical studies were noted: PROTECT EXTENSION was a single arm, non-randomised open label study to evaluate the long-term safety of teplizumab in adolescent patients with recent onset T1D; PETITE T1D was a single-arm, non-randomised, open-label study to assess the safety and pharmacokinetics of teplizumab in participants <8 years of age with Stage 2 T1D; and OBS18117/NA was an observational long term safety study of teplizumab in patients with Stage 2 T1D.

2.4 The submission stated that the sponsor intends to seek expansion of the TGA indication in the future to include children aged under 8 years, based on the PETITE study (NCT05757713[1]), and this will form the basis of a future PBAC submission.

2.5 Teplizumab has been granted approval for use in delaying the onset of Stage 3 T1D in the United States of America (USA), Canada, the United Kingdom (UK), and the European Union (EU). In the UK, The National Institute for Health and Care Excellence (NICE) published draft guidance[2] for teplizumab in August 2025. Similarly, guidance[3] from the Canadian Drug Agency for teplizumab was published in December 2025. The Sub-Committees noted the NICE and CDA did not recommend teplizumab due to the uncertainties in the economic model (NICE) and due to the uncertainty surrounding teplizumab's long-term efficacy, safety and impact on quality-of-life (CDA). Both submissions to the NICE and CDA made use of a 3-health state Markov cohort model (which appears similar to the current submission). On 23 June 2026, NICE announced that it had recommended teplizumab as an option for delaying the onset of stage 3 T1D in people 8 years and over with stage 2 T1D, noting that teplizumab will be available to the NHS at a confidential discounted price[4].

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

[1] https://clinicaltrials.gov/study/NCT05757713, accessed 6 May 2026.
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10981
[3] https://www.cda-amc.ca/teplizumab
[4] https://www.nice.org.uk/news/articles/teplizumab-to-delay-the-onset-of-type-1-diabetes-recommended

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TEPLIZUMAB					
teplizumab 2 mg/2 mL injection, 2 mL vial	Public: $[redacted] published $[redacted] effective Private: $[redacted] published $[redacted] effective	14	14	0	Tzield

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Highly Specialised Drugs Program – Public (Code HB)/Private (Code HS)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒*Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic submission)* (authority type was not stated by submission)
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Episodicity: BLANK
		Severity: BLANK
		Condition: *Stage 2 type 1 diabetes*
		Indication: Stage 2 Type 1 diabetes
		Clinical criteria:
		Patient must have at least two positive islet autoantibodies *confirmed on two occasions, with the most recent test undertaken within 6 months of commencement of treatment with this drug*
		AND
		Clinical criteria:
		Patient must have dysglycaemia without overt hyperglycaemia *confirmed on two occasions, with the most recent test undertaken within 52 days of commencement of treatment with this drug*
		Treatment criteria:
		Must be treated by an endocrinologist, *or* paediatric endocrinologist ~~or an authorised prescriber in consultation with an endocrinologist~~
		AND
		Treatment criteria:
		Patient must not be undergoing PBS-subsidised treatment with this drug more than once per lifetime.
		Population criteria:
		Patient must be *at least 8 years of age* ~~aged 8 years or older~~
		Prescribing Instructions: ~~The diagnostic criteria for Stage 2 Type 1 Diabetes includes islet autoantibodies (usually multiple *minimum two*) confirmed on at least 2 samples and dysglycaemia confirmed by:~~ *Dysglycaemia without overt hyperglycaemia is defined as:*

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	• ~~OGTT: 2-h plasma glucose 140–199 *200* mg/dL (7.8–11.0 *11.1* mmol/L) during 75g OGTT, (Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L); OR~~ • Impaired fasting glucose: fasting plasma glucose *110* ~~100–~~125 mg/dL (*6.1* ~~5.6–~~6.9 mmol/L); OR • Impaired glucose tolerance: 2-h plasma glucose140~~–199~~ *200* mg/dL (7.8~~–11.0~~ *11.1* mmol/L); OR • HbA1C *6.0* ~~5.7–~~6.4% (*42* ~~39–~~47 mmol/mol) ~~or ≥10% increase in A1C~~. ~~The MBS lists pathology services for the detection of pancreatic islet autoantibodies (items 71165, 71119, 71121, 71123, 71125), the oral glucose tolerance test (item 66542), the quantification of HbA1c (items 66551, 66841, 73812, 73826, 73839) and the quantification of plasma glucose (item 66500). Screening can also be accessed via the Australian Type 1 Diabetes National Screening Pilot, Type1Screen, the Pathway to Prevention Study and the ENDIA (Environmental Determinants of Islet Autoimmunity) Study.~~
	Prescribing Instructions: *At the time of the authority application, medical practitioners should request sufficient number of vials to complete the course of treatment with teplizumab based on the patient's body surface area (BSA) according to the Therapeutic Goods Administration (TGA) approved product information. A maximum of 24 vials will be authorised.*
	Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

3.2 The secretariat suggested an Authority Required (written) listing is preferred. This would require the prescriber to provide test results and confirmation of the appropriate indication. This would also manage the risk of possible use in unintended patient populations (e.g. newly diagnosed Stage 3 T1D or possibly Stage 1 T1D).

3.3 A special pricing arrangement (SPA) was requested. The submission proposed a published dispensed price for the maximum quantity (DPMQ) of $[redacted] and an effective DPMQ of $[redacted] for public hospitals. This equates to a published ex-manufacturer price of $[redacted] per vial and an effective ex-manufacturer price of $[redacted] per vial per vial.

3.4 The proposed maximum quantity would provide for the full 14-day course of treatment for most patients based on body surface area (BSA) dosing requirements. Each vial is intended for a single dose only. Most patients would require a single 2 mg/2 mL vial per dose. However, 2 vials per infusion may be required from days 5-14 for patients with a BSA >1.94m^2. It was not stated in the submission what proportion of patients would meet this requirement, only that it would be a small proportion of patients. For these patients, an increase in the maximum quantity may be needed to achieve the recommended dose according to the draft Product Information. The Sub-Committees estimated that approximately 5% of patients would need 2 vials per infusion. The maximum quantity should be one vial with a prescribing instruction to

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allow prescribers to request the appropriate quantity for a full course of treatment based on the patient's body surface area.

3.5 The PSCR supported separate initiation and continuation scripts as a mechanism to minimise wastage.

3.6 Both the proposed TGA indication and the proposed PBS restriction require patients to be 8 years of age or older. This aligns with the lower age limit of the pivotal TN-10 study, but not the upper age limit in the key trial where patients could be enrolled between the ages of 1 and 45. The PSCR noted that incidence data indicates that patients over the age of 45 years are being diagnosed with T1D and teplizumab has been prescribed to older adults in the US and in managed access programs across multiple countries.

3.7 The submission stated that an expanded PBAC indication will be requested in the future to include children aged <8 years (see paragraph 2.4).

3.8 The submission did not indicate that patients will be re-treated with teplizumab, however the proposed wording of the PBS restriction did not prevent this. Furthermore, the PROTECT trial used two, twelve-day courses of teplizumab in Stage 3 T1D patients between the ages of 8 and 17. Dosing occurred 26 weeks apart. Although the PROTECT trial did not inform the current submission, the wording of the proposed restriction and the dosing regimen of the PROTECT trial indicate that retreatment is a possibility. The evaluation suggested the proposed restriction should be amended to prevent this or evidence for the efficacy and safety of re-treatment should be provided to support the inclusion of re-treatment in the restrictions. The PSCR proposed inclusion of the criterion 'Patient must not undergo PBS-subsidised treatment with this drug for this indication more than once per lifetime'. The Secretariat noted that the addition of 'for this indication' to the criterion would only be required once additional indications for the drug were available.

3.9 The TN-10 trial included only participants with a first-, second-, or third-degree relative with T1D, with >95% of participants having a first- or second-degree relative with T1D, but this was not proposed as a population criterion. The Sub-Committees considered the population proposed in the submission was reasonable and considered that the rate of progression of Stage 2 T1D was likely similar in patients with and without family history[5].

3.10 The evaluation noted that pilot studies of screening for T1D have been conducted in Australia, but an ongoing national program has not been implemented yet. Additionally, Type1Screen currently offers screening for people with a relative who is diagnosed with T1D. At the time of the evaluation, Type1Screen had screened 3,994 people and had documented 196 positive screens[6]. The pathway to prevention study,

[5] Laura M. Jacobsen, Emily K. Sims; Going From Stage 2 to Stage 3 Type 1 Diabetes—Does Not Matter How You Got Here. *Diabetes Care* 20 February 2026; 49 (3): 378–380.

[6] Type1Screen – Screening for Type 1 Diabetes

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a TrialNet type 1 diabetes risk screening study has participating sites in Australia and is for people who are aged between 2 and 45 years who have a relative diagnosed with T1D or have tested positive for at least one T1D related autoantibody. There is also the ENDIA (Environmental Determinants of Islet Autoimmunity) Study, which screens and follows a cohort of children with a family history of T1D, from birth, to identify environmental and genetic factors associated with islet autoimmunity development. Although these studies provide some diagnostic coverage, they are limited to patients who have a relative diagnosed with T1D. While this aligns with the TN-10 inclusion criteria, these programs would not identify the Stage 2 T1D patients who do not a family history of T1D, which is estimated to be 90% of all T1D patients[7]. Outside of these programs, diagnosis currently relies on either patient/family or clinicians to identify potential signs of Stage 2 T1D, and as patients are often asymptomatic before Stage 3 T1D, this approach has limitations. The submission noted that few endocrinologists currently have patients diagnosed with Stage 2 T1D with most reporting limited or no caseload experience. This was attributed to the uncertain value of screening without an intervention. The submission stated that the availability of teplizumab would be expected to drive uptake of screening.

3.11 The submission assumed that a national screening program will be established in the future although acknowledged that the details are not yet known. Despite this, the submission assumed that a national screening program will be implemented for six-year-olds. This program was modelled in the financial estimates, with six-year-olds commencing in Year 3 of the proposed listing (2029) and becoming eligible for teplizumab when they turn eight in Year 5 of the proposed listing (2031).

3.12 The evaluation and Sub-Committees considered very few eligible patients would be identified in the absence of national population-based screening. Currently, it is estimated that for every person diagnosed, eight more people are living with early, pre-symptomatic stages of type 1 diabetes (T1D) [8]. The pre-PBAC response disagreed that very few patients will be identified in the absence of a national screening program, stating that MBS-reimbursed tests and screening in the research setting are available. It was stated that screening aims to identify people with early-stage T1D and offer them early education, and support as part of routine care. The response stated there is growing interest regarding the active management of pre-symptomatic T1D within the clinical community.

3.13 The PSCR noted beyond MBS-funded autoantibody and dysglycaemia testing identified in the submission, targeted screening is already accessed via Type1Screen, Pathway to Prevention Study, and the ENDIA (Environmental Determinants of Islet Autoimmunity) Study.

3.14 The Sub-Committees noted the proposed restriction included testing for pancreatic islet autoantibodies, oral glucose tolerance, HbA1c, or plasma glucose to support the

[7] Steck AK, Rewers MJ. Genetics of type 1 diabetes. *Clin Chem*. 2011;57(2):176-185.
[8] https://breakthrought1d.org.au/app/uploads/2025/11/Cost-Of-Not-Knowing-Report-Digital-Single-Page.pdf

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diagnosis of a patient with suspected Stage 2 T1D, and that these services would be eligible for a Medicare benefit where they meet the relevant item descriptors and are clinically relevant. However, Medicare benefits are not payable for services that are not reasonably required for the management of the patient's condition. This includes broad population screening or testing undertaken in the absence of clinical indication.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 T1D is a chronic autoimmune condition characterised by the destruction of insulin-producing β-cells in the pancreas, resulting in insulin deficiency[9]. The underlying physiology involves an immune-mediated process in which autoreactive T cells target and progressively destroy pancreatic β-cells. As β-cell mass declines, insulin secretion becomes insufficient to regulate blood glucose[10]. In the absence of insulin, glucose cannot be effectively taken up by peripheral tissues, leading to persistent hyperglycaemia[11].

4.2 T1D has significant health impacts even when well managed[12]. In the short term, individuals are at risk of hypoglycaemia due to insulin therapy[13] and diabetic ketoacidosis in the setting of insulin deficiency[14]. Over the long term, chronic hyperglycaemia contributes to microvascular complications, including diabetic retinopathy, which can lead to vision loss, diabetic nephropathy, which may progress to chronic kidney disease, and diabetic neuropathy, which causes pain and sensory impairment[15]. Macrovascular complications are also increased, with higher risks of coronary artery disease, stroke, and peripheral vascular disease[16]. These risks are reduced with good glycaemic control but are not completely eliminated.

[9] Lucier J MP. Type 1 Diabetes. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK507713/: Treasure Island (FL): StatPearls Publishing; 2024.

[10] Aamodt KI, Powers AC. The pathophysiology, presentation and classification of Type 1 diabetes. Diabetes Obes Metab. 2025 Aug;27 Suppl 6(Suppl 6):15-27.

[11] Ghimire P DA. Ketoacidosis. https://www.ncbi.nlm.nih.gov/books/NBK534848/: Treasure Island (FL): StatPearls Publishing; 2023.

[12] Colom C, Rull A, Sanchez-Quesada JL, Pérez A. Cardiovascular Disease in Type 1 Diabetes Mellitus: Epidemiology and Management of Cardiovascular Risk. *J Clin Med*. 2021 Apr 20;10(8).

[13] Urakami T. Severe Hypoglycemia: Is It Still a Threat for Children and Adolescents With Type 1 Diabetes? *Front Endocrinol (Lausanne)*. 2020;11:609.

[14] Dhatariya KK. Defining and characterising diabetic ketoacidosis in adults. *Diabetes Res Clin Pract*. 2019 Sep;155:107797.

[15] Kulkarni A, Thool AR, Daigavane S. Understanding the Clinical Relationship Between Diabetic Retinopathy, Nephropathy, and Neuropathy: A Comprehensive Review. *Cureus*. 2024 Mar;16(3):e56674.

[16] Zakir M, Ahuja N, Surksha MA, Sachdev R, Kalariya Y, Nasir M, et al. Cardiovascular Complications of Diabetes: From Microvascular to Macrovascular Pathways. *Cureus*. 2023 Sep;15(9):e45835.

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4.3 T1D is now understood to develop through distinct stages prior to clinical diagnosis[17]. Stage 1 is defined by the presence of two or more diabetes-related autoantibodies with normal blood glucose levels and no symptoms. Stage 2 involves ongoing autoimmunity with the development of dysglycaemia, where blood glucose levels become abnormal, but symptoms are still absent. Stage 3 corresponds to clinical disease, characterised by symptomatic hyperglycaemia, including polyuria, polydipsia, weight loss, and fatigue, and often presenting with diabetic ketoacidosis[18]. Importantly, although the preclinical stages are well defined, most individuals are still diagnosed at Stage 3 in routine clinical practice.

4.4 In Australia, T1D affects approximately 134,000 to 145,000 people[19], representing around 10% of all diabetes cases. The incidence is approximately 12 cases per 100,000 population annually, with a peak in children aged 10 to 14 years and a slight predominance in males. Among children and adolescents aged 0 to 19 years, around 13,000 are living with the condition[20].

4.5 Teplizumab is a CD3-directed monoclonal antibody. It preserves β-cell function by binding to CD3 on T lymphocytes. This may delay the onset of Stage 3 T1D in Stage 2 patients. The mechanism may involve partial agonistic signalling and deactivation of pancreatic β-cell autoreactive T lymphocytes. Teplizumab leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.

4.6 The submission proposed that the place in therapy for teplizumab is after patients are diagnosed with Stage 2 T1D but before they develop Stage 3 T1D. Treatment with teplizumab is proposed to delay (but not prevent) the onset and subsequent treatment of Stage 3 T1D. Treatment for Stage 3 T1D consists of insulin therapy, either injection or an insulin pump, blood sugar monitoring, and lifestyle changes. Insulin is known to generally be safe, and is widely used, but has some known risks such as hypoglycaemia and injection site reactions[21].

4.7 The submission stated that teplizumab treatment in Stage 2 T1D improves glycaemic measures and metabolic stability, and delays the onset of Stage 3 T1D. The submission claimed that each additional year free from clinical T1D represents a meaningful reduction in lifetime glycaemic burden and downstream complication risk (Rawshani,

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[17] Breakthrough T1D. The stages of type 1 diabetes and why they're important [Internet]. 2025 [cited 2026 May 14]. Available from: https://breakthrought1d.org.au/app/uploads/2025/03/Stages-of-T1D-V2.pdf

[18] Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015 Oct;38(10):1964-74.

[19] Isitt JJ, Roze S, Tilden D, Arora N, Palmer AJ, Jones T, et al. Long-term cost-effectiveness of Dexcom G6 real-time continuous glucose monitoring system in people with type 1 diabetes in Australia. *Diabet Med*. 2022 Jul;39(7):e14831

[20] AIHW. Diabetes: Australian facts: AIHW, Australian Government2024

[21] Podwojniak A, Flemming J, Tan IJ, Ghani H, Neubauer Z, Jones A. Cutaneous adverse effects from diabetes devices in pediatric patients with type 1 diabetes mellitus: systematic review. *JMIR Dermatol*. 2024;7:e59824.

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et al., 2018), which may support early intervention with teplizumab once stage 2 disease is identified.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated best supportive care (BSC) as the main comparator (referred to as established clinical management [ECM] in the economic evaluation). The main justification for this nomination was that there is no currently listed PBS medicine for the proposed population. Current clinical management of Stage 2 T1D consists of metabolic monitoring for progression as well as education and psychosocial support. The Sub-Committees considered the nominated comparator was appropriate.

5.2 With regard to subsequent treatments, the submission claimed that use of teplizumab will postpone the onset of Stage 3 T1D, thereby maintaining glycaemic control for additional years and therefore delay the need for exogenous insulin. The submission model assumed that the components of disease management will be the same for the teplizumab and ECM groups after progression to Stage 3 T1D, however teplizumab-treated patients spend less time in the Stage 3 T1D health state.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The hearing described the impact of a diagnosis of Stage 3 T1D on patients and their families, and the complexities of managing the condition, particularly for children and young adults. It was noted that awareness is increasing in the clinical community regarding identification of people with stage 2 T1D. There is increasing interest in T1D screening and increasing enrolment in pilot studies of T1D screening.

6.2 The clinical expert indicated that delaying a diagnosis of Stage 3 T1D by 2 years would particularly benefit children who may be better able to manage T1D with greater developmental maturity. It was highlighted that delayed progression would increase the time available for children and families to prepare for an eventual diagnosis. Other potential benefits from delayed progression to Stage 3 T1D were reduced exposure to hypoglycaemia and diabetic ketoacidosis during that 2 year period. The hearing referred to a study of people with T1D (Rawshani et al 2018) that reported substantially higher mortality and cardiovascular disease in patients diagnosed with T1D before 10 years of age. However, the clinical expert confirmed the study did not demonstrate that a substantial reduction in the lifetime risk of cardiovascular disease would occur from a two-year delay in diagnosis for a child treated with teplizumab aged 8 years old and diagnosed with Stage 3 T1D at 10 years old. The clinical expert

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advised that patients treated with teplizumab appeared to have better HbA1c which could plausibly lead to better long-term cardiovascular outcomes. The PBAC noted that Rawshani et al 2018 reported an adjusted hazard ratio of 4·11 (95% CI: 3·24, 5·22) for all-cause mortality for people who were diagnosed with T1D at 0-10 years compared to 3·21 (95% CI: 2·58, 4·00) for people diagnosed aged 11-15 years. The PBAC also noted that the Rawshani 2018 study which included patients registered in the Swedish National Diabetes Register (NDR) between 1998 and 2012, may not reflect contemporary practice, and that improvements in clinical practice over time (e.g. continuous glucose monitoring) should lead to reductions in long-term complications.

6.3 The PBAC considered that the hearing was informative as it provided a clinical perspective on the impacts to patients and families of a delay in diagnosis of Stage 3 T1D, particularly for children and young adults.

Consumer inputs

6.4 The PBAC noted and welcomed the input from individuals (82), health care professionals (3) and organisations (5) via the Office of Health Technology Assessment Consultation Hub. The inputs described the substantial impact of Stage 3 T1D on patients and their families, including the need to carefully monitor blood glucose levels and diet, as well as managing insulin requirements and the risks of hypoglycaemia. The inputs highlighted the significant psychological impact of Stage 3 T1D including: anxiety; emotional distress; fear of hypoglycaemia (particularly at night); and reduced confidence in participating in regular activities. The inputs reported that delaying the onset of Stage 3 T1D would allow children to be older and better able to manage their T1D, and provide patients and families more time to prepare for Stage 3 T1D.

6.5 The effectiveness of teplizumab was noted to depend on early identification of 'at-risk' individuals, particularly those in Stage 2 of the disease. While it was acknowledged the treatment effect is temporary and does not prevent eventual progression to T1D, contributors consistently stated the delay provides valuable time. This was described as enabling families to prepare for disease management and offering hope for future advances in treatment. Contributors also reported uncertainty regarding long-term safety, eligibility criteria, and cost.

6.6 The input from medical organisations included Australia and New Zealand Society for Paediatric Endocrinology and Diabetes Incorporated, Australian Diabetes Educators Association, Australian Diabetes Society and Queensland Children's Hospital. The medical organisations described how Stage 2 and 3 T1D are currently treated. It was noted that teplizumab does not cure T1D but has been shown to slow the progression of the disease. The input discussed advantages of teplizumab including the potential to delay the need for daily insulin and reduce diabetes-related complications. The input also described disadvantages of teplizumab, including the administration

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regimen which requires two weeks of intravenous infusions that requires hospitalisation, and lack of information about long-term effects.

6.7 The input from Breakthrough T1D described teplizumab as a significant advancement for early intervention and proactive management of T1D, that could reduce or delay the risk of short- and long-term complications. It was noted that even with optimal care, every year lived with T1D increases the risk of serious health complications. In the short term, hypoglycaemia (low blood glucose) can cause sweating, dizziness, confusion, weakness and blurred vision, and in severe cases may lead to seizures, loss of consciousness and death. While hyperglycaemia (high blood glucose) can result in DKA in the short term, over time, it contributes to long-term complications including diabetic retinopathy, kidney disease, nerve damage and cardiovascular disease. The input emphasized that for many people living with T1D, even delaying the onset of insulin-dependent disease by months or years would have a profound impact on quality of life, health outcomes and emotional wellbeing. Some potential concerns in relation to teplizumab have been identified including potential side effects, such as nausea, headaches, fatigue and rash. Other concerns in relation to teplizumab may include: uncertainty around how long the therapy will delay progression to stage 3 T1D; the possibility that the therapy may not work equally well for all individuals; concerns about receiving a relatively new therapy, and the intensity and invasiveness of receiving daily infusions over 14 consecutive days, particularly when an individual may not yet have symptoms.

6.8 With regard to general population screening, Breakthrough T1D noted there is a need for general population screening to support access to emerging disease-modifying therapies such as teplizumab. It was noted that most diagnoses occur suddenly and without warning, often only once a person has become seriously unwell. Without population-level screening, it is unlikely that many individuals would be identified during stage 2 T1D, when therapies such as teplizumab would be effective. It was noted that the Type 1 Diabetes National Screening Pilot, supported by Breakthrough T1D, is being piloted across the country, demonstrating the feasibility of broader implementation. Screening is also available to families with a relative living with T1D through Type1Screen, another Breakthrough T1D-supported initiative.

Clinical trials

6.9 The submission was based on one head-to-head trial comparing teplizumab to placebo, the TN-10 trial (n=76). TN-10 was a phase 2, randomised, placebo-controlled, double-blind trial of teplizumab involving relatives of patients with type 1 diabetes who did not have clinical symptoms of diabetes but were at high risk for development of clinical disease (defined as Stage 2 T1D). Patients were randomly assigned to a single 14-day course of teplizumab or placebo and a follow-up for progression to clinical type 1 diabetes (defined as Stage 3 T1D) was performed with the use of oral glucose-tolerance tests at 6-month intervals. Of the study population, 55 (72%) were ≤18 years of age at randomisation.

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6.10 Details of the trial and associated reports presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
TN-10 ClinicalTrials.gov number, NCT01030861 (TN-10) NCT04270942 (TN-10 Extension)	TN-10 CSR Herold KC, Bundy BN, Long A et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. Sims EK, Bundy BN, Stier K et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Lledo-Delgado A, Preston-Hurlburt P, Currie S et al. Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes.	03 September 2020 *NEJM* 2019; 381(7), 603-613 *Sci. Transl. Med* 2021; *13*, eabc8980. *J Clin Invest* 2024: 134(18), e177492.

Source: Table 2-3, p38 of the submission.
CSR = clinical study report.

6.11 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Teplizumab vs. placebo						
TN-10	76	R, DB, MC	Low	Patients aged 8 to 45 with Stage 2 T1D*	Time to onset of Stage 3 T1D C-peptide levels Safety	Time to onset of Stage 3 T1D

Source: Table 2-4, pp41-42, Table 2-16, pp47-48, Table 2-7, pp48-49, and Table 2-10, pp55-57 of the submission.
DB = double blind; MC = multi-centre; R = randomised; T1D = type 1 diabetes.
* Two or more diabetes-related autoantibodies detected in two samples obtained within 6 months before randomisation (1 sample for those <18 years) and evidence of a dysglycemia during an oral glucose tolerance test.

6.12 Initially, the protocol for the TN-10 trial required the enrolment of 144 participants. However, because of slower than anticipated enrolment, this was revised to require a minimum of 71 participants. After the change in protocol, the TN-10 trial was designed to continue until 40 patients (just over half) had received a diagnosis of Stage 3 T1D. This allowed for the detection of a 60% lower risk of Stage 3 T1D in the teplizumab arm than with the placebo arm, with 80% statistical power at an alpha level of 0.025.

6.13 44 participants were enrolled to the teplizumab group and 32 to the placebo group. The submission stated that the randomisation process may have resulted in unequal numbers because of the small number of participants at some study sites, randomisation stratification, or other unknown factors. The Sub-Committees considered given the small study size and the imbalance in participant numbers between treatment arms, there would be uncertainty regarding the magnitude and durability of the estimated treatment effect. Additionally, there was an imbalance in the proportion of participants under 18 years of age in each of the arms of the study. The teplizumab arm had 65.9% of participants under 18 years old while the placebo arm had 81.3% of participants under the age of 18. The evaluation considered it was unknown what impact this may have had on outcomes.

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6.14 In the key TN-10 trial participants were randomised to receive either a 14-day course of teplizumab or placebo. The treatment course was administered on study Days 0-13. The two treatment arms were:

- Arm #1: A 14-day course of teplizumab consisting of daily intravenous (IV) doses of:
  - Day 0: 51 µg/m^2
  - Day 1: 103 µg/m^2
  - Day 2: 207 µg/m^2 and
  - Day 3: 413 µg/m^2
  - Days 4 to 13: 826 µg/m^2
- Arm #2: A 14-day course of IV placebo only.

6.15 The dosing regimen used in the TN-10 trial does not align with the dosing regimen detailed in the product information (PI). The dosing regimen in the PI is an IV infusion (over a minimum of 30 minutes), using a BSA-based dosing, once daily for 14 consecutive days as follows:

- Day 1: 65 µg/m^2
- Day 2: 125 µg/m^2
- Day 3: 250 µg/m^2
- Day 4: 500 µg/m^2
- Days 5 through 14: 1030 µg/m^2

6.16 The submission stated that this difference was due to a change in the manufacturing process for teplizumab which resulted in the commercial product of teplizumab being different to the product that was used in the trial. The submission stated that the updated dosing regimen and formulation matched the total exposure, peak concentration, as well as trough concentrations after the last dose, in comparison to the clinical trial product during the 14-day regimen.

6.17 The data cut-off (DCO) for the primary analysis was November 2018 with a median duration of follow-up of 24.4 months. The second DCO was March 2020 with a median duration of follow-up of 30.3 months. The extended follow-up had a DCO of July 2023 with a median duration of follow up of 80.46 months (6.71 years). Participants were monitored every three months using either an oral glucose tolerance test (OGTT) or a random non-fasting glucose level. Additionally, at each visit and via routine contact between visits, participants were asked about the presence or absence of symptoms associated with diabetes. If a participant responded affirmatively to any of the questions or if any of the post-prandial glucose values were greater than 200 mg/dL [11.1 mmol/L], further evaluation, including fasting glucose or an OGTT, was performed.

6.18 Overall, the risk of bias for the key trial was considered low. Due to the differences in adverse events (AEs) (e.g. 43.2% of participants in the teplizumab group had rash-related AEs, while no participants in the placebo group did), it is possible that some patients were unblinded. However, as the diagnosis of Stage 3 T1D required laboratory testing by blinded researchers, it is not likely that unblinding would have

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had a significant impact. Subjective outcomes such as health-related quality of life (HRQoL) were not measured in the trial.

6.19 Treatment compliance was high across both arms of the trial with 93.2% of participants in the teplizumab arm and 87.5% of participants in the placebo arm receiving all 14 doses of study drug. Although the compliance rate across the two arms was similar, the small number of patients in the trial may not have allowed for a full characterisation of treatment compliance.

6.20 The submission provided an overview of six real world studies in an Appendix to the submission, including three studies with results available: Mahesh et al 2025 (Retrospective observational real world cohort study); Karakus et al 2026 (Prospective observational real-world cohort study) and O'Donnell et al 2025 (Cross-sectional observational study (online survey).

Comparative effectiveness

6.21 The results for the primary outcome of time to onset of stage 3 T1D are summarised in Table 4. The Kaplan-Meier (KM) curves are presented for the November 2018 primary DCO (Figure 1), the March 2020 secondary DCO (Figure 2), and the July 2023 extended follow-up DCO (Figure 3).

Table 4: Summary of clinical effectiveness: time from randomisation to onset of Stage 3 T1D

DCO	Teplizumab		Placebo		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
	n/N (%)	median time to Stage 3 T1D	n/N (%)	median time to Stage 3 T1D			
November 2018[a]	20/44 (45%)	49.5 months	23/32 (72%)	24.9 months	24.6 months	**p=0.0066**	**0.41 (0.22, 0.78)**
March 2020[b]	22/44 (50%)	59.6 months	25/32 (78%)	27.1 months	32.5 months	**p=0.01**	0.46 (NR)
July 2023[c]	28/44 (64%)	52.2 months	28/32 (87.5%)	27.3 months	24.9 months	**p=0.0026**	NR

Source: Table 2-11, p59 of the submission, Lledo-Delgado et al 2024.
CI = confidence interval; DCO = data cut-off; n = number of participants reporting data; N = total participants in group; NR = not reported; T1D = type 1 diabetes.
Bold indicates statistically significant results.
[a] Median duration of follow up for the November 2018 DCO was 24.4 months.
[b] Median duration of follow up for the March 2020 DCO was 30.3 months.
[c] Median duration of follow up for the July 2023 DCO was 80.46 months.

6.22 At the November 2018 primary DCO, patients treated with teplizumab reported a median elapsed time to stage 3 T1D of 49.5 months compared to patients treated with placebo who reported a median elapsed time of 24.9 months. This corresponds to a statistically significant difference of 24.6 months (hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.22, 0.78). At the March 2020 secondary DCO the difference had increased to 32.5 months (HR: 0.46, 95% CI not reported). However, the difference in median time to onset of stage 3 T1D had reduced to 24.9 months at the July 2023 DCO.

6.23 There was a trend towards an increasing HR as the trial progressed. As seen in Table 5, early time points have HRs that are more favourable to teplizumab, this was likely due to the large number of Stage 3 T1D diagnoses in the placebo arm that occurred

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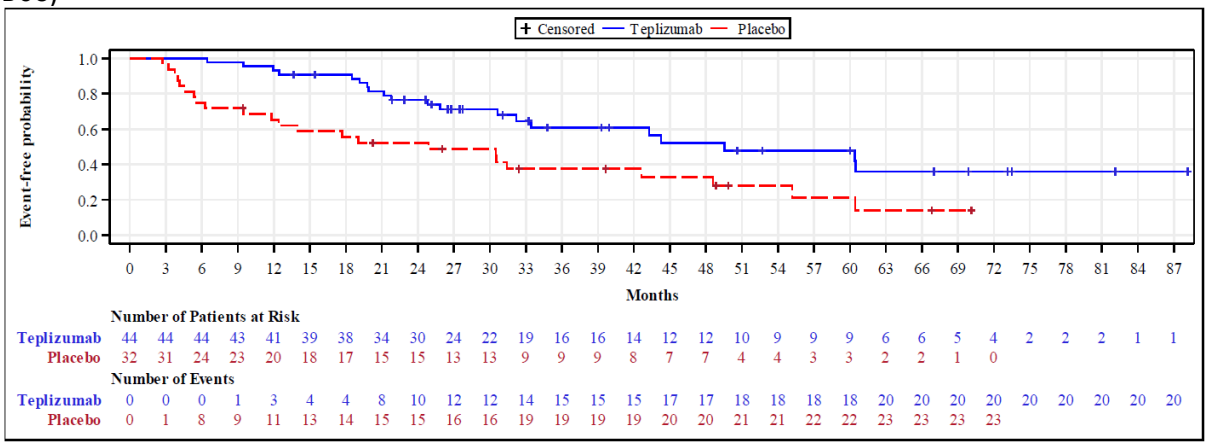
during the first year of follow-up. The change in HR over time could reflect random chance e.g. differing age distributions of enrolled patients over the years, a slight waning of effect in the teplizumab arm over time, or differences in censoring of patients over time. In conjunction with the small patient numbers, this means that the magnitude and direction of treatment effect in each year of the trial should be interpreted with caution.

Table 5: Yearly interval and cumulative hazard ratios of time to Stage 3 T1D onset (ITT population, November 2018 primary DCO)

	No. (%) T1D diagnosed			Hazard Ratio (95% CI)	
Year	Teplizumab	Placebo	Chi Square Test	Cumulative	Interval
1	4 (9.1)	13 (40.6)	9.16	0.177 (0.0576, 0.5432)	0.177 (0.0576, 0.5432)
2	8 (18.2)	3 (9.4)	5.92	0.394 (0.1859, 0.8340)	1.215 (0.3224, 4.5806)
3	3 (6.8)	3 (9.4)	6.58	0.411 (0.2087, 0.8108)	0.502 (0.1012, 2.4868)
4	3 (6.8)	2 (6.3)	6.09	0.452 (0.2404, 0.8491)	0.853 (0.1426, 5.1067)
5	2 (4.5)	2 (6.3)	7.16	0.440 (0.2409, 0.8026)	0.338 (0.0474, 2.4025)

Source: Table 2-12, p60 of the submission.
CI = confidence interval; DCO = data cut-off; ITT = intention to treat; T1D = type 1 diabetes.

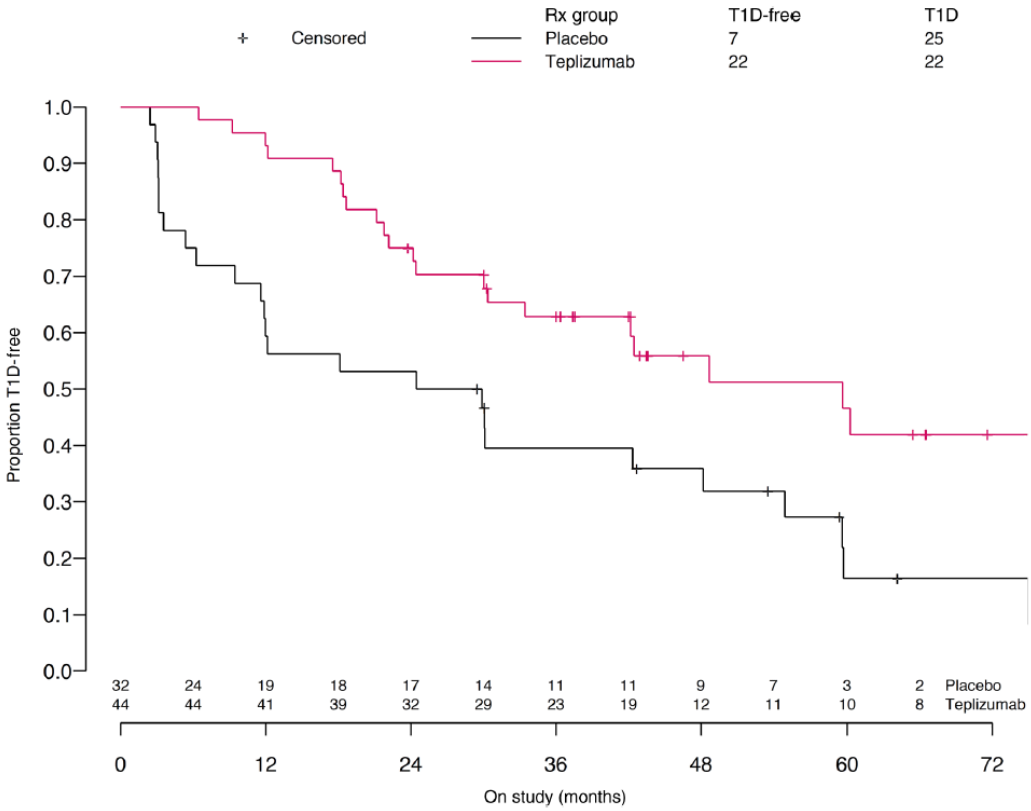
Figure 1: Kaplan-Meier curve of time to T1D diagnosis by treatment group (ITT population, November 2018 primary DCO)



Source: Figure 2-3, p60 of the submission.
DCO = data cut-off; ITT = intention to treat; T1D = type 1 diabetes.

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Figure 2: Kaplan-Meier curve of time to T1D diagnosis by treatment group (Sims extended follow-up, March 2020 secondary DCO)

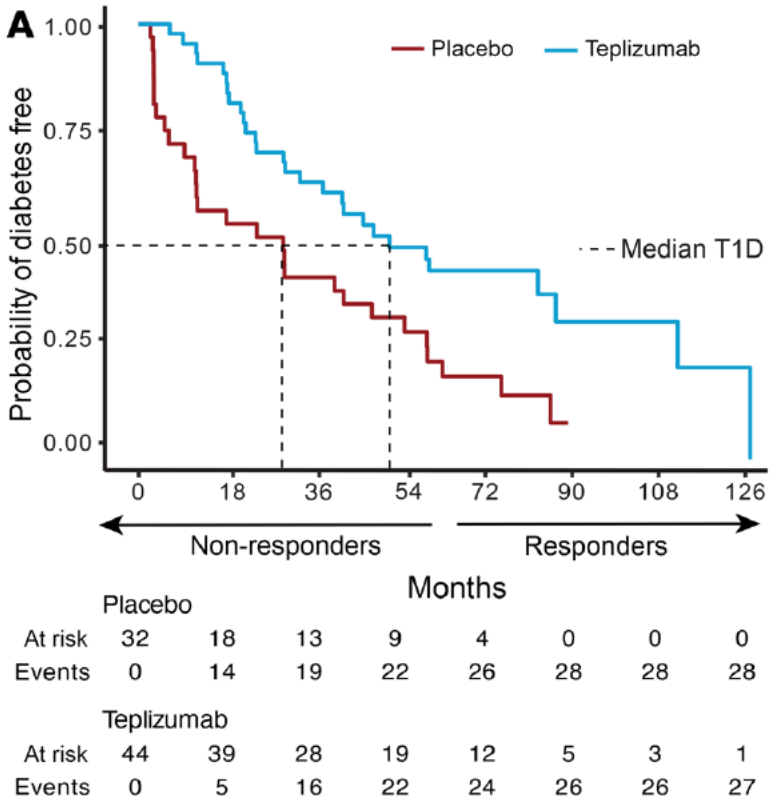


Source: Figure 2-8, p64 of the submission.
DCO = data cut-off; T1D = type 1 diabetes.

6.24 The pre-PBAC response suggested that the KM curves for the March 2020 data cut off based on 30.3 months median follow-up (Figure 2) showed no evidence of convergence of placebo and teplizumab groups, however the pre-PBAC response did not acknowledge that the corresponding KM curves for the July 2023 data cut-off based on 80.5 months median follow-up (Figure 3) indicated that almost all participants had progressed to T1D diagnosis which was the basis of the Sub-Committee's advice to assume convergence between years 8 and 15 in the economic model (paragraph 6.71).

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Figure 3: Kaplan-Meier curve of time to T1D diagnosis by treatment group (Lledo-Delgado, July 2023 extended follow-up DCO)



Placebo								
At risk	32	18	13	9	4	0	0	0
Events	0	14	19	22	26	28	28	28
Teplizumab								
At risk	44	39	28	19	12	5	3	1
Events	0	5	16	22	24	26	26	27

Source: Figure 2-9, p65 of the submission.
DCO = data cut-off; T1D = type 1 diabetes.

6.25 Notably, a large number of placebo subjects converted to stage 3 T1D during the first year, resulting in this period showing the greatest difference in number of events (stage 3 T1D onset) compared to teplizumab. The Sub-Committees noted that in the extended follow-up there were no patients at risk in the placebo arm and only 5 in the teplizumab arm at 7.5 years, with no data beyond 10 years. Censoring was not explicitly shown in the KM curve in Lledo-Delgado 2024 (see Figure 3), however supplementary data provided on the journal website indicated that 16 patients in the teplizumab arm and 4 patients in the placebo arm were censored at the time of the analysis[22].

6.26 In the primary analysis, eighteen subjects had follow-up durations <12 months, including 14 placebo participants and 4 teplizumab participants. Of these participants, 16 were diagnosed with stage 3 T1D, 13 receiving placebo and 3 receiving teplizumab. Six participants had early study terminations. Three of these (2 placebo and one teplizumab) were diagnosed with Stage 3 T1D, thus meeting the primary endpoint (T1D onset) and were already included in the primary endpoint analysis. For the other

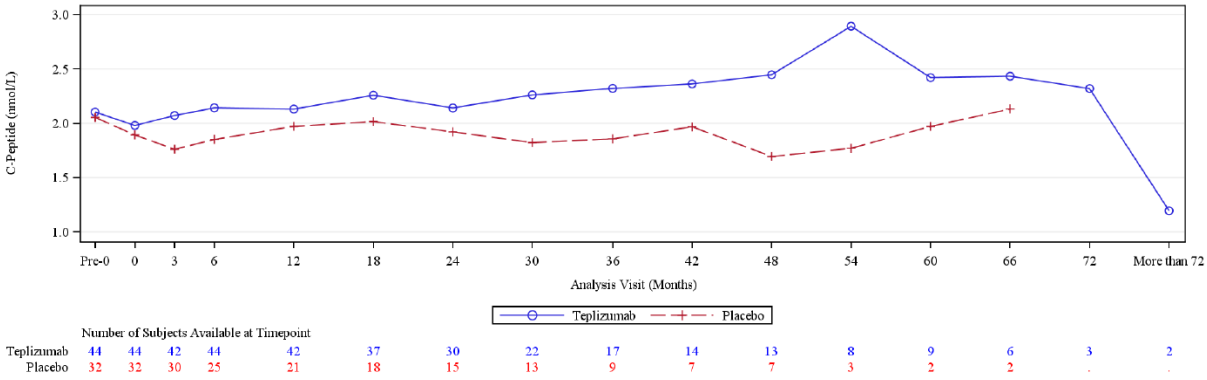
[22] JCI177492.sdval.xlsx available from https://www.jci.org/articles/view/177492#sd.

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3 participants (one placebo and 2 teplizumab), 2 withdrew consent and one was lost to follow-up.

6.27 C-peptide was assessed as a marker for β-cell function and endogenous insulin production, with preserved C-peptide levels indicating more residual β-cell mass and endogenous insulin production. Figure 4 presents the absolute mean C-peptide area under the curve (AUC) values over time, including the pre-baseline value.

Figure 4: Absolute mean C-peptide AUC values in 2-hour OGTT including pre-baseline value (ITT population)



Source: Figure 2-10, p66 of the submission.
AUC = area under the curve; ITT = intention to treat; OGTT = oral glucose tolerance test.

6.28 The submission included other measures of C-peptide level, glucose, and insulin sensitivity. The results of these measures supported the results of the primary outcome, indicating that patients treated with teplizumab retain β-cell function longer than patients who received placebo.

Comparative harms

6.29 Table 6 presents a summary of the treatment emergent adverse events (TEAEs) in the TN-10 trial. A total of 43 (97.7%) participants in the teplizumab group and 22 (68.8%) participants in the placebo group had at least 1 TEAE. There were no deaths in the study. Treatment-emergent serious adverse events (SAEs) occurred in 7 (15.9%) people in the teplizumab arm and 1 (3.1%) in the placebo arm. Three people discontinued study treatment because of TEAEs, including 1 (2.3%) receiving teplizumab and 2 (6.3%) receiving placebo.

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Table 6: Summary of key adverse events in the TN-10 trial

People with at least 1:	Teplizumab N=44 n (%)	Placebo N=32 n (%)	RD (95% CI) RR (95% CI)
TEAE	43 (97.7)	22 (68.8)	0.29 (0.12, 0.46) 1.42 (1.12, 1.80)
Treatment-emergent AESI[a]	4 (9.1)	0	0.09 (0.01, 0.18) -
Treatment-emergent SAE	7 (15.9)	1 (3.1)	0.13 (0.00, 0.25) 5.09 (0.65, 39.36)
TEAE leading to treatment interruption	1 (2.3)	0	0.02 (-0.02, 0.07) -
TEAE leading to dose reduction[b]	3 (6.8)	4 (12.5)	-0.06 (-0.19, 0.08) 0.55 (0.13, 2.27)
TEAE leading to treatment withdrawal[c]	1 (2.3)	2 (6.3)	-0.04 (-0.13, 0.06) 0.36 (0.03, 3.84)
TEAE related to study drug	42 (95.5)	11 (34.4)	0.61 (0.44, 0.79) 2.78 (1.71, 4.50)
Death	0	0	- -

Source: Table 2-16, p70 of the submission.

AESI = adverse event of special interest; ALT = alanine transaminase; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event; WBC = white blood cell.

Risk differences and relative risks were calculated during the evaluation using StataMP 18.

[a] The AESIs were grade 3 events of cellulitis, gastroenteritis, pneumonia, and wound infection.

[b] The reasons for dose reduction or withholding for teplizumab included 1 case each of rash, vomiting and increased WBC, and ALT increased. The reasons for dose reduction or withholding for placebo subjects included 2 cases of protocol specified criteria (hyperbilirubinemia) and 1 case each of insufficient blood withdrawn and lack of IV access.

[c] The participant in the teplizumab who discontinued treatment was due to increased ALT. The two placebo participants who withdrew were both due to hyperbilirubinemia.

6.30 The most common adverse events (AEs) reported in the teplizumab group were lymphopaenia (72.7% vs. 6.3% in placebo), leukopaenia (20.5% vs. 0% in placebo), pruritic rash (15.9% vs. 0% in placebo), and nasopharyngitis (15.9% vs. 6.2% in placebo). When all rash-related terms (including rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic, and urticaria) are combined, 19 of 44 (43.2%) subjects in the teplizumab group had rash-related AEs. The most common AEs in the placebo arm were headache (9.4% vs. 11.4% in teplizumab) and vomiting (6.3% vs. 4.5% in teplizumab).

6.31 Infections and infestations were reported in 23 (52.3%) teplizumab participants and 8 (25.0%) placebo participants. The most common infections reported were nasopharyngitis (7 [15.9%] in the teplizumab arm and 2 [6.3%] in the placebo arm), pneumonia (4 [9.1%] in the teplizumab arm and 1 [3.1%] in the placebo arm), sinusitis (4 [9.1%] in the teplizumab arm and 1 [3.1%] in the placebo arm) and upper respiratory infection (4 [9.1%] in the teplizumab arm and 1 [3.1%] in the placebo arm). No participants discontinued participation in the trial due to these AEs.

6.32 Eight (18.2%) participants had a total of 9 serious adverse events (SAEs) during the study, including 7 (15.9%) people in the teplizumab arm and 1 (3.1%) in the placebo group. In the teplizumab arm, 1 participant experienced 2 SAEs (dizziness and ankle fracture). The other SAEs in the teplizumab arm were: 4 participants experienced

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infections (pneumonia, cellulitis, wound infection, and gastroenteritis); 1 experienced serum sickness; and 1 experienced musculoskeletal pain. One SAE was reported in the placebo arm (pelvi-ureteric obstruction).

6.33 Due to the small number of patients in the trial, it is possible that the comparative safety of teplizumab compared to placebo was not completely characterised. The product information for teplizumab noted that its use would be subject to additional monitoring including for liver enzymes and bilirubin, for signs and symptoms of infection, white blood cell counts, and blood glucose levels.

6.34 The extended assessment of comparative harms identified cytokine release syndrome, lymphopaenia, serious infections, and hypersensitivity reactions as safety concerns. An integrated safety analysis of five clinical trials of teplizumab in 1,018 people with Stage 2 T1D (TN-10) or Stage 3 T1D (AbATE, Protégé, Encore and Delay) found that the majority of AEs were grade 1 or 2 in severity and resolved without intervention. Although most AEs in the integrated safety analysis were grade 1 or grade 2, 59% of patients that received teplizumab experienced a grade 3 AE compared with 22.9% of patients who received placebo. In this analysis the rates of cytokine release syndrome were 5.8% and 1.2% for participants treated with teplizumab or control, respectively. Additionally, a study of subcutaneous teplizumab for psoriasis was terminated when the first patient enrolled developed an injection site reaction that met the study stopping criteria. However, the psoriasis study delivered teplizumab subcutaneously while the proposed delivery mechanism for stage 2 T1D is via infusion[23].

6.35 The trial did not collect HRQoL data. It is likely that treatment with teplizumab would have an impact on HRQoL as patients are required to undergo two weeks of daily infusions and have an increased risk of AEs. The need for repeated healthcare visits, potential infusion related discomfort, and the psychosocial impact of treatment have the potential to negatively affect HRQoL. The PSCR suggested that teplizumab treatment effects were transient and manageable. The PSCR also stated that, based on a market research survey of Australian endocrinologists (n=44), the diagnosis of Stage 2 T1D would significantly impact patients QoL and the submission assumed teplizumab-induced Stage 3 transition delay translated into equivalent delay for all progressive QoL decline occurring throughout Stage 3, maintained for life. The Sub-Committees did not consider this interpretation of lifetime QoL gains was reasonable, given the limitations of the evidence.

Benefits/harms

6.36 A summary of the comparative benefits and harms for teplizumab versus placebo is presented in Table 7.

[23] https://clinicaltrials.gov/study/NCT00954915?term=NCT00954915&viewType=Card&rank=1

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Table 7: Summary of comparative benefits and harms for teplizumab and placebo

Time to diagnosis of T1D, November 2018 primary DCO (median follow up: 24.4 months)				
Event	**teplizumab**	**placebo**	**Absolute Difference**	**HR (95% CI)**
Progressed to T1D at 12 months, n (%)	3/44 (7%)	11/20 (34%)	27%	**0.41 (0.22, 0.78) p=0.0066**
Progressed to T1D at 24 months, n (%)	10/44 (23%)	15/32 (47%)	24%	
Median time to T1D, months	49.5 months	24.9 months	24.6 months	
Time to diagnosis of T1D, March 2020 secondary DCO (median follow up: 30.3 months)				
Progressed to T1D, n (%)	22/44 (50%)	25/32 (78%)	28%	0.46 (NR)
Median time to T1D, months	59.6 months	27.1 months	32.5 months	**p=0.01**
Time to diagnosis of T1D, July 2023 (median follow up: 80.46 months)				
Progressed to T1D, n (%)	28/44 (64%)	28/32 (88%)	24%	NR (NR)
Median time to T1D, months	52.2 months	27.3 months	24.9 months	**p=0.0026**

Harms						
	teplizumab n/N	**PBO n/N**	**RR# (95% CI)**	**Event rate/100 patients***		**RD# (95% CI)**
				teplizumab	**PBO**	
SAE	7/44	1/32	5.09 (0.65, 39.36)	16	3	0.13 (0.00, 0.25)
Lymphopaenia	32/44	2/32	11.64 (3.00, 45.07)	73	6	0.66 (0.51, 0.82)
Leukopaenia	9/44	0/32	-	21	0	0.21 (0.09, 0.32)
Rash pruritic	7/44	0/32	-	16	0	0.16 (0.05, 0.27)

Source: Figure 2-3, p60, Table 2-11, p59, and Table 2-18, p72 of the submission.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; PBO = placebo; RD = risk difference; RR = risk ratio; T1D = type 1 diabetes.
* Median duration of follow-up: Trial I = 24.4 months.
# calculated during the evaluation using StataMP 18.
Bold = statistically significant.

6.37 On the basis of the direct evidence presented by the submission, for every 100 patients treated with teplizumab in comparison with placebo over a median duration of follow-up of 24.4 months:

- Approximately 27 fewer patients would progress to Stage 3 T1D at 12 months.
- Approximately 24 fewer patients would progress to Stage 3 T1D at 24 months.
- Approximately 67 additional patients would have abnormally low lymphocyte counts
- Approximately 21 additional patients would have abnormally low white blood cell counts.
- Approximately 16 additional patients would experience an itchy rash.
- Additionally, an extended safety analysis of 5 teplizumab studies indicated that for every 100 patients treated with teplizumab in comparison with placebo, 5 additional patients would experience cytokine release syndrome.

Clinical claim

6.38 The submission described teplizumab as superior in terms of effectiveness compared to placebo. The Sub-Committees considered this claim was adequately supported by the TN-10 trial and extended follow-up (median follow-up 80.46 months; 6.7 years),

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however the extent of clinical benefit beyond the trial duration is uncertain, noting the small size of the study (n=76). In the TN-10 trial the primary outcome was time to onset of Stage 3 T1D. At the November 2018 primary DCO (median follow-up: 24.4 months), the patients treated with teplizumab reported a median elapsed time to Stage 3 T1D of 49.5 months compared to patients treated with placebo who reported a median elapsed time of 24.9 months. This corresponds to a statistically significant difference of 24.6 months (HR 0.41, 95% CI 0.22, 0.78). At the November 2020 secondary DCO (median follow-up: 30.3 months) the difference had increased to 32.5 months, however the hazard ratio was less favourable with longer follow-up (HR: 0.46, 95% CI: not reported). These results indicate that patients treated with teplizumab have a statistically significant delay in progression to Stage 3 T1D when compared to patients treated with placebo. However the evaluation considered that, due to the changes in HR over time, the small number of patients in the trial, the different number of patients in each arm, and the change in dosing regimen, the results should be interpreted with caution as these factors introduce uncertainty into the magnitude of benefit. Overall, the Sub-Committees considered the teplizumab was likely effective at delaying the onset of Stage 3 T1D by approximately 2 years, however the value of this was uncertain as there was no information on the health-related quality of life (HRQoL) gained or the impact on long-term macrovascular and microvascular complications from this delay. The Sub-Committees noted the PSCR claims in paragraph 6.35; however, considered that an interpretation of lifetime gains in QoL was not supported by the evidence.

6.39 The submission described teplizumab as inferior in terms of safety compared to placebo. The Sub-Committees considered this claim was adequately supported. In the TN-10 trial 97.7% of participants in the teplizumab arm and 68.8% of participants in the placebo arm had at least 1 TEAE. Treatment-emergent SAEs occurred in 15.9% of people in the teplizumab arm and 3.1% in the placebo arm. More patients in the teplizumab groups reported lymphopaenia (72.7% vs. 6.3%), leukopenia (20.5% vs. 0%) and infections and infestations (52.3% vs. 25%), with 43.2% of participants in the teplizumab group had rash-related AEs, compared with zero in the placebo group. Due to the small number of participants in the trial, it is possible that the comparative safety of teplizumab compared to placebo was insufficiently characterised.

6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable as the clinical trial demonstrated that teplizumab was effective at delaying the onset of Stage 3 T1D compared with placebo in the TN-10 trial and extended follow-up. However, the PBAC considered that the magnitude of long-term clinical benefits was uncertain, noting there was no evidence that teplizumab would lead to improved outcomes over a patient's lifetime compared with BSC as claimed by the submission.

6.41 The PBAC considered that the claim of inferior comparative safety was reasonable.

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Economic analysis

6.42 The submission presented a stepped economic evaluation for the use of teplizumab in patients aged 8 years or older with Stage 2 T1D for the purpose of delaying the onset of stage 3 T1D. The economic evaluation was based on the direct randomised trial, TN-10, which compared treatment with teplizumab to established clinical management (ECM). The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.43 The key components of the economic evaluation are summarised in Table 8.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Teplizumab vs ECM
Time horizon	Lifetime time horizon in the model base case versus vs a median follow-up of 24.9 months in the TN-10 trial (primary analysis).
Outcomes	LYs gained, QALYs gained
Methods used to generate results	Markov cohort model
Health states	Stage 2 T1D, stage 3 T1D and Dead
Cycle length	6 months
Transition probabilities	Stage 2T1D → Stage 3T1D: transitions were based on extrapolation of the time-to-event curves from the TN-10 trial via the fitting of independent parametric functions to the observed KM data. KM data were utilised until 42 months in the teplizumab arm and 28 months in the ECM arm of the model. In the base case analysis, log-normal and exponential functions were fitted to the KM data in the teplizumab and ECM arms, respectively. Stage 2 T1D → dead: the risk of transitioning to the death health state was assumed to be equal to the risk of all-cause mortality as observed in the general population (sourced from Australian life-tables ([2022-2024]). Stage 3 T1D → dead: the risk of transitioning to the dead health state was assumed to be higher than the all-cause mortality in the general population. HRs of 1.57 and 1.285 were applied to the risk of mortality in the general population for patients aged < 18 years old and for patients aged ≥ 18 years, respectively. The HRs were sourced from a Swedish Diabetes registry. An alternate approach, that used a multi-regression model to determine the risk of mortality, was also presented in the submission. The probability of remaining in the stage 3 T1D health state was calculated as: 1 – the probability of transitioning to the dead health state.
Health related quality of life	HRQoL data were not collected in the trial. Utility values for patients in the stage 2 and 3 T1D health states were estimated based on disutility values associated with the diagnosis of stage 2 (0.075) and stage 3 disease (0.025), reported in literature, and applied to general population utility values. Disutility values for stage 3 disease (0.0621) and ongoing aggregated disutility values - based on time spent in the stage 3 disease health state - were applied to general population disutility values. A carer disutility of 0.04, applied at the rate of 1.78 carers per patient, was also included for all patients younger than 25 years of age.
Costs	Direct treatment costs, costs for ongoing disease management (glucose monitoring, insulin and long-term complications), costs for DKA and costs for the management of AEs were included.

Source: tabulated during the evaluation, from Table 3-1, p86 of the submission and the "Attachment 4.1 – Tzield CEM March 2026" workbook provided in the submission.
DKA = diabetic ketoacidosis; ECM = established clinical management; HRQoL = health-related quality-of-life; KM = Kaplan-Meier; LYs = life-years; QALYs = quality-adjusted life-years; T1D = Type 1 diabetes.

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6.44 The submission constructed a Markov model with three health states: stage 2 T1D, Stage 3 T1D and dead. All patients entered the model in the stage 2 T1D health state and could receive teplizumab or ECM.

6.45 The submission assumed that there will be no change to screening rates for T1D in clinical practice. However, the evaluation considered that if teplizumab were listed, screening would likely increase owing to the availability of a therapy option. Screening and auto antibody testing are integral to patient diagnosis and treatment eligibility. Thus, it may have been appropriate to include these costs in the economic analysis. The positive yield rates of these tests are relatively low, which would increase the average additional test expenditure per teplizumab-eligible patient. The exclusion of screening/diagnostic costs from the analysis favoured teplizumab.

6.46 The submission modelled a population with a starting age of 13.58 years, which represented the median age in the TN-10 trial (although the age distribution was skewed, and the mean age was approximately 19 years). The study age distribution appears likely consistent with Australian clinical practice where a majority of people are diagnosed between the ages of 10 and 14 (per AIHW 2021 data[24]). Subgroup analyses of the TN-10 trial suggested that the treatment effect in terms of the HR of progression did not differ by age (<18 years or ≥18 years). However, the model assumed an ongoing benefit over a lifetime, and therefore the modelled absolute benefit is reduced as the patient treatment age is increased. Given the right-skewed age distribution, modelling the cohort with only one starting age, rather than a distribution of ages, likely favoured teplizumab.

6.47 The submission nominated a lifetime time horizon in the base case, compared to a median follow-up of 24.4 months in the TN-10 trial primary DCO. A high degree of uncertainty surrounding the implicit assumptions associated with the lifetime analysis were noted during the evaluation. These were related to: i) the accuracy of the extrapolations utilised to estimate the transition probabilities from the Stage 2 T1D health state to the Stage 3 T1D health state, which were based on a small sample size of 76 patients enrolled in the TN-10 trial, ii) the use of observed Kaplan-Meier (KM) data of only 42 and 28 months duration in the teplizumab and ECM arms, respectively, extrapolated over the modelled lifetime time horizon (average lifespan of ~86 years) and iii) the assumption that teplizumab not only delays the onset of Stage 3 T1D but, in turn, also equally delays the progressive decline in QoL assumed to occur throughout the Stage 3 T1D health state. The Sub-Committees believed that a significantly shorter time horizon would be more appropriate given the multiplicity of uncertainties associated with assumptions over a lifetime time horizon. The ICER was sensitive to shorter time horizons of 25 and 30 years, increasing by [redacted]% and [redacted]%, from the revised base case ICER of $115,000 to < $135,000/QALY, respectively.

[24] https://www.aihw.gov.au/reports/diabetes/diabetes/contents/how-common-is-diabetes/type-1-diabetes

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6.48 The transition probabilities from the Stage 2 T1D health state to the Stage 3 T1D health state were determined via fitting of independent parametric functions to the time to clinical diabetes onset curves from the TN-10 trial, extrapolated over the modelled lifetime time horizon. In the base case, the log-normal and exponential functions were utilised for extrapolation in the teplizumab and ECM arms, respectively. The parametric functions were chosen based on goodness-of-fit statistics using Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC) values, clinical plausibility and visual inspection. However, as noted previously, the parametric functions were based on a small sample size (44 and 32 patients in the teplizumab and ECM arms, respectively), making them inherently uncertain. Further, the selected function predicted more than 10% of patients in the teplizumab arm remained unprogressed at year 15 in the model, which was not consistent with extended follow-up data (July 2023 data cut-off) from the TN-10 trial reported by Lledo-Delgado et al (2024).[25] The evaluation considered in the absence of supportive long-term data, the estimate that 10% of patients remained unprogressed at 15 years appeared overly optimistic. The ICER was highly sensitive to this, increasing by [redacted]% from the revised base case when the extrapolated curve is converged to the SOC curve between years 8 and 15. The PSCR stated that the KM curves showed no convergence at 30.3 months, providing evidence against imminent treatment effect waning and suggested these data contradicted an assumption of waning between years 8–15. The Sub-Committees advised the extended follow-up DCO from TN-10 suggests the teplizumab curve in the model is very optimistic (see paragraph 6.25). The pre-PBAC response disagreed with the Sub-Committee's advice, suggesting that the KM data from the analysis at 30.3 months median follow-up showed a strengthening of the treatment effect of teplizumab over time. However, the pre-PBAC response did not address the concerns raised in the evaluation regarding the less favourable HRs that were reported with longer follow-up and the reduced difference between treatment groups reported in the Lledo-Delgado et al (2024) analysis at 80.5 months median follow-up (see para 6.22, 6.38).

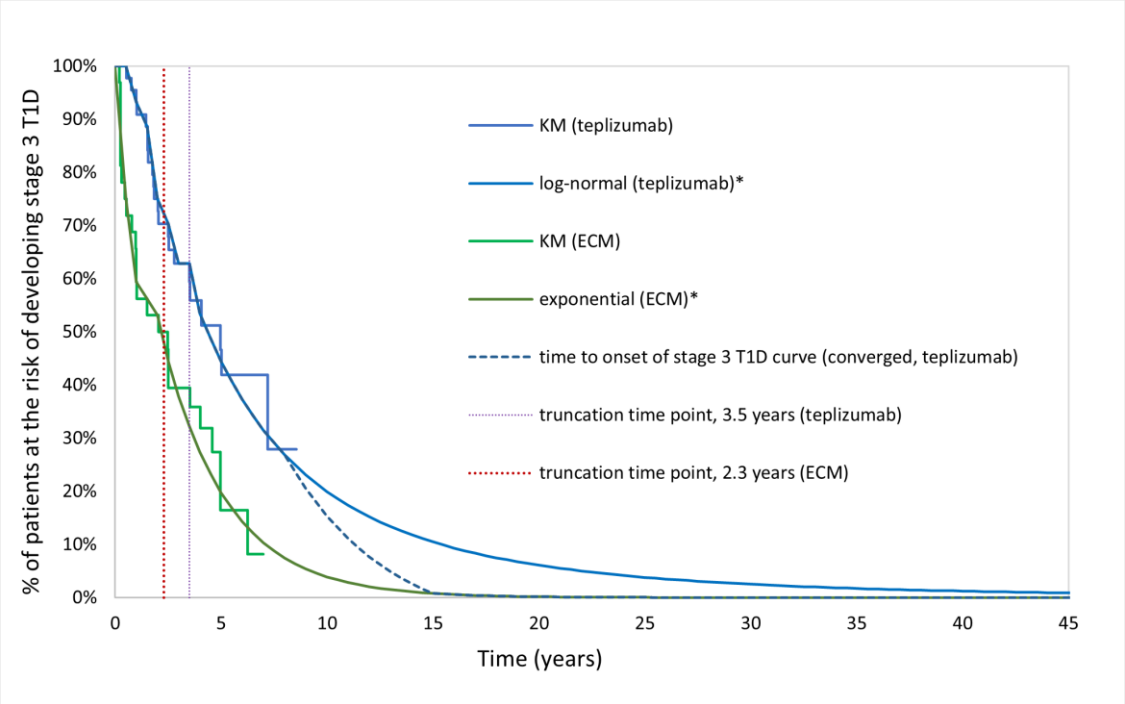
6.49 KM data were used until the time point at which it became unreliable based on the Gebski criterion[26], i.e., until 42 months and 28 months in the teplizumab and ECM arms, respectively. The model was marginally sensitive to the use of shorter observed KM data in the ECM arm. When 42 months of observed data are used in both the teplizumab and ECM arms (8 of 32 patients are still at risk of progressing to stage 3 disease in the ECM arm), the ICER increased by [redacted]% to $135,000 to < $155,000/QALY. The modelled and observed time-to-event curves for both treatment arms are presented in Figure 5.

[25] Lledó-Delgado A, Preston-Hurlburt P, Currie S, Clark P, Linsley PS, Long SA, et al. Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes. J Clin Invest. 2024 Aug 13;134(18).

[26] Gebski V, Garès V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. Int J Epidemiol. 2018 Jun 1;47(3):850-9.

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Figure 5: Modelled vs observed time to Stage 3 T1D onset curves (both treatment arms)



Source: constructed during the evaluation, from the "Attachment 4.1 – Tzield CEM March 2026" workbook provided in the submission
ECM = established clinical management; KM = Kaplan-Meier

6.50 The transition probabilities from the stage 2 T1D health state to the dead health state were assumed to be equal to the general population all-cause related mortality which was consistent with published literature on pre-symptomatic T1D. Since early diagnosis and ongoing monitoring of T1D is likely to reduce the risk of a DKA event, the Sub-Committees considered this assumption was likely reasonable.

6.51 Transition probabilities for transitions from the Stage 3 T1D health state to the death health state could not be estimated from the trial data as there were no deaths in the TN-10 trial. Thus, the submission estimated the transition probabilities by applying age-stratified HRs for mortality due to diabetes to Australian general population all-cause mortality rates. The risk of mortality was based on a publication by Rawshani et al (2018)[27]. The model assumed that all patients enter the model at 13.58 years of age. HRs of 1.57 and 1.285 were applied when patients were aged < 18 years and ≥ 18 years, respectively. The HR of 1.57 that was applied to all patients aged < 18 years was based on a Swedish National Diabetes Registry study that reported on mortality risk in children and young adults with type 1 diabetes.[28] In the absence of Australian

[27] Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson A-M, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. The Lancet. 2018;392(10146):477-86.

[28] Samuelsson J, Bertilsson R, Bülow E, Carlsson S, Åkesson S, Eliasson B, et al. Autoimmune comorbidity in type 1 diabetes and its association with metabolic control and mortality risk in young people: a population-based study. Diabetologia. 2024 Apr;67(4):679-89.

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literature to inform the transition probabilities for patients in this health state, the evaluation considered these estimates were reasonable. The HR of 1.285 applied to adult patients was calculated in the submission and was based on a meta-analysis which reported that the risk ratio of mortality for adult patients was approximately half that observed in patients aged <18 years of age.[29] The submission presented an alternate approach for modelling mortality via the use of a regression model. The Sub-Committees considered mortality risk for Stage 3 T1D was uncertain but, as the population is young, mortality occurs late in the model and hence was not a major driver of the ICER.

6.52 The submission modelled the following health outcomes: life years (LYs) gained and quality adjusted life-years (QALYs) gained. Since HRQoL data were not collected in the trial, disutility values relating to Stage 2 T1D (at diagnosis) and Stage 3 T1D (at diagnosis), versus the general population, and ongoing disutility associated with disease duration were sourced from published literature on T1D. The disutility values were applied to the Australian general population utility values reported for individuals aged < 18 years[30] and those aged ≥ 18 years[31]. The evaluation considered that the general population utility values used in the base case were appropriate. However, a number of issues were identified regarding the modelling of health outcomes in the Stage 2 and Stage 3 T1D health states as discussed below.

6.53 The submission assumed that patients with Stage 2 T1D have the same HRQoL as individuals in the general population. However, a disutility of 0.075 associated with a diagnosis of Stage 2 T1D was applied to the general population utility values for patients in the ECM arm of the model only, for one cycle. This was based on a UK cross-sectional vignette-based survey of 300 participants aged ≥ 18 years[32]. The study reported that access to an effective treatment option for Stage 2 T1D was associated with a perceived benefit of 0.075, which was applied for one cycle. The evaluation noted several issues regarding the inclusion of this disutility. It was noted that applying a disutility for lack of access to a treatment option effectively double counts the benefits associated with teplizumab treatment. Furthermore, the disutility estimate was based on HRQoL data from a vignette-based survey that used hypothetical health status scenarios and reported a pooled baseline utility of 0.837 for all participants.

[29] Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PM. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. PLoS One. 2014;9(11):e113635.

[30] Le LK, Richards-Jones S, Chatterton ML, Engel L, Lawrence D, Stevenson C, et al. Australian adolescent population norms for the child health utility index 9D-results from the young minds matter survey. Qual Life Res. 2021 Oct;30(10):2895-906.

[31] Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D–5L, and relationships with sociodemographic characteristics. Quality of Life Research. 2024 2024/03/01;33(3):721-33.

[32] Guenther O, Abdul Jabbar OA, Bonnemaire M, Mahieu A, Mitchell H, Nicholls C. PCR263 Valuing Health States When Transitioning From Stage 2 to Stage 3 Type 1 Diabetes in a Sample of the General Population in the United Kingdom. Value in Health. 2025;28(12):S601.

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Thus, it is uncertain whether the change from baseline was apparent in each group separately, and whether baseline differences, bias or confounding contributed to the reported difference in each group from the pooled baseline. The PSCR stated that this disutility is associated with the futility of having a diagnosis for a chronic condition but no available treatment. However, the Sub-Committees did not agree with the PSCR about futility of the diagnosis, noting that diagnosis of Stage 2 T1D patients would allow an opportunity to be better informed about the consequences of Stage 3 T1D and being better able to manage their HbA1c and potentially avoid diabetic ketoacidosis (DKA) events. The Sub-Committees considered the inclusion of this disutility was inappropriate and noted the ICER was highly sensitive to the removal of this disutility, increasing by [redacted]% to $155,000 to < $255,000/QALY from the revised base case of $115,000 to < $135,000/QALY.

6.54 The submission did not include infusion related disutility for patients treated with teplizumab (claimed to be in line with previous PBAC advice relating to IV infusions); however as noted by the evaluation, this may not be reasonable for this submission. Given that teplizumab is administered intravenously over 14 days, to non-symptomatic patients (often children), a tangible reduction in QoL over the treatment period would be expected. Thus, the evaluation proposed that application of an infusion-related disutility to patients treated with teplizumab may have been appropriate.

6.55 For patients progressing to the stage 3 T1D health state, disutility was applied in three ways: a one-cycle disutility of 0.025 at diagnosis of Stage 3 T1D, a baseline disutility of 0.0621 less than the general population, and further ongoing accumulating disutility based on time since Stage 3 diagnosis (i.e., the model assumed worsening of QoL each year after transition to Stage 3). Overall, the additive application of three different disutilities introduces unnecessary complexity in the economic model.

6.56 The disutility on diagnosis of Stage 3 T1D and ongoing disutilities associated with time of onset of Stage 3 T1D was based on a Swedish population-based study (Sparring et al 2013[33]) which included 839 individuals with diabetes and 1,564 matched controls. HRQoL data was collected using the EQ-5D instrument with disutilities reported for patients based on time from diagnosis, i.e., 8, 15 and 24 years since diagnosis. The HRQoL of patients with 1 year as the time from diagnosis was used as a reference value. Given that patients are typically diagnosed with Stage 3 T1D following a DKA event, have clinical manifestations of the disease and have to initiate insulin treatment via pumps or injections, the Sub-Committees considered the application of a disutility associated with the diagnosis of Stage 3 T1D is likely to be reasonable. The ongoing aggregated disutilities applied in the model were based on a linear regression model, y = 0.0031x, wherein x represents the years since disease onset and y is the resulting

[33] Sparring V, Nyström L, Wahlström R, Jonsson PM, Ostman J, Burström K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15-34 years - a Swedish population-based study using EQ-5D. BMC Public Health. 2013 Apr 22;13:377.

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disutility value. The linear regression model assumed a continuous increase in disutility based on time since diagnosis for stage 3 disease, up to the maximum modelled age of 100 years. The evaluation considered this may not be reasonable as patients' QoL trajectories are highly variable and are also influenced by adaptation to the disease and management strategies. For patients who adequately control their disease, a plateau in the disutility associated with Stage 3 T1D would be expected. Further, the evaluation considered that the linear regression model was highly uncertain as it was based on 3 time points only (8, 15 and 24 years since diagnosis) while the model continued over 85 years. Since patients in the ECM arm spend more time in the Stage 3 T1D health state compared to patients in the teplizumab arm, this approach favours teplizumab. The Sub-Committees considered the linear decline for the duration of the model was inappropriate and likely double counts the disutility versus the general population (see paragraph 6.57 below). The pre-PBAC response proposed an alternative approach that it claimed was superior to the approach used in the submission and stated this was accepted by NICE. The pre-PBAC response proposed a revised base case which removed the linear decline in Stage 3 disutility based on Sparring 2013 and replaced this with an approach which it described as "NICE's piece-wise disutility approach". Limited information was provided in the response. This analysis was not evaluated.

6.57 A decrement of 0.0621 compared to the general population was also applied to patients in the Stage 3 T1D health state, based on a US HRQoL catalogue of chronic conditions, with UK preferences applied (Sullivan et al. 2011)[34]. The evaluation considered it was unclear why a decrement versus the general population was applied given that progressive disutilities were already anchored to the general population utility values and reflect the reduced HRQoL of individuals with diabetes. Thus, the application of the decrement versus the general population is likely to double count the disutility associated with stage 3 disease. The ICER is highly sensitive to the application of this disutility, increasing by [redacted]% from the revised base case ICER to $155,000 to < $255,000/QALY, when the decrement is removed. The pre-PBAC response retained the decrement estimated from Sullivan 2011.

6.58 The submission included carer disutility of 0.04 for all patients aged 25 or younger across both treatment arms owing to the deterioration of QoL for carers of adolescents or young adults with T1D. The disutility was based on a study conducted in Spain which reported utility values of 0.92 in caregivers of children (18 years old or younger) with T1D and utility value of 0.96 in the general population using the EQ-5D instrument. [35] In the base case analysis, the submission applied the disutility to 1.78 carers per family. In accordance with PBAC guidelines, the Sub-Committees advised

[34] Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011 Nov-Dec;31(6):800-4.

[35] López-Bastida J, López-Siguero JP, Oliva-Moreno J, Vázquez LA, Aranda-Reneo I, Reviriego J, et al. Health-related quality of life in type 1 diabetes mellitus pediatric patients and their caregivers in Spain: an observational cross-sectional study. Current Medical Research and Opinion. 2019 2019/09/02;35(9):1589-95.

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that HRQoL outcomes related to individuals other than those receiving treatment should not be included in the base case but can be presented as supplementary analyses. The ICER is highly sensitive to the inclusion of this disutility, increasing by [redacted]% from the submission's base case ICER when it is excluded.

6.59 Costs for 14 days of treatment with teplizumab, routine monitoring costs, costs for management of AEs, disease management costs (in the stage 2 T1D and stage 3 T1D health states) and a one-off cost associated with DKA events were included in the base case.

6.60 The submission estimated the total costs associated with ongoing management of Stage 3 T1D and costs arising from long-term complications using a linear regression model. The evaluation identified several issues with the estimation of total costs and disease management costs for patients in the Stage 3 T1D health state. These are discussed below.

6.61 Disease management in the Stage 3 T1D health state included costs for blood glucose monitoring, insulin pumps and insulin, healthcare resource utilisation (tests and specialist consultations) and private health insurance (PHI) premiums (as a cost to patients/carers). The submission proposed inclusion of PHI premiums on the basis that patients purchased or increased their level of PHI cover to assist with the costs of managing T1D. The evaluation noted that the cost of disease associated healthcare resources such as glucose monitoring devices, consumables, insulin pumps and insulin are costed directly in the analysis and generally subsidised by Government programs, although subsidy for insulin pumps is limited to people under 21. The submission estimated the costs associated with blood glucose monitoring via the use of continuous glucose monitoring devices (CGM), flash glucose monitoring devices (FGM) and blood glucose test strips. The evaluation noted that for CGM devices, the submission overestimated the total costs associated with blood glucose monitoring due to an error in the base case analysis. Costs for rapid-acting insulin used in insulin pumps, were based on PBS item 9224L (DPMQ of $101.58 per pack). The submission estimated that each script provides five 10 mL vials (100 units/mL), equivalent to 5,000 units. At an assumed usage of 30 units per day, one pack was estimated to last 167 days, resulting in 2.19 scripts per year and an annual insulin cost of $222.61. The evaluation noted that the submission did not provide any reference for the assumption that patients will require 30 units of insulin per day throughout the model, however the PBAC noted that the WHO Defined Daily Dose (DDD) for insulin is 40 units[36]. Further, insulin can no longer be dispensed under PBS item 9224L (as it is supply only until 1 October 2026). Thus, PBS items for pre-filled pen devices and cartridges for type 1 diabetes, i.e. PBS items 9040T and 12236B (100 unit/mL injection, 5 x 3 mL pen devices/cartridges) may have been more appropriate for the estimation of costs associated with insulin. The PSCR argued that PHI is purchased by patients to complement what the government programs cover. The PSCR stated that patients can

[36] https://atcddd.fhi.no/atc_ddd_index/?code=a10

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expect higher than average healthcare costs driven by T1D, and the market research survey of Australian endocrinologists (n=44) indicated that a high proportion of T1D patients purchase PHI. The Sub-Committees considered that, in line with the PBAC guidelines, the base case ICER should capture only direct healthcare resource use and costs. As PHI is not considered a direct cost of T1D management, its inclusion in the base case was inappropriate and it should only be considered in supplementary analyses.

6.62 Costs associated with long-term complications arising from T1D were also included in the base case analysis. The submission assumed that 40% of individuals will develop one or more long-term complications such as neuropathy and foot ulcers as reported in a JRDF report [37]. Annual costs of $35,000, for individuals aged between 10–20 years, were inflated to 2025 costs, i.e., $41,976 (based on the healthcare CPI). The costs were then adjusted to reflect direct healthcare expenditure, reported to be 24% of total costs. Thus, an annual cost of $2,729 associated with long-term complications was estimated in the submission. The validity of this estimate was uncertain as the source costs are based on a UK prevalent population and may not be applicable to the Australian population.

6.63 Based on literature which suggests increasing costs for management of diabetes with increasing age, the submission estimated the total Stage 3 T1D health state costs (costs for disease management and long-term complications) via linear regression models for total healthcare spending and diabetes related spending, based on age at diagnosis. The regression models made use of data points from the cost curves reported in a Taiwanese study that tracked healthcare spending of patients with diabetes over 14 years and only included patients up to the age of 40 [38]. The cost curves for total healthcare spending and diabetes-related spending, based on age at diagnosis, are presented in Figure 6.

[37] https://breakthrought1d.org.au/app/uploads/2025/03/The-economic-cost-of-T1D.pdf

[38] Ou HT, Yang CY, Wang JD, Hwang JS, Wu JS. Life Expectancy and Lifetime Health Care Expenditures for Type 1 Diabetes: A Nationwide Longitudinal Cohort of Incident Cases Followed for 14 Years. Value Health. 2016 Dec;19(8):976-84.

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Figure 6: Observed average health care costs (total and diabetes-related) based on age of onset, reported in Ou et. al, 2016

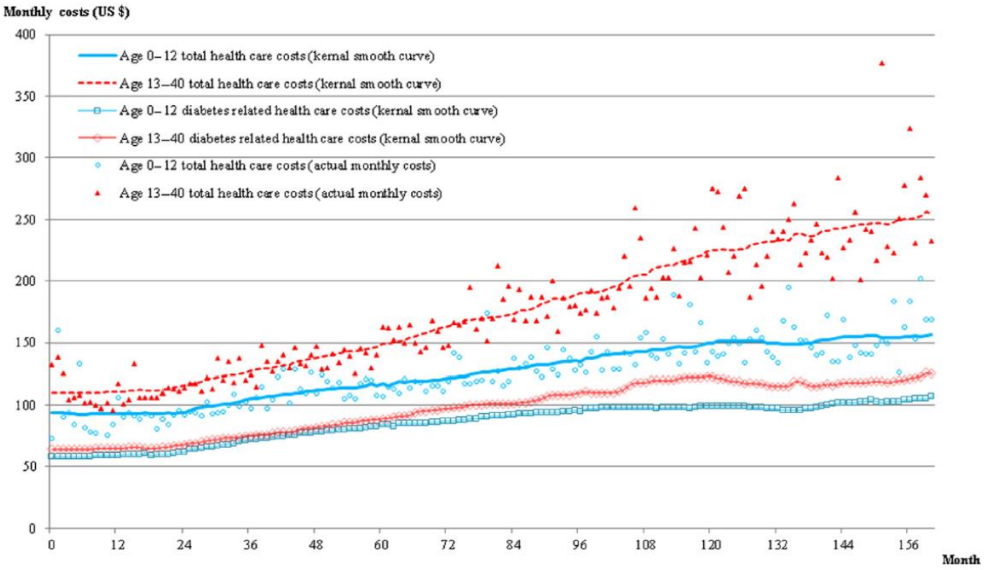


Fig. 2 – Observed average monthly total health care costs and diabetes-related health care costs for patients with early (0–12 y old) and late (13–40 y old) diagnosis of type 1 diabetes up to 14 years of follow-up.

Source: Figure 3-8, p121 of the submission.

6.64 Costs associated with disease management and long-term complications were based on regression models for total health care costs and diabetes-related health care costs, respectively. The evaluation considered it may not be reasonable to assume that disease management costs would continue to increase linearly over the modelled time horizon. Usage of insulin pumps, insulin, and requirements for medical services and consultations are likely to remain relatively stable over time. In addition, the cost curves for total healthcare expenditure reported in the study may include spending unrelated to diabetes. As such, it may have been more appropriate to apply fixed, ongoing disease management costs for patients in the Stage 3 T1D health state within the economic model. However, this could not be adjusted during the evaluation and therefore, the impact remains uncertain but is likely to be substantial. Furthermore, although costs linked to long-term complications may increase over time, the applicability of the observed cost trajectory for diabetes-related spending in the Taiwanese population to the Australian setting remains uncertain. Additionally, the study only included patients up to the age of 40. Given that the maximum modelled age in the submission is ~86 years, the extrapolation of the observed cost trajectory over the modelled time horizon introduces further uncertainty. The Sub-Committees noted that Stage 3 disease management costs ($75,092, revised down from $95,403 during the evaluation) represent a major offset compared to drug acquisition costs ($) (see Table 12).

6.65 A fortnightly allowance of $162 was included in the base case for all patients aged 16 or younger. As above, indirect social care costs should not be included in the base case

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analysis. Exclusion of the carer allowance has a minimal impact on the ICER (increases by [redacted]% from the submission's base case ICER), but the Sub-Committees agreed that this exclusion was appropriate.

6.66 The key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact Revised base case: $[redacted][1]/QALY gained
Treatment effect	Assumption of indefinitely maintained treatment effect assumed in the base case.	High, favours teplizumab, When it is assumed that teplizumab benefit is only associated with delay to progression to Stage 3, the ICER increases by [redacted]% to $[redacted][2]/QALY.
Time horizon	Lifetime time horizon in the base case	High, favours teplizumab. A shorter time horizon of 25 years increases the ICER by [redacted]% to $[redacted][2]/QALY.
Stage 3 disutility	A decrement of 0.0621 compared to the general population, applied in addition to the disutility at diagnosis of Stage 3T1D and ongoing progressive disutilities based on time since diagnosis of Stage 3 T1D.	High, favours teplizumab. Exclusion of the decrement versus the general population increases the ICER by [redacted]% to $[redacted][2]/QALY
Stage 2 disutility	A decrement of 0.075 (applied to general population utility values) to patients in the ECM arm only.	Moderate, favours teplizumab. Exclusion of the disutility increases the ICER by [redacted]% to $[redacted][2]/QALY.
Extrapolation	The log-normal and exponential functions utilised in the base case analysis to model transitions from the Stage 2 to Stage 3 T1D health states, respectively, across both treatment arms.	High, favours teplizumab. Alternate parametric functions have varied impacts on the ICER. In addition, when the curves are converged between years 8 and 15, the ICER increases by [redacted]% to $[redacted][2]/QALY.
Stage 3 costs	Ongoing disease management and long-term complications' costs estimated based on a linear regression model.	Uncertain (limited model flexibility) but likely to be high, favours teplizumab.

Source: tabulated during the evaluation.
ECM = established clinical management; ICER = incremental cost-effectiveness ratio; T1D = Type 1 diabetes.
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000*
[2] *$155,000 to < $255,000*

6.67 The results of the stepped economic evaluation are presented in Table 10. As noted above, the inclusion of carer disutility, carer allowance and PHI premium costs in the base case analysis was not reasonable. Further errors relating to the incorporation of RDI in estimation of teplizumab treatment costs, the estimation of drug administration costs, CGM system costs, BGL lancets costs and insulin costs were also identified during the evaluation. These were corrected during the evaluation, and the results of the revised base case are presented in Table 11.

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Table 10: Results of the stepped economic evaluation (submission)

Step and component	Teplizumab	ECM	Increment
Step 1: trial-based costs and outcomes (to 4 years follow-up)[a]			
Costs	$[redacted]	$0	$[redacted]
Time in stage 2 T1D (years)[a]	3.147	2.109	1.039
Incremental cost/year delay of stage 3 T1D			$[redacted][1]
Step 2: utility weights applied within trial period			
Costs	$[redacted]	$0	$[redacted]
QALYs	2.79	2.62	0.166
Incremental cost/QALY gained			$[redacted][2]
Step 3: incorporation of medical resources costs			
Costs	$[redacted]	$35,299	$[redacted]
QALYs	2.79	2.62	0.166
Incremental cost/QALY gained			$[redacted][3]
Step 4: extrapolated over the lifetime time horizon (discounted)			
Costs	$[redacted]	$636,038	$[redacted]
QALYs	14.590	14.029	0.560
Incremental cost/extra QALY gained (base case)			**$[redacted][4]**

Source: Table 3-33, p126 of the submission and sheets 'Model Engine_Tep' and 'Model Engine_NoTx' of the "Attachment 4.1 – Tzield CEM March 2026" workbook provided in the submission.

a. Truncated mean estimates. Follow up period approximates the 49.5 months of median follow up in the Sim publication.

ECM = established clinical management; LYG = life-years gained; QALYs = quality-adjusted life-years.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$755,000 to < $855,000*

[3] *$655,000 to < $755,000*

[4] *$55,000 to < $75,000*

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Table 11: Results of the stepped economic evaluation (revised)

Step and component	Teplizumab	ECM	Increment
Step 1: trial-based costs and outcomes (to 4 years follow-up)[a]			
Costs	$[redacted]	$0	$[redacted]
Time in stage 2 T1D (years)[a]	3.147	2.109	1.039
Incremental cost/year delay of stage 3 T1D			$[redacted][1]
Step 2: utility weights applied within trial period			
Costs	$[redacted]	$0	$[redacted]
QALYs	2.84	2.74	0.097
Incremental cost/QALY gained			$[redacted][2]
Step 3: incorporation of medical resources costs			
Costs	[redacted]	$24,639	$[redacted]
QALYs	2.84	2.74	0.097
Incremental cost/QALY gained			$[redacted][2]
Step 4: extrapolated over the lifetime time horizon (discounted)			
Costs	$[redacted]	$500,618	$[redacted]
QALYs	14.903	14.487	0.415
Incremental cost/extra QALY gained (revised base case)			**$**[redacted][1]

Source: tabulated during the evaluation from the "Attachment 4.1 – Tzield CEM March 2026" workbook provided in the submission.
Note: Revised estimates excluded RDI from teplizumab drug and administration costs, used MBS item 116 for administration costs, excluded PHI premiums, carer allowance, carer disutility and corrected errors identified with the estimation of CGM systems, BGL lancets and insulin.
a. Truncated mean estimates. Follow up period approximates the 49.5 months of median follow up in the Sim publication.
ECM = established clinical management; LYG = life-years gained; QALYs = quality-adjusted life-years.
Italics: corrections made during Sub-Committee consideration
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000*
[2] *> $1,055,000*

6.68 The disaggregated costs and outcomes for the economic analysis are presented in Table 12 and Table 13. The largest contributor to the incremental costs were the costs associated with teplizumab treatment. Treatment costs were largely offset by disease management costs in the Stage 3 T1D health state. Patients treated with teplizumab accrued substantially more benefits in the Stage 2 T1D health state compared to patients receiving ECM only. This was attributable to the delay in the onset of stage 3 disease in patients treated with teplizumab.

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Table 12: Disaggregated summary of the costs included in the economic evaluation (discounted)

	Teplizumab	ECM	Increment	% of increment
Drug acquisition	$[redacted]	$0	$[redacted]	[redacted]%
Revised	$[redacted]	$0	$[redacted]	[redacted]%
Drug administration	$1,753	$0	$1,753	[redacted]%
Revised	$1,252	$0	$1,252	[redacted]%
Adverse event management	$218	$0	$218	[redacted]%
Revised	-	-	-	[redacted]%
Treatment related HRU	$140	$0	$140	[redacted]%
Revised	-	-	-	[redacted]%
Disease management (stage 2)	$2,425	$1,304	$1,122	[redacted]%
Revised	-	-	-	[redacted]%
Disease management (stage 3)	$539,331	$634,735	($95,403)	-[redacted]%
Revised	$424,222	$499,314	($75,092)	-[redacted]%
Total	**$[redacted]**	**$636,038**	**$[redacted]**	**100%**
Revised	**$[redacted]**	**$500,618**	**$[redacted]**	**100%**

Source: Table 3-34, p127 of the submission.
Note: Revised estimates excluded RDI from teplizumab drug and administration costs, PHI premiums, carer allowance, carer disutility and corrected errors identified with the estimation of CGM systems, BGL lancets and insulin.
ECM = established clinical management; HRU = healthcare resource utilisation.

Table 13: Disaggregated summary of health outcomes included in the economic evaluation (discounted)

Outcome	Teplizumab	ECM	Increment	% of increment
LYs				
Stage 2	5.205	2.613	2.593	7,284.0%
Stage 3	14.675	17.232	-2.557	-7,184.0%
Total	**19.880**	**19.845**	**0.036**	**100%**
QALYs				
Stage 2	4.161	1.965	2.196	391.9%
Revised	**-**	**-**	**-**	528.74%
Stage 3	10.749	12.522	-1.773	-316.4%
Revised	**-**	**-**	**-**	-426.86%
Carer disutility	-0.313	-0.458	0.145	25.9%
Revised	0.00	0.00	0.00	-
AEs disutility	-0.0078	0.0000	-0.008	-1.4%
Revised	**-**	**-**	**-**	-1.86%
Total	**14.590**	**14.029**	**0.560**	**100%**
Revised	**14.903**	**14.487**	**0.415**	**100%**

Source: Table 3-36, p128 of the submission.
Note: Revised estimates excluded RDI from teplizumab drug and administration costs, PHI premiums, carer allowance, carer disutility and corrected errors identified with the estimation of CGM systems, BGL lancets and insulin.
ECM = established clinical management; LYs = life-years; QALYs = quality-adjusted life-years.

6.69 The results of key univariate and multivariate sensitivity analyses for the revised base case are summarised in Table 14.

Table 14: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change from baseline
Revised base case [a]	$[redacted]	0.415	$[redacted]	**-**

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Analyses	Incremental cost	Incremental QALY	ICER	% change from baseline
Discount rate (base case: 5% costs and outcomes)				
• 0% costs and outcomes	-$[redacted]	1.382	Dominant	-
• 3.5% costs and outcomes	$[redacted]	0.532	$[redacted][2]	-[redacted]%
Starting age of patients (base case: 13.58 years, median age in the TN-10 trial)				
• 19 years: mean age in TN-10	$[redacted]	0.394	$[redacted][3]	[redacted]%
Time horizon (base case: lifetime time horizon)				
• 10 years	$[redacted]	0.220	$[redacted][4]	[redacted]%
• 15 years (#1)	$[redacted]	0.270	$[redacted][5]	[redacted]%
• 25 years (#2)	$[redacted]	0.329	$[redacted][6]	[redacted]%
• 30 years (#3)	$[redacted]	0.348	$[redacted][3]	[redacted]%
• 40 years	$[redacted]	0.374	$[redacted][3]	[redacted]%
Treatment effect (base case: ongoing)				
• TEP benefit is only associated with delay to progression to stage 3. Once progressed, disease related disutility is equivalent to the comparator (i.e. no further treatment benefit)	$[redacted]	0.264	$[redacted][6]	[redacted]%
Extrapolation (base case: log-normal [teplizumab], exponential [ECM])				
• Weibull (teplizumab)	$[redacted]	0.341	$[redacted][6]	[redacted]%
• Gompertz (teplizumab)	$[redacted]	0.351	$[redacted][6]	[redacted]%
• Gamma (ECM)	$[redacted]	0.411	$[redacted][3]	[redacted]%
• Weibull (ECM)	$[redacted]	0.409	$[redacted][3]	[redacted]%
• Assume treatment waning between years 8 and 15 (#4)	$[redacted]	0.344	$[redacted][6]	[redacted]%
Utilities				
• Include carer utility	$[redacted]	0.560	$[redacted][7]	-[redacted]%
• Exclude disutility on diagnosis of stage 2 T1D in the ECM arm (#5)	$[redacted]	0.334	$[redacted][6]	[redacted]%
• Exclude disutility of stage 3 T1D versus general population (#6)	$[redacted]	0.257	$[redacted][6]	[redacted]%
Costs				
• 16.5 teplizumab vials per patient (patients with BSA>1.94 m^2)	$[redacted]	0.415	$[redacted][6]	[redacted]%
• Life expectancy of an insulin pump	$[redacted]	0.415	$[redacted][3]	[redacted]%
• Remove long-term complications in stage 3 T1D	$[redacted]	0.415	$[redacted][6]	[redacted]%

Source: tabulated during the evaluation from the "Attachment 4.1 – Tzield CEM March 2026" workbook provided in the submission.
[a] Revised base case corrects the following errors: teplizumab drug and administration costs (excluded RDI of 99.35% and MBS item 116 applied for administration), costs of CGM systems (revised to $650), BGL lancets (revised to $515.4), insulin costs (revised to $515.43) and excludes disutility associated with carers (0.04), PHI premium costs and fortnightly carer allowances.
BGLs = blood glucose levels; CGM = continuous glucose monitoring; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PHI = private health insurance; RDI = relative dose intensity; T1D = Type 1 diabetes.
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000*
[2] *$75,000 to < $95,000*
[3] *$135,000 to < $155,000*
[4] *$355,000 to < $455,000*
[5] *$255,000 to < $355,000*
[6] *$155,000 to < $255,000*
[7] *$95,000 to < $115,000*

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6.70 Given the uncertainty in the long-term treatment effect of teplizumab, and the uncertainties associated with the modelling of the health outcomes and costs in the Stage 3 T1D health state, a shorter time horizon is likely to increase the confidence in the results of the model presented in the submission. The impact of varying the time horizon on the revised base case ICER is presented in Figure 7.

Figure 7: Impact of varying the time horizon on the revised base case ICER



Source: constructed during the evaluation, from the 'Attachment 4.1 – Tzield CEM March 2026' workbook provided in the submission.
ICER = incremental cost-effectiveness ratio; SA = sensitivity analysis

6.71 The Sub-Committees suggested several parameter changes for consideration in a respecified base case:

- Revised base case from evaluation
- 25-year time horizon (#1)
- Assuming a proportion of patients (~5% as estimated by Sub-Committees) will require 2 vials for treatment between days 5 and 14 for those with a BSA>1.94 m^2 (#2)
- Convergence of the time to stage 3 T1D curves between years 8 and 15 (#3)
- Removal of ongoing aggregated disutilities for patients in the stage 3 T1D health state based on time since diagnosis (#4)
- Removal of disutility for patients with stage 2 T1D in the ECM arm (#5)

Results of the multivariate sensitivity analyses are provided in Table 15 below. Inclusion of all the revised parameter results in a respecified base case of $555,000 to < $655,000/QALY gained.

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Table 15: Results of the multivariate sensitivity analyses (MVSA)

Input	Incremental cost	Incremental QALYs	ICER	% change from baseline
Revised base case from evaluation[a]	$[redacted]	0.415	$[redacted][1]	-
MVSA results				
#1	$[redacted]	0.329	$[redacted][2]	[redacted]%
#1, #2	$[redacted]	0.329	$[redacted][2]	[redacted]%
#1, #2, #3	$[redacted]	0.286	$[redacted][3]	[redacted]%
#1, #2, #3, #4	$[redacted]	0.204	$[redacted][4]	[redacted]%
#1, #2, #3, #4, #5	$[redacted]	0.123	$[redacted][5]	[redacted]%

Source: Attachment 4.1 – Tzield CEM March 2026.

a Assumes 100% RDI for drug and administration costs, applies MBS item 116 fee for administration costs, excludes PHI premiums, carer allowances and carer disutility. Revised estimates also correct costs of CGM systems, BGL lancets and insulin.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$155,000 to < $255,000*

[3] *$255,000 to < $355,000*

[4] *$355,000 to < $455,000*

[5] *$555,000 to < $655,000*

6.72 The pre-PBAC response presented a revised base case that incorporated some of the sub-committee feedback:

- Accepted the evaluation's revised base case except relative dose intensity;
- Accepted advice to assume two vials for 5% of patients;
- Did not accept 25-year time horizon and instead retained the lifetime model time horizon;
- Did not accept convergence of the time to stage 3 T1D curves between years 8 and 15 and instead used a gamma extrapolation for ECM which reduced the incremental benefits of teplizumab
- Did not accept removal of ongoing aggregated disutilities for patients in the stage 3 T1D health state based on time since diagnosis, but removed the submission's approach (based on Sparring 2013) and replaced with a piece-wise disutility approach.
- Did not accept removal of disutility for patients with stage 2 T1D which the submission had inappropriately applied to the ECM arm only, and instead reduced the disutility arbitrarily from 0.075 to 0.049.

This resulted in an ICER of $255,000 to < $355,000/QALY gained.

6.73 The pre-PBAC response considered the 5% discount rate, as required in the PBAC Guidelines, to be high and considered this biased against teplizumab, which has a large upfront cost and longer-term benefits. The pre-PBAC response presented a supplementary analysis which included carer disutility, PHI costs and a discount rate of 3.5% which resulted in an ICER of $75,000 to < $95,000/QALY gained.

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Teplizumab cost/patient/course

6.74 The per patient cost for teplizumab, as used in the economic model and the financial estimations, was estimated to be $[redacted] (drug acquisition costs only), based on a cost of $[redacted] per vial and a treatment duration of 14 days (one vial per day). The submission adjusted the total treatment cost for the compliance observed in the TN-10 trial, i.e., 99.35%, which would not occur in practice if the whole course of treatment is dispensed in a single script as proposed by the submission (cost = $[redacted] per patient).

Table 16: Drug cost per patient for proposed drug

	Trial dose and duration	Model	Financial estimates
Mean number of vials	14	14	14
RDI	99.35%[a]	99.35%[a]	100%
Cost/patient/course	$[redacted][b]	$[redacted][b]	$[redacted]

Source: Table 3-1, p86 of the submission. Italicised values have been calculated.
[a] RDI of 99.35% observed in the TN-10 trial.
[b] RDI of 99.35% applied to total treatment cost of teplizumab. Estimated PBS usage & financial implications.

Estimated PBS usage and financial implications

6.75 This submission was considered jointly by DUSC and ESC. The submission used an epidemiological approach to estimate the number of patients each year who would be eligible for the proposed teplizumab treatment. A summary of the data sources and parameter values used to estimate the utilisation and financial impacts associated with the proposed listing of teplizumab for the treatment of Stage 2 T1D is shown in Table 17. The submission estimated that < 500 patients would be treated in Year 1, increasing to 500 to < 5,000 in Year 6 (in the presence of a National Screening Program) or < 500 in Year 6 (if the screening program is removed from the estimates) (Table 17). The evaluation considered these estimates appear very low in comparison to estimates of the number of Australians with early stages of diabetes. The Cost of Not Knowing report estimated that 25,000 Australians are unknowingly living in the early stages of the condition[39].

Table 17: Key inputs for financial estimates

Parameter	Value	Source	Commentary	Sub-Committees' comment
Incident population				
Incident Stage 3 T1D	4,030 in 2025	NDSS Data Snapshot December 2025	The population was new T1D patients who registered with the NDSS in 2025. This was an appropriate data source.	Appropriate as it reflects diagnosed Stage 3 only.

[39] https://breakthrought1d.org.au/app/uploads/2025/11/Cost-Of-Not-Knowing-Report-Digital-Single-Page.pdf

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Parameter	Value	Source	Commentary	Sub-Committees' comment
Annual growth	Constant at 3.8%	T1D index	The evaluation could not reproduce this value. The average annual growth between 2020 and 2025 was 2.21%. The annual growth reported in the same period by NDSS was 1.83%.	Overestimate. While there is a steady increase in diagnoses, Australia's age-standardized incidence rates for children and young adults have otherwise remained stable (AIHW).
FDR per Stage 3 patient	[redacted][1]	Assumption	It was uncertain how many of these patients would already be captured in the incident and prevalent populations.	Uncertain. Unlikely that these patients would be captured in incidence as they are relatives and not diagnosed yet.
FDR uptake of screening	Increasing from [redacted]% in Year 1 to [redacted]% in Year 6	Market research survey slide 51	The value for Year 1 was drawn from the market research survey, but it was unclear why patient sentiment would change over time. This value was uncertain.	Overestimate. In comparison, it was noted that when TrialNet contacts eligible FDRs and offers free screening <50% decide to participate. An increase to [redacted]% appears overestimated, noting that listing of teplizumab will increase testing to a certain degree (unlikely to [redacted]%).
SDR per Stage 3 patient	[redacted][1]	Assumption	It was uncertain how many of these patients would already be captured in the incident and prevalent populations.	Uncertain. Incidence and prevalence estimates count patients in Stage 3, and do not record family associations.
SDR uptake of screening	Increasing from [redacted]% In Year 1 to [redacted]% in Year 6	Assumption	It was unclear why patient sentiment would change over time. This value was uncertain.	Agree with the Commentary.
Adult proportion of the population	Constant at 57.70%	Templeman 2025	This figure was calculated as the balance of patients once children were accounted for. This may underestimate the number of adult patients as the Templeman study did not limit the age of children included. The average age of children in the study was 8.96 years. Note, the composition of the eligible population would also be impacted by screening practices, such as access to studies of T1D screening.	Uncertain, but no better evidence identified.

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Parameter	Value	Source	Commentary	Sub-Committees' comment
Adult proportion with mAA	Constant at 0.83%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Adult proportion with Stage 2 mAA	Constant at 45.8%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Child proportion with mAA	Constant at 42.3%	Templeman 2025	This may overestimate the number of child patients as the Templeman study did not limit the age of children included. The average age of children in the study was 8.96 years.	
Child proportion with mAA	Constant at 2.80%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Child proportion with Stage 2 mAA	Constant at 37.4%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Prevalent population				
Prevalent Stage 3 T1D	145,022	NDSS Data Snapshot (Dec 2025)	The population was T1D patients who were registered with the NDSS in 2025. This was an appropriate data source.	Reasonable.
Prevalence Growth	1%	5-year average of NDSS Data Snapshot	The evaluation could not reproduce this value. The average annual growth between 2020 and 2025 was 2.63%. The annual growth reported in the same period by T1D was 2.99%.	Agree with Commentary.
FDR per Stage 3 patient	[redacted]1	Assumption	It was uncertain how many of these patients would already be captured in the incident and prevalent populations.	Uncertain.
FDR uptake of screening	[redacted]%	Assumption, METIS survey slide 51	The value was drawn from the METIS survey. However, it is unclear how this figure was derived. This value was uncertain.	Uncertain.

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Parameter	Value	Source	Commentary	Sub-Committees' comment
SDR per Stage 3 patient	[redacted][1]	Assumption	It was uncertain how many of these patients would already be captured in the incident and prevalent populations.	Very small number of SDRs would get screened.
SDR uptake of screening	[redacted]%	Assumption	The value was drawn from the market research survey. However, it is unclear how this figure was derived. This value was uncertain.	Uncertain. The screening rate is usually lower than for FDRs – may be reasonable to use.
Adult proportion of total people screened	Constant at 57.7%	Templeman 2025	This may overestimate the number of adult patients as the Templeman study did not limit the age of children included. The average age of children in the study was 8.96 years.	Uncertain, but no better evidence identified.
Adult proportion with mAA	Constant at 0.83%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Adult proportion with Stage 2 mAA	Constant at 45.8%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Child proportion of total people screened	Constant at 42.3%	Templeman 2025	This may underestimate the number of child patients as the Templeman study did not limit the age of children included. The average age of children in the study was 8.96 years.	
Child proportion with mAA	Constant at 2.80%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
Child proportion with Stage 2 mAA	Constant at 37.4%	Templeman 2025	This was appropriate data source. However, the study had a significantly different racial mix to that found in Australia.	
General population				

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Parameter	Value	Source	Commentary	Sub-Committees' comment
Population 8–65 years	Increasing from 20.6 million in Year 1 to 21.7 million in Year 6	ABS population less relatives of incident and prevalent patients and warehoused patients	This was an appropriate data source.	Reasonable. The population accounted for FDR and SDR adult and child patients, National Screening Program patients and warehoused patients. These adjustments were appropriate to avoid double counting of patients.
Stage 2 identified from screening	0.0995%	Average of ELSA 0.18% (Quinn et al 2026) and Fr1da 0.019% (Ziegler et al 2020)	The evaluation could not reproduce the ELSA value. The cohort average age was 8 years (IQR 5-10 years). The evaluation could not reproduce the Ziegler value. The cohort was all less than 6 years old, below the threshold for teplizumab. The PSCR clarified that the ELSA value was derived by dividing the number of children with Stage 2 T1D by the number of children with sufficient blood sample obtained for islet autoantibody screening (31/17283=0.18%) sourced from Quinn et al 2026 Supplementary Figure 3, p66. The PSCR clarified that the Zeigler value was derived by dividing the number of children with Stage 2 T1D by the number of children with sufficient blood sample obtained for islet autoantibody screening (17/90205=0.019%) sourced from Ziegler et al 2020 (Figure 1).	Uncertain but likely an overestimate. The 2 studies are not fully comparable (different populations, screening pathways and staging approaches). 0.0995% may overestimate Stage 2 prevalence relative to Fr1da study. A sensitivity analysis using the range observed across 2 studies may be more appropriate than relying on a single midpoint estimate.
Screening rate	Increasing from [redacted]% in Year 1 to [redacted]% in Year 6	Expert opinion		Uncertain. May be appropriate that screening will increase if teplizumab is listed but uncertain to what extent.
National Screening Program (Proposed)				

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Parameter	Value	Source	Commentary	Sub-Committees' comment
6-year-olds screened	Increasing from 325,883 in Year 5 to 326,454 in Year 6	ABS population estimates	This was an appropriate data source, however the calculation applied in the estimates did not match the submission's description. The submission claimed to estimate 6-year-olds in 2029 who will be treated in 2031 as 8-year-olds. The data presented was 6-year-olds in 2031.	Not appropriate to include as no such program exists. Should be scenario-only and removed from base case.
Stage 2 patients identified	0.0995%	Average of ELSA 0.18% (Quinn et al 2026) and Fr1da 0.019% (Ziegler et al 2020)	The evaluation noted that the cohort average age was 8 years (IQR 5-10 years) in the Quinn study. For the Ziegler study, the cohort was all less than 6 years old, below the threshold for teplizumab.	Not appropriate to include as no such program exists. Should be removed from base case – program is not established.
Warehoused population				
Stage 2 patients	[redacted][1]	Expert opinion	It was unclear how these patients would be a discrete cohort not covered by the other cohorts included in the model.	Not appropriate. Poorly defined; overlaps with relatives and general population. High risk of double counting.
Patients progressed to Stage 3 each year	Constant at 28%	Fr1da	The Ziegler data shows the rate of progression to T1D increasing across time. It was more than 30% after 1 year and more than 40% after 2 years.	
Common parameters				
Patients prescribed teplizumab	Constant at [redacted]%	Market research survey (range [redacted]%-[redacted]%)	This was an appropriate source. The survey included both adult and paediatric endocrinologists, it may be more appropriate to use the adult figure rather than average.	Agree with Commentary.
Patient uptake	Constant at [redacted]%	Market research survey (range [redacted]%-[redacted]%)	This was an appropriate source. The survey includes both adult, child and adolescent values, it may be more appropriate to use the adult figure rather than average.	Agree with Commentary.
Year 1 adjustment (5/12 months listed)	[redacted]%	Assumption	This was not appropriate. No adjustment should be made for a particular listing month. This adjustment will be applied in the post-PBAC processes.	Agree with Commentary.

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Parameter	Value	Source	Commentary	Sub-Committees' comment
Treatment duration (days)	14	Product Information		Reasonable.
Teplizumab scripts all treatment	0.99 scripts, based on 14 days of treatment, and 99.35% compliance	TN-10 RDI	This was not appropriate. As proposed, a single script will dispense all required doses. Therefore, even if a patient required a reduced dose or missed a dose, this would have no impact on the already dispensed medicine. The dosing of teplizumab is based on BSA. Patients with BSA > 1.94 m^2 will require 2 vials for days 5-14. The submission proposed an increased number of vials will be approved for these patients. However, the utilisation and cost model assumed all patients receive 1 vial per administration and does not capture the impact of patients requiring 2 vials.	Agree with Commentary – not appropriate. Uncertain how many patients will require 2 vials. In the FDA pooled teplizumab trial population (n=729) 12.1% had BSA >1.94m^2. This estimate is from the overall pooled teplizumab population, which included a broader age range and larger adults. Paediatric patients will have lower BSA. A value of 5% requiring 2 vials is considered appropriate.

Source: The financial estimates from the submission: 9. AIHW population; 2a. Patients - incident; 2d. Patients - DTG; 3a. Scripts - proposed; 8. ABS population; 2b. Patients - prevalent; 3b. Impact - proposed (pub); 3c. Impact - proposed (eff); 2e. Scripts - market; 7. Net changes - MBS.

ABS = Australian Bureau of Statistics; ELSA = The Early Surveillance for Autoimmune diabetes; FDR = first-degree relative; Fr1da = Frühstadium Typ-1-Diabetes (Early stage Type 1 diabetes); IQR = Inter-quartile range; mAA = multiple autoantibodies; NDSS = National Diabetes Services Scheme; PBAC = Pharmaceutical Benefits Advisory Committee; RDI = relative dose intensity; SDR = second-degree relative; T1D = Type 1 diabetes.

The redacted values correspond to the following ranges:

[1] < 500

6.76 The Sub-Committees considered that the utilisation estimates in the submission's base case were uncertain, noting uncertainties around screening rates and current Australian practice (no routine screening in children), and no population level screening. The Sub-Committees requested revisions to the analysis that excluded the national 6-year-old screening program and the warehoused Stage 2 population and adjusted the general population screening rates. The input parameters specific for revised financial estimates are outlined in Table 18.

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Table 18: Input parameters specific for revised financial estimates

Description	Input parameters
Prevalent patients	True prevalent population used
Warehoused patients	Population removed
National screening program	Population removed
Incident population growth rate	T1D growth rate applied – 2.21%
Prevalent population growth rate	T1D growth rate applied – 2.99%
First year adjustment	Adjustment removed
Patients prescribed teplizumab	Paediatric endocrinologist rates applied to child population Endocrinologist rates applied to adult patients
Patients electing treatment	Paediatric endocrinologist rates applied to child population Endocrinologist rates applied to adult patients
Compliance rate	Adjustment removed
Patients with BSA > 1.94m^2	5% of patients received 2 vials each day of treatment. Dispensed quantity increased to 28, dispensed on a single prescription.
MBS item for liver function test	Cost corrected to $17.70
MBS item for infusion	MBS item changed to MBS item 116 (specialist appointment)

Source: Financial estimates model provided with the submission.
MBS = Medicare Benefits Schedule; T1D = Type 1 diabetes.

6.77 The estimated use and financial impacts of listing teplizumab are shown in Table 19. This includes the submission's estimates and revised base case estimates based on advice from the Sub-Committees.

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Table 19: Estimated use and financial impact of listing teplizumab (effective)

Submission estimates						
Scripts - teplizumab						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Incident FDR – Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident SDR - Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident FDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident SDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident general population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
National Screening Program	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent FDR – Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent SDR – Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent FDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent SDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Warehouse patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net financial impact						
Net PBS/RPBS	$[redacted][2]	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][7]	$[redacted][8]
MBS impact	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net PBS/RPBS/MBS impact	$[redacted][2]	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][7]	$[redacted][8]
Sub-Committee Revised Base Case						
Scripts - teplizumab						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Incident FDR – Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident SDR - Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident FDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident SDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident general population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent FDR – Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent SDR - Adults	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent FDR – Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Prevalent SDR - Child	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	—
Net financial impact						
Net PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]
MBS impact	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net PBS/RPBS/MBS impact	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]

Source: The financial estimates from the submission: 3a. Scripts - proposed; 3c. Impact - proposed (eff); 5. Impact - net; 7. Net changes - MBS. Revised base case constructed by evaluators following Sub-Committees' advice using the submission's financial estimates: 5. Impact - net; 7. Net changes - MBS.

FDR = first-degree relative; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Schedule; SDR = second-degree relative.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$0 to < $10 million*

[3] *$20 million to < $30 million*

[4] *$30 million to < $40 million*

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[5] *$40 million to < $50 million*
[6] *$50 million to < $60 million*
[7] *$60 million to < $70 million*
[8] *$70 million to < $80 million*

6.78 The submission estimated a net cost to PBS/RPBS of $80 million to < $90 million in Year 6, and a total of $200 million to < $300 million in the first 6 years of listing of teplizumab. The Sub-Committee revised base case estimated the total cost to the PBS/RPBS to be $60 million to < $70 million in Year 6, and a total of $200 million to < $300 million in the first 6 years of listing.

6.79 The submission presented 11 patient populations:

- incident adult relatives screened (FDR / SDR)[40]
- incident child relatives screened (FDR / SDR)
- incident 8 to 65-year-olds in the general population
- incident National Screen Program children (future population). The Sub-Committees advised this population should be removed from the revised base case.
- prevalent adult relatives screened (FDR / SDR)
- prevalent child relatives screened (FDR / SDR)
- prevalent warehoused patients. The Sub-Committees advised this population should be removed from the revised base case.

6.80 The incident Stage 3 T1D population was derived from the T1D Index website (T1D Numbers - Type 1 Diabetes Data & Statistics) from 2020 to 2025 and projected by the average annual growth rate from 2027 to 2032. This was an appropriate data source; however, the proposed annual growth rate (3.8%) could not be reproduced during the evaluation. The Sub-Committees considered that the growth rate applied was an overestimate, and a rate of 2.21% would be more reasonable as it was based on the source data.

- The Stage 3 T1D population was used to identify first and second-degree adult and child relatives (3 and 6 respectively) of these patients to be screened for undiagnosed Stage 2 T1D. The evaluation considered the number of undiagnosed patients appeared high especially given the relatively small size (1.2 children[41]) of the average contemporary Australian family.
- The screening rate applied to these populations was taken from an Australian market research survey conducted in 2025, with an annual growth rate

[40] FDR – first degree relative; SDR – second degree relative
[41] https://www.ceicdata.com/en/australia/survey-of-income-and-housing-average-number-of-dependent-children-in-household-by-family-composition

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applied. The evaluation considered the source was appropriate, but it was unclear if the applied growth rates were appropriate.

- The proportion of screened patients who were identified with multiple autoantibodies (mAA) and Stage 2 mAA was taken from a US study (Templeman 2025). This was an appropriate source, however the significant demographic difference between the US and Australian populations makes its unadjusted application to the Australian context uncertain.
- The proportion of patients prescribed teplizumab in these cohorts and the proportion of patients electing treatment were taken from an Australian market research survey. This was an appropriate source.
- The submission applied a first-year adjustment to account for part year listing. This was not appropriate as it artificially reduces the cost of the first year of listing. By convention, any adjustments for part year listing are applied during the post-PBAC processing of submissions.

6.81 The submission proposed an incident population drawn from the ABS population projections for people 8-65 years, less those patients identified as first and second-degree relatives of T1D patients.

- The patient identification rate applied to the population was based on an average of the ELSA (Quinn 2026) and Fr1da (Ziegler 2019) values. The Sub-Committees advised that as no such program exists, it should be removed from the base case.
- The screening rate applied to the population was taken from expert opinion.
- The proportion of patients prescribed teplizumab in these cohorts and the proportion of patients electing treatment were taken from an Australian survey (METIS 2025). This was an appropriate source.
- The submission applied a first-year adjustment to account for part year listing. This was not appropriate as it artificially reduces the cost of the first year of listing. By convention, any adjustments for part year listing are applied during the post-PBAC processing of submissions.

6.82 The submission proposed an incident child population derived from a National Screening Program that may start during the first six years of listing, however there was no evidence to justify the assumptions used for the modelled cohort. Given the uncertainty of the scope and start date for this cohort its inclusion is not appropriate.

6.83 The submission only presented direct costs associated with treating patients with teplizumab: the cost of infusion (MBS Item 13950), blood test (MBS Item 65060) and liver function test (MBS Item 65500). The evaluation noted that the item chosen for the liver function test was incorrect and this underestimated the MBS cost of treating patients. The submission did not include any costs associated with screening patients as these were considered to occur before treatment. The evaluation noted this does

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not account for the growth in screening demand once teplizumab becomes available. This additional cost would include not just patients who test positive, but the whole tested cohort, including those who return a negative test result.

6.84 The submission identified several currently listed MBS Items that could be used to the purposes of screening. While OGTT (MBS Item 66542) was identified as the gold standard, the other options were proposed if this was not available were:

- Detection of pancreatic islet autoantibodies (MBS Items 71165, 71119, 71121, 71123, 71125)
- Quantification of HbA1c (MBS Items 66551, 66841, 73812, 73826, 73839)
- Quantification of plasma glucose (MBS Item 66500)

6.85 The prevalent Stage 3 T1D population was derived from the T1D Index website (T1D Numbers - Type 1 Diabetes Data & Statistics) from 2020 to 2025 and projected by the average annual growth rate from 2027 to 2032. The evaluation considered this was an appropriate data source; however, the proposed growth rate could not be reproduced during the evaluation. The same derivation steps and sources were used to apply to the prevalent population as described for the incident population in 6.79.

6.86 The submission did not propose any grandfathered patients but included a cohort of < 500 warehoused prevalent patients. The exclusion of the grandfathered patients was appropriate, but given the extensive populations included in the model, the source of the warehoused patients is unclear, and its inclusion is not appropriate. The Sub-Committees agreed with the Commentary and this patient population was removed from the revised base case.

Quality Use of Medicines

6.87 The submission did not provide details of quality use of medicines (QUM) activities to be undertaken. The Sub-Committees noted that teplizumab is the first disease-modifying therapy for Stage 2 T1D and has limited long-term experience. Post-marketing surveillance studies should be undertaken by the sponsor (see paragraph 6.89).

6.88 The Sub-Committees noted that most adverse events are mild to moderate and occur during or shortly after treatment. Appropriate monitoring during infusions should be included as a QUM activity. In addition, consideration should be given to the quality of life impacts of the potential side effects of the medicine, even if they are largely tolerable.

6.89 The submission reported that two ongoing safety monitoring studies are being conducted in Canada, UK, US, Czech Republic, France, Germany and Poland. The submission also identified an additional US study that is comparing treated to untreated patients from a safety perspective.

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Financial Management – Risk Sharing Arrangements

6.90 The submission did not seek a risk share arrangement for the listing of teplizumab for T1D.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of teplizumab for the treatment of Stage 2 T1D in patients aged 8 years or older to delay the onset of Stage 3 T1D. The PBAC considered that the submission's proposed approach to identify patients with Stage 2 T1D through screening family members of those with diagnosed T1D and through studies of T1D screening would not provide equitable access to the medicine. This view was formed as the majority of individuals diagnosed with T1D do not have a family member with the condition. The PBAC considered that teplizumab was effective in delaying the onset of Stage 3 T1D compared with placebo, based on the results of the TN-10 trial. The PBAC considered that delaying the onset of stage 3 T1D would be valuable for some patients, especially for children, as it would provide additional time free from symptomatic T1D, and the demands of insulin treatment and blood glucose management. However, the PBAC considered that the limited evidence presented in the submission did not adequately support the submission's claim regarding extended time to delaying Stage 3 T1D and long-term benefits of teplizumab after progression to Stage 3 T1D, such as reduced cardiovascular mortality and morbidity or other long-term complications of T1D. The PBAC also noted that teplizumab was associated with a higher rate of adverse events, including serious adverse events compared with placebo. Due to the unknown impact of teplizumab on long-term outcomes the PBAC considered the cost-effectiveness of teplizumab highly uncertain. Further, the PBAC considered that the value of a 2-year delay in onset of Stage 3 T1D would likely differ by age, with the greatest benefit likely to accrue for patients treated as children or adolescents. The PBAC noted that the impact of age on the cost-effectiveness of teplizumab was not considered by the submission.

7.2 The primary reason for this outcome was due to the comparative clinical evidence. While a short-term benefit of treatment was accepted, no evidence was presented to show whether the delay in progression to Stage 3 T1D from the TN-10 trial would reduce vascular complications of diabetes or lead to better health outcomes over the medium or long term. In the absence of relevant evidence to support this claim, the PBAC did not accept that teplizumab would be associated with a substantial reduction in the lifetime risk of cardiovascular disease as proposed by the submission.

7.3 The PBAC noted and welcomed the input from health care professionals, individuals and organisations who supported PBS listing for teplizumab. The PBAC acknowledged the need for treatments that reduce the impact of T1D. The PBAC recognised Stage 3 T1D places a substantial burden on patients and their families, and considered that delaying T1D would be impactful to quality of life. The PBAC considered additional

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time without Stage 3 T1D would be particularly beneficial for children and adolescents as they would be more developmentally mature and better able to manage their Stage 3 disease. The PBAC also noted that treatment with teplizumab was for asymptomatic patients and it does not cure the condition. The PBAC considered this should be made clear to patients and their families when discussing screening and treatment options, and that education to recognise the symptoms of T1D and minimise the risk of diabetic ketoacidosis (DKA) and hospitalisation was important for patients treated with teplizumab, as it is for all patients diagnosed with Stage 2 T1D. The PBAC noted that treatment with teplizumab requires infusions in a hospital setting over 14 consecutive days, which would be a considerable burden for patients and families. The PBAC acknowledged that a delay in time without insulin therapy and its associated lifestyle burdens would be important to people, however considered the long-term clinical significance of this delay was unknown. Further the PBAC noted that teplizumab treatment burden and potential long-term benefits will vary according to age.

7.4 The PBAC noted that the submission and consumer input described pilot screening studies that are underway. However, there are currently no national screening programs for T1D, or proposals under active consideration by government. The Department has been engaging with stakeholders regarding research grants to consider priority policy issues including screening, prevention and treatment, and the Department encourages continued engagement through these channels. The PBAC noted the submission had requested PBS listing of teplizumab for patients who have been diagnosed with Stage 2 T1D but before they develop Stage 3 T1D, regardless of familial history with T1D. The PBAC considered the proposed place in therapy was reasonable, however noted that although most diagnoses of T1D occur in individuals with no family history of the condition, the submission had not adequately considered how pre-symptomatic T1D patients would be identified in the broader community given current screening is generally limited to patients who have a relative diagnosed with T1D. The PBAC noted this would result in access to teplizumab not being equitable. The submission identified MBS items that could be used for islet autoantibody testing and dysglycaemia testing. The PBAC noted these MBS services would be eligible for a Medicare benefit in cases where eligibility criteria are met and the test is clinically relevant for care of the individual patient, however use of these MBS items is not suitable for broad population screening. The PBAC considered a coordinated approach to diagnosing Stage 2 T1D would be important to ensure equitable early diagnosis and access to potential treatments such as teplizumab.

7.5 The PBAC considered the proposed comparator of best supportive care was appropriate as there is no other therapy to delay Stage 2 T1D progressing to Stage 3 T1D.

7.6 The PBAC noted the submission was based on clinical evidence from the TN-10 (n=76) trial, which compared time to diagnosis of Stage 3 T1D in patients aged 8 to 45 years with Stage 2 T1D treated with teplizumab or placebo. The PBAC noted that the median time to diagnosis of T1D was 27.3 months in the placebo group of TN-10, which was

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extended to 52.2 months in the teplizumab group, corresponding to a difference in median time to diagnosis of 24.9 months (July 2023 data cut-off). The PBAC noted that KM curves for the July 2023 data cut-off based on 80.5 months median follow-up (Figure 3) indicated that the probability of being diabetes free approached zero within approximately 10 years.

7.7 The PBAC noted that the latest analysis of TN-10 provided by the submission was dated July 2023, and considered that further data cuts may be informative in a resubmission. However, it was noted that only 16 teplizumab patients and 4 placebo patients were censored at the time of the July 2023 analysis (see paragraph 6.25) and hence the results would be expected to be consistent with those presented in the submission.

7.8 The PBAC considered the TN-10 trial, which included 76 patients, was very small in the context of approximately 3,000 Australians being diagnosed with Stage 3 T1D each year.[42]

7.9 Overall, the PBAC considered the clinical claim of superior comparative effectiveness was supported as the clinical trial demonstrated that teplizumab was effective at delaying the onset of Stage 3 T1D. However, the PBAC considered there was insufficient evidence to support a claim that teplizumab would lead to longer-term clinical benefits beyond delaying the onset of Stage 3 T1D.

7.10 The PBAC noted that teplizumab was associated with a higher rate of adverse events, including serious adverse events compared with placebo and there was no evidence on its long-term safety. The PBAC noted the most common AEs reported in the teplizumab group were lymphopaenia (72.7% vs. 6.3% in placebo), leukopaenia (20.5% vs. 0% in placebo), pruritic rash (15.9% vs. 0% in placebo), and nasopharyngitis (15.9% vs. 6.2% in placebo). When all rash-related terms were combined, 19 of 44 (43.2%) subjects in the teplizumab group had rash-related AEs. The PBAC considered the claim of inferior comparative safety was reasonable.

7.11 The submission presented a cost-utility analysis that compared treatment with teplizumab to established clinical management (ECM) for patients aged 8 years and older with Stage 2 T1D. The PBAC considered the sponsor's economic model substantially overestimated the benefits of teplizumab treatment. The PBAC noted that teplizumab is not proposed as a cure for T1D and that all patients with Stage 2 T1D are expected to develop Stage 3 T1D. The PBAC considered that subsequent treatment of Stage 3 T1D with insulin and blood glucose management would be expected to have a greater influence on long-term T1D outcomes and mortality than was modelled in the submission.

7.12 The PBAC noted that the Sub-Committees had suggested several parameter changes

[42] Australian Institute of Health and Welfare. (2026). Diabetes: Australian facts (Web report). https://www.aihw.gov.au/reports/diabetes/diabetes/contents/about (updated 27 May 2026).

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for the economic evaluation as set out in paragraph 6.71. This included applying the corrections made during the evaluation, a 25-year time horizon, assuming 5% of patients will have BSA>1.94 m^2 (require 2 vials), convergence of the time to stage 3 T1D curves between years 8 and 15, removal of ongoing aggregated disutilities for patients in the stage 3 T1D health state based on time since diagnosis, and removal of disutility for patients with stage 2 T1D in the ECM arm. The PBAC noted this analysis resulted in an ICER of $555,000 to < $655,000/QALY gained. The PBAC considered this ICER was above the range that could be considered cost-effective. The PBAC noted that the pre-PBAC response presented further analyses in which the Sub-Committee advice was partially accepted and resulted in lower ICERs (paragraphs 6.72 and 6.73), however the PBAC considered that the response did not adequately address the concerns described by the Sub-Committees. The PBAC noted that the time-horizon of the model had a significant impact on the results (Figure 7), and agreed with the Sub-Committees that a significantly shorter time horizon would be more appropriate given the multiplicity of uncertainties associated with assumptions over a lifetime time horizon. The PBAC accepted that teplizumab is associated with a delay in progression to Stage 3 disease which is clinically meaningful, however the modelled benefits in life years gained and quality adjusted life years gained in the stage 3 T1D health state were not adequately supported and as such the cost-effectiveness of teplizumab was not demonstrated.

7.13 The PBAC noted the submission had included utilisation estimates based on patients identified through a national screening program, which was not appropriate as there are currently no national screening programs for T1D, or proposals under active consideration by government. The estimated utilisation of teplizumab remained uncertain, even after the impact of the proposed screening program was removed, as it was highly dependent on the uptake of screening for Stage 2 T1D outside a formal screening program. The PBAC noted that the submission estimated that < 500 patients would be treated in Year 1, increasing to 500 to < 5,000 in Year 6 (with a National Screening Program) or < 500 in Year 6 (without a screening program). The PBAC considered these estimates appear very low in comparison to estimates of the number of Australians with early stages of diabetes. The Cost of Not Knowing report estimated that 25,000 Australians are in the early stages of T1D.

7.14 The PBAC considered a resubmission for teplizumab should address the following issues:

- Provide details on how patients could be diagnosed with Stage 2 T1D in an equitable manner for the purposes of access to teplizumab (see paragraph 7.4).
- Provide updated analyses of the TN-10 study if available.
- Provide additional evidence to support modelled long-term benefits of teplizumab. For example, the resubmission should provide evidence that the delay in needing insulin leads to improved patient relevant outcomes, such as less diabetes-related complications, better HRQoL, better psychological

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health, improved survival and/or reduced cardiovascular events. Data in relation to long term glycaemic control or less insulin dependence following teplizumab may also be informative. Alternatively, if this is not possible, the PBAC considered that a resubmission could focus on the short-term benefits of a delayed diagnosis of Stage 3 T1D and submit an economic model that assumed no benefits after diagnosis of Stage 3 T1D.

- Ensure that the concerns about the economic model raised by the PBAC and the Sub-Committees are addressed (see paragraph 7.12).
- Ensure that extrapolation of treatment effects in the economic model are consistent with observed data (with the longest duration of follow-up available), noting the submission's extrapolation was not consistent with the analysis published by Lledo-Delgado et al 2024.
- Present evidence regarding benefit of teplizumab by age of treatment initiation, including clinical and economic evidence. The PBAC considered that the benefits would be greater in children and adolescents compared with adults.
- Ensure that the concerns about the financial estimates raised by the Sub-Committees are addressed consistent with the revised estimates (see Table 19), and the PBAC's advice in paragraph 7.13.
- Propose a risk-sharing arrangement to address the risks of: 1) Use beyond the restrictions; and 2) Uncertain overall cost to the PBS.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.15 The PBAC noted that this submission is eligible for an Independent Review

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.

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