CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

Teplizumab (Tzield)

sanofi-aventis Canada Inc.

Indication: The anticipated indication is to delay the onset of Stage 3 Type 1 Diabetes in adult and pediatric patients 8 years of age and older with Stage 2 Type 1 Diabetes.

March 3, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Teplizumab (TZield)
Indication: The anticipated indication is to delay the onset of Stage 3 T1D in adult and pediatric patients 8 years of age and older with Stage 2 T1D.
Name of Patient Group: Breakthrough T1D Canada and Diabetes Canada
Author of Submission: Luka Stevanovic (Breakthrough T1D Canada) and Laura O'Driscoll (Diabetes Canada)

1. About Your Patient Group

Breakthrough T1D Canada (https://breakthrought1d.ca/) is the leading national patient advocacy and research funding organization specifically dedicated to Canadians living with type 1 diabetes (T1D). Since our founding in 1974 by parents seeking cures for their children, we have since grown to be the largest supporter of T1D research in the country. Our mission is to accelerate life-changing breakthroughs to cure, prevent, and treat T1D and its complications, ensuring that people with the disease live healthier lives while we work toward a world without T1D. Through funding research, to advocating for government support and improved access to therapies, and deep engagement with the T1D community, we are making every day better for those living with T1D as we drive toward cures.

Diabetes Canada (www.diabetes.ca) is a national health charity representing the millions of Canadians who are affected by diabetes. Our mission is to prevent diabetes and its complications; help people with diabetes live healthy lives; and work to find a cure. It has a heritage of excellence and leadership, and its co-founder, Dr. Charles Best, along with Dr. Frederick Banting, is credited with the co-discovery of insulin. Diabetes Canada is supported in its efforts by a community-based network of volunteers, employees, health-care professionals, researchers, and partners. By providing education and services, advocating on behalf of people living with diabetes, supporting research, and translating it into practical applications, Diabetes Canada is delivering on its mission. Diabetes Canada will continue our work to prevent diabetes and its complications; help people with diabetes live healthy lives; and work to find a cure.

2. Information Gathering

This submission includes patient input gathered through an online survey conducted from January 10 to February 14, 2025. The survey targeted individuals living with T1D and their caregivers, reaching the T1D community through email outreach to digital subscribers and social media channels (Facebook, LinkedIn, X) in a collaborative effort by Breakthrough T1D, Diabetes Canada, and Connected in Motion. Open to participants across Canada, the self-administered questionnaire explored respondents' lived experiences with T1D, their use of diabetes technologies (such as continuous glucose monitors and insulin pumps), awareness of T1D screening, and expectations for new drug therapies in Canada. Additionally, the survey included specific questions about the drug under review, teplizumab (TZield).

A total of 463 people responded to the survey – of those who responded to the general information section of the survey, 257 identified as living with T1D,182 identified as a caregiver (for example, family member) to a person living with T1D, 20 respondents identified as a person living with T1D AND a caregiver (for example, family member) to a person living with T1D, and 6 respondents identified as having no relationship to T1D. Of those who responded to questions about age and time since diagnosis (n=451), 68% were over the age of 35, with the largest number of respondents (18%, n=83) in the 25–34-year-old category.43% reported having lived with T1D for over 20 years.

The majority of respondents live in Ontario (n=226), British Columbia (n=74), Alberta (n=63), Manitoba (n=24), and Quebec (n=19), with fewer than 15 respondents from Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, and Saskatchewan, and only 2 respondents from the Territories. 82% of respondents indicated that they live in an urban or suburban region (n=367), with 18% indicating that they live in a rural or remote area (n=83). 35% (n=156) respondents identified as male and 63% (n=285) identified as female, 1% of respondents identified as non-binary. 86% of respondents identified as White Caucasian (n=385), 2% of respondents identified as being South Asian (n=9). Just over 10% of respondents identified as being Indigenous (n=3), African, Caribbean, Black (n=6), Arab (n=2), Latin American/ Hispanic (n=5), or Chinese (n=6).

3. Disease Experience

Background on the Disease

T1D is a disease in which the pancreas does not produce any insulin. Insulin is a vital hormone that helps your body to control the level of glucose (sugar) in your blood.

Roughly 10 per cent of people living with diabetes have type 1, insulin-dependent diabetes. It's estimated that 300,000 Canadians live with T1D. Nationally, the number of people living with T1D is growing at an estimated 4.4% per year – much higher than Canada's population growth of approximately 1.0% per year. At this rate, there is expected to be more than 450,000 Canadians living with T1D by 2040. T1D is thought to be a childhood disease, but in actuality, nearly 70% of new cases are diagnosed in adulthood. Parents, children and siblings of individuals with T1D have a 15-fold greater risk of developing the disease than the rest of the population, however 85% of people diagnosed with T1D do not have a family connection.

Diagnosis

Since the early symptoms of T1D often present similar to a virus or flu, it is not uncommon for symptoms to be ignored or misdiagnosed initially. In children and adolescents, the progression of T1D is typically faster than in adults and a misdiagnosis of initial symptoms can lead to diabetic ketoacidosis (DKA). DKA is a traumatic, life-threatening and costly complication that is seen in approximately 40% of pediatric T1D diagnoses in Canada (60% during the COVID-19 pandemic) (Ho et al., 2021, doi: 10.1111/pedi.13205). Not only does it cause acute medical trauma (such as extreme dehydration, loss of consciousness, risk of coma and cerebral edema), it typically results in a costly hospital admission, and psychological trauma to the individual and family members. Long-term, an instance of DKA has been shown to affect glucose management over the lifespan, increase risk of diabetic complications later in life, decrease cognitive functioning, and increase risk of repeat DKA episodes.

Post-Diagnosis

People with T1D need multiple daily insulin injections via syringe or a continuous infusion of insulin via pump to constantly regulate blood glucose levels in the body in order to survive.

When someone living with T1D does not have their blood glucose levels in target range, the consequences can be quite serious. Low blood glucose (hypoglycemia) can be an acute crisis, causing confusion, coma, and/or seizure that, in addition to being medically dangerous, may also contribute to a motor vehicle, school/workplace or other type of accident, causing harm. High blood glucose (hyperglycemia) can cause weakness, nausea, vomiting, abdominal pain, and other symptoms. Over time, glucose levels that are consistently above target can irreversibly damage blood vessels and nerves, resulting in long-term health complications like blindness, heart disease, kidney dysfunction, foot ulcers, and non-traumatic lower limb amputations. One of the goals of diabetes management is to keep glucose levels

within a target range to minimize symptoms and decrease the risk of complications and consequences. However, even with vigilant management, there is always a risk of life-threatening complications.

The majority of survey respondents (83%, n=351) living with T1D indicated that they are either extremely concerned or very concerned about the progression of T1D and its impact on daily life over time. With respect to the impact T1D has on the daily life and overall quality of life for either the person living with diabetes or the person caring for them, respondents offered the following insights:

> "*It impacts our daily life significantly. While we cope, it's always painful to watch my child navigate typical childhood experiences differently than her peers because of type 1 diabetes. As a parent, the late nights and disrupted sleep takes such a toll. Always having to be on top of management and maintaining records and supplies is just one more thing added to the mental load of being a mother. I fear for the day the management becomes solely my child's responsibility. I pray she values herself to take care of herself with pride so that she remains healthy and free of complications. The thought of complications developing as she ages always festers in the back of my brain since she was diagnosed so young. The amount of time I've needed off from work to deal with diabetes has been extensive at times and I'm grateful to have such an understanding employer. My daughter is just beginning to understand and realize that she is different from other children. I see instances where she becomes self conscious when we need to take out her pump to bolus. Having to sit out of sports or other fun activities temporarily to treat or prevent a hypo is frustrating at times for her. Fortunately she has currently maintained a positive relationship with food but I do fear that it may not always be that way. Being so young she dislikes pump and CGM site changes as well as finger pokes. It's so hard for us both having to endure and power through those moments. My husband and I do not have reliable family support that can comprehend diabetic management and thus we do not have any childcare options for our daughter come evenings or weekends. Since diagnosis my husband and I have never had the opportunity to go out as a couple just the two of us for dinner or anything. It's hard on our marriage. Very few people recognize that a T1D diagnosis can affect family life in such a way."*

> *"T1D is a daily challenge, both physically (constant attachment to devices, needles, symptoms of lows and highs, etc.), and mentally (persistent worry about managing BGs, constant pharmacy visits and medical appointments, and fear of developing complications such as losing eyesight). There is also a lot of stigma and misconceptions about the disease that make it difficult to live with every day."*

> *"Constantly monitoring blood sugars, making sure I have enough supplies, restocking supplies, doctors appointments, money toward medical supplies and premium individual health care benefits that others would not have to pay."*

> *"Impacts every decision I make. Causes anxiety. Dread for my long term health."*

> *"Its constantly thinking and calculating and making many many decisions a day that all revolve around type 1 diabetes. Trying to save my daughter's life every single day is the hardest thing I'll ever have to do in my life. Sleepless nights of worry if her sugar will drop or if her sugar is too high. Constantly worried at school when she's doing activities, if she's upset, etc these things affect her sugar. Having to deal with the constant emotional Rollercoaster of my daughters emotions, her irritations, her outbursts, her frustrations, not being able to control her emotions as it is part of her up and down sugars."*

> *"Heavy mental load, increased pressures on diet/exercise, dependence on technology and medication, medical costs, dependence on insurance, feeling stuck in a job because of health benefits, anxiety for future, living with chronic illness"*

"Indescribable amount of time spent managing medication, diet, exercise, mental health. Impacts every aspect of life even with no major complications"

"It impacts my life every moment of every day. I rely on unreliable technology, and any tech failure can have drastic impacts on my function. I have had T1D for more than 50 years. When I was diagnosed there was really no way to manage, other than urine testing. Consequently I have gastroparesis (constant nausea and pain with eating) and other forms of neuropathy. I have difficulty breathing, dizziness, and early stage kidney disease."

Respondents were also asked which conditions, in conjunction with diabetes, they experience. The table below represents conditions that respondents experience.

Condition	Not at all	Less than once a month	2 to 4 times a month	More than once a week	More than once a day	In the past, but not anymore	Don't know	Prefer not to answer
Hyperglycemia (high blood sugar)	0.96% (n=4)	3.83% (n=16)	12.44% (n= 52)	45.22% (n= 189)	35.41% (n= 148)	0.24% (n= 1)	0.96% (n= 4)	0.96% (n= 4)
Hypoglycemia (when daily activities are affected, or help is needed)	9.07% (n=38)	13.13% (n= 55)	21.96% (n= 92)	39.86% (n= 167)	12.41% (n= 52)	0.48% (n= 2)	1.67% (n= 7)	1.43% (n= 6)
Mental health challenges	14.94 % (n=62)	18.07% (n= 75)	20.00% (n= 83)	20.72% (n= 86)	13.01% (n= 54)	1.93% (n= 8)	7.95% (n= 33)	3.37% (n= 14)

Most respondents (56%) indicated that they themselves, or the person they care for, had been hospitalized because of T1D. Of those who had been hospitalized, 43% had been hospitalized for one day or less, 15% had been hospitalized for 2 days, 16% had been hospitalized for 3 days and 26% had been hospitalized for 4 or more days.

4. Experiences With Currently Available Treatments

In individuals living without T1D, insulin producing beta cells regulate blood sugar by precisely releasing insulin when and where it is needed. In those living with T1D, the immune system has destroyed the pancreas's insulin-producing beta cells, preventing the body from naturally regulating blood sugar. Without insulin, glucose builds up in the bloodstream, leading to high blood sugar (hyperglycemia) and requiring lifelong insulin therapy for survival.

Currently, ***the only treatment that exists for those living with T1D is external insulin***, administered multiple times a day via injection or through an insulin pump. Insulin therapy has been the cornerstone of T1D management and treatment since its discovery. While essential for survival, it does not come without medical risks, suboptimal clinical

outcomes, and a heavy burden on patients. ***There are no other adjunct therapies approved for T1D management, and no disease-modifying treatments have been approved*** that address the underlying autoimmune dysfunction that destroys pancreatic beta cells and impairs insulin production.

Too much insulin can lead to severe hypoglycemia, causing confusion, unconsciousness, seizures, or even death. Conversely, insulin deficiency results in hyperglycemia, increasing the risk of long-term complications such as kidney failure, heart disease, vision loss, and nerve damage. Managing T1D requires relentless attention, as insulin needs fluctuate daily due to factors like diet, activity, stress, and illness. With early onset and lifelong treatment, the physical, emotional, and financial burdens of T1D are profound and enduring.

People living with T1D must rely on external insulin through injections or pumps, a method that does allow for survival, but is far less effective than the body's own processes. Even with advanced technologies, exogenous insulin delivery is delayed and imprecise, often resulting in excessive or insufficient insulin levels, which comes with its own risks. Research has shown that maintaining an HbA1c of 7% or less and/or a time-in-range (a narrow range of 'healthy' blood glucose levels, typically defined as 3.9-10.0 mmml/L) of 70% or greater, will minimize the risk of diabetic complications over the lifespan. However, even with advances in diabetes technology the majority of people living with T1D do not meet these thresholds (McKnight et al. 2015 doi:10.1111/dme.12676). In contrast, individuals without diabetes have an average HbA1c <6% and spend an average of >95% time in range (Shah et al., 2019 doi:10.1210/jc.2018-02763).

With respect to currently available treatments for diabetes, the majority of respondents reported that they use some form of diabetes technology. 85% (n=350) of respondents reported using a real-time continuous glucose monitor, 10% (n=42) reported using a flash continuous glucose monitor, 66% (n=270) reported using an insulin pump and 38% (n=154) reported using a hybrid closed loop system/ automatic insulin delivery (AID) system.

The majority of respondents indicated that their current treatment options and/or management strategies are very effective (35%, n=143) or somewhat effective (61%, n=253) in addressing T1D. Only 4% (n=18) of respondents indicated that their current treatment options and/or management strategies are not so effective or limited in addressing T1D.

The majority of respondents (63%, n=264) indicated that they have experienced financial challenges related to managing their condition such as loss of income, inability to work the hours they would like to, or high out-of-pocket costs. Respondents offered the following insights related to their experiences with the financial challenges of managing their diabetes:

> *"I am so dependent on my work sponsored health insurance, makes it harder to consider moving to a different job even when needed/desired. Also paying in advance for diabetes supplies and waiting for reimbursement from insurance is a continual concern."*
>
> *"Stayed at jobs solely due to insurance coverage, extra sick time, negative effects to my performance at work, paying for supplies out of pocket."*
>
> *...[I]f I lost my job it would be a difficult decision balancing the cost to maintain my current level of diabetic health and other necessities like quality food, caring for my dependence or carrying on with the activities I love."*
>
> *"Now my daughter has aged out of my benefits, and hasn't got a job with benefits yet, she is concerned that she isn't independent and still needs help from parents to cover. Limits her job options since she needs to have benefit package."*

"My husband and I maintain expensive private health coverage, in part due to me having T1D. We are both retired."

"I don't have insurance and diabetes is a very expensive condition to live with - especially when the government doesn't cover essentials things like insulin and CGM"

"I was born in Ontario and benefitted from the Assisted Devices Program for nearly 15 years before transitioning my life to Quebec. Sadly, the government support for T1D is significantly lacking, and I am currently needing to make major life changes and decision based on how I may be able to afford ongoing insulin pump (and CGM) treatment. My current insulin pump has been outside of its warranty for nearly 2 years, however I do not have the financial means to purchase a new pump, and likely won't be able to continue pump therapy should this insulin pump be damaged."

5. Improved Outcomes

The majority of respondents (54%, n=216) indicated that they feel there are significant gaps in the availability of immunotherapy medications for T1D, such as Tzield, in Canada.

Due to this drug being unavailable in Canada and that there are no similar or alternative drugs, respondents were asked on their views about how this drug would have improved their quality of life had it been available to them.

"Even [a] 1 day delay would help my mental wellness. 2-3 years would be a gift, a miracle"

"Would be less of a shock. Going from one day to the next with type 1 diabetes was challenging for me"

"For young children, the delay of 2-3 years for a T1D diagnoses is significant. Children mature a lot over 2-3 years and they have a better understanding of why they have to take medicine and follow rules around food and activity. My daughter was 6 at diagnosis. Diabetes at any age is difficult, but if she had been a little older and better able to communicate how she was feeling – perceiving her lows – that would have alleviated a lot of our stress as caregivers."

"Ability to educate and prepare the patient for what is ahead. Also the longer they can have normal glucose the better in the long run for complications"

"It would have been a huge benefit! Every day not having to deal with this disease is physically, emotionally, socially, and financially beneficial. Delaying the onset of diabetes gives the medical community more time to develop solutions for diabetes so perhaps in that 2-3 years there could be another intervention/cure that would help!!"

"It would definitely give a person more time to research the change that they are about to experience. If we come to a point where lifestyle or other drug options were available to stop the process of becoming a type one diabetic, Tzield would be a game changer."

"Any delay in onset would improve my overall wellbeing and decrease risk of diabetes complications, short and long term"

"I've had T1D my whole life but can imagine several scenarios where being able to delay a diagnosis would be helpful and could prevent negative outcomes. Some of my most challenging experiences with T1D have been

as a young adult navigating healthcare systems and treatment options and I imagine a young adult at risk of T1D who knew they had the option to delay it would benefit immensely from having 2-3 years to prepare as best as possible rather."

"May help one become more armed or familiar with whats involved in daily life with T1D or meet with someone living with it, for comfort and time to learn how to administer insulin, how to deal with flus or sugars that wont come up, hospital runs, or how to lessen fears surrounding the disease (fear of amputation, fear of loss of eyesight etc)...fear of infections, or even still the stigma of a child having it and mentally trying to deal with not only the disease itself, but feeling "alone" or "weird" at school. So working on supports, buddy sytem, or bringing in MORE AWARENESS to all schools etc as opposed to just 1 or 2 meetings about it."

"If it was available to my children who are at a higher risk than the general population, I would be happy that allow them the 2-3 years to continue to grow and mature before requiring daily insulin."

"It would've allowed us to research and have the knowledge base prior to onset. This would be a game changer for anyone caring for a child with T1D. My daughter was diagnosed at the peak of the pandemic and it blindsided us as there is no one on either side of the family that hasT1D. We didn't know we recognize the symptoms which led to my daughter being diagnosed while in DKA and requiring a long hospital stay. She was in the hospital for four days, we only received a virtual training because of the pandemic and then sent home, absolutely terrified and exhausted With how to care for our daughter. Never mind the worries about what this diagnosis meant for our daughter, her life going forward, her life expectancy, her ability to have children… Knowing in advance, would allow both the patient and parents to be prepared and have a much better understanding and knowledge base of this life threatening illness. Most importantly, it would prepare the child"

6. Experience With Drug Under Review

Prior to this survey, the majority of respondents (72%, n=296) were not aware of Tzield. Of those respondents who did receive Tzield (n=8), the majority of them accessed it through participation in a clinical trial (n=6), while the other 2 respondents received the treatment in the US by paying the full cost out-of-pocket or through their private medical insurance. For those respondents who have received Tzield, they offered the following insights regarding how the treatment impacted their life or the person they care for:

"I believe it extended my daughter's honeymoon phase."

"Delayed the onset of T1D."

"I went into the double-blind study for TZield November 2013. I believe that the delay of a T1D diagnosis has helped my ability to maintain independence, improve my physical health, and I am in a [g]ood state of mental health. We are OK financially and other activities have been improved through my good physical and mental being. I cannot think of anything that I would describe as a disadvantage or drawback due to TZield."

Due to this drug being unavailable in Canada and that there are no similar or alternative drugs, there were a limited number of respondents with experience with the drug.

7. Companion Diagnostic Test

The indication for TZield is Stage 2 T1D, which means that an individual has 2 or more persistent autoantibodies associated with T1D and a measure of dysglycemia, but symptoms have not yet presented to warrant initiation of insulin

therapy. Autoantibody testing is performed via a blood test and associated assay. Dysglycemia can be screened for with various measures, but oral glucose tolerance tests (OGTT) are the most common.

Availability in Canada

Autoantibody testing is not yet standard practice in Canada. A healthcare provider who suspects diabetes may order an autoantibody panel, however, availability and cost vary greatly across the country. There are 5 main autoantibodies associated with T1D and in many provinces only 1-3 of these can be tested for. Coverage by provincial health programs is limited and many hospitals absorb the costs of these tests internally. For individuals who have a family member (first or second degree) with T1D, they can enroll in an observational research study called TrialNet. This program has been active since 2001 and offers autoantibody testing to family members of people with T1D as well as follow-up monitoring. Funding for this program is through international grants (particularly the NIH in the US) and the testing and activities are rooted firmly in a research setting, however, results are shared with physicians. This testing is available to all Canadians with a family member with T1D (up to age 45 for a first-degree relative and up to age 20 for a second-degree relative).

Cost of screening

Since current autoantibody tests are conducted at a regional or even institutional level, it is unknown what the cost of screening is for the healthcare system. To our knowledge, the cost of screening is never passed on to the individual. Activities are currently in place to expand the availability of screening country-wide, including a screening research consortium funded by Breakthrough T1D and Canadian Institute of Health Research (CIHR) called CanScreen T1D (https://canscreent1d.ca/our-research/). The limited cost-effectiveness studies assessing T1D screening have determined that screening becomes more cost-effective the more widespread and integrated into the healthcare system it is (Karl et al., 2022, doi: 10.2337/dc21-1648). Furthermore, screening has been found to be cost effective with a modest improvement in DKA rates at diagnosis and associated HbA1c reduction over an individual's lifespan (McQueen et al., 2020, doi: 10.2337/dc19-2003). A study that addresses costs of screening and cost-effectiveness of screening in the Canadian context is underway and expected to report in 2026-2027.

Patient thoughts on screening

The majority of respondents indicated that they either strongly agree (25%, n=103) or agree (31%, n=131) that knowing there is an increased risk of developing T1D if a family member has the condition has negatively impacted their emotional well-being or mental health.

With respect to screening for T1D associated autoantibodies (via a blood test), 28% (n=118) indicated that they have had such screening done and 52% (n=218) of respondents indicated that they have not had such screening done, 19% (n=80) of respondents were unsure whether they had such screening done.

The majority of respondents (70%, n=292) indicated that they would be more inclined to participate in screening for T1D associated autoantibodies if medication to delay the onset of T1D was available.

8. Anything Else?

The majority of respondents (71%, n=283) indicated that public funding should prioritize disease-modifying therapies that can delay onset of a disease even if they do not provide a cure.

Despite there being limited experience with TZield in Canada due to its lack of availability, it has been made abundantly clear to us by the T1D community in Canada that having access to TZield and the potential to delay the onset of stage 3 T1D will have a significant positive impact on lives. Canada's T1D community is eager for access to this novel drug.

Regarding limitations with the treatment:

> *"[O]nly available to 8 and older. our kid developed T1D at 6, her sibling is 6 now, so we haven't gotten them tested since there's no point."*

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   Breakthrough T1D worked collaboratively with Diabetes Canada on the drafting of this submission. Laura O'Driscoll assisted with the analysis of the data gathered from the survey and in drafting responses to this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Senior leadership from Connected in Motion helped promote the survey to ensure a greater number of responses.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi				X
Novo Nordisk				X
AstraZeneca	X			
Moderna	X			

Eli Lilly Canada Inc				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Luka Stevanovic
Position: National Director, Government Relations & Advocacy
Patient Group: Breakthrough T1D Canada
Date: February 27th, 2025

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novo Nordisk				X
AstraZeneca	X			
Janssen			X	
Sanofi				X
Bayer	X			
Janssen				X
Novartis Pharmaceuticals Canada Inc.			X	
Moderna Canada			X	
Eli Lilly Canada Inc			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Laura O'Driscoll
Position: Senior Manager, Policy
Patient Group: Diabetes Canada
Date: **February 26, 2025**

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0867-000
Generic Drug Name (Brand Name): Teplizumab
Indication: The anticipated indication is to delay the onset of Stage 3 Type 1 Diabetes in adult and pediatric patients 8 years of age and older with Stage 2 Type 1 Diabetes.
Name of Clinician Group: Canadian Society for Endocrinology and Metabolism
Author of Submission: Dr. Anna Lam

1. About Your Clinician Group

The Canadian Society of Endocrinology and Metabolism (CSEM) is an accredited national professional organization bringing together academic and community-based endocrinologists and researchers engaged in providing health care, education, and research within the broad domain of endocrinology. The CSEM is also a national advocate for excellence in endocrinology research, education, and patient care, and its mandate is to advance the discipline of endocrinology and metabolism in Canada. CSEM website

We are responding to this call for clinician input as medical experts regarding teplizumab for the delay of Stage 3 type 1 diabetes. As lead of this group, I am privileged to present this information. I am an assistant professor in the Department of Medicine and Division of Endocrinology at the University of Alberta. I conduct clinical practice and research in type 1 diabetes.

The group of clinicians being represented includes several leading experts specialized in the treatment of patients with type 1 diabetes from across Canada, including:

Dr. Anna Lam, Assistant Professor, Department of Medicine, Division of Endocrinology and Metabolism, University of Alberta

Dr. Seth Marks, Associate Professor, Department of Pediatrics and Child Health, Section of Pediatric Endocrinology and Metabolism, University of Manitoba.

Dr. Peter Senior, Professor, Department of Medicine, Division of Endocrinology and Metabolism, University of Alberta

Dr. Nadine Vaninetti, Assistant Professor, Department of Medicine, Division of Endocrinology and Metabolism, Dalhousie University

Dr. Diane Wherrett, Professor, Department of Pediatrics, Division of Endocrinology, Hospital for Sick Children and University of Toronto

2. Information Gathering

Contributors reviewed the available data and literature. An initial draft was first developed based on a discussion with the above group of clinicians. The same group was asked to review the draft. Based on group input, a final document was completed and shared with the broader CSEM membership for review. Any disagreements or regional specific issues were maintained in the document to provide CADTH with a full sense of how this regimen is anticipated to impact clinical practice across the provinces that are being represented by the clinician group.

3. Current Treatments and Treatment Goals

Type 1 diabetes (T1D) is an autoimmune disease characterized by progressive destruction of pancreatic beta cells. As beta cells are destroyed, the body is increasingly unable to produce insulin, eventually resulting in complete dependence on exogenous insulin. This process begins years before and continues for years after clinical T1D diagnosis and occurs in distinct stages (1–3) :

- **Stage 1:** This is the pre-clinical phase, where two or more diabetes-related autoantibodies are present, indicating an ongoing autoimmune attack on the pancreatic beta cells. However, blood glucose levels remain normal, and no clinical symptoms are evident.
- **Stage 2:** The autoimmune process continues to advance, leading to detectable abnormalities in glucose, but not yet meeting the criteria for a diagnosis of diabetes. The 5-year risk of progression to Stage 3 is about 75%, and lifetime risk is close to 100% (4).
- **Stage 3:** This is the point of clinical diagnosis, where significant beta cell loss results in overt hyperglycemia and associated symptoms, including polyuria, polydipsia, unintentional weight loss, and fatigue. At this stage, insulin therapy becomes necessary as a life-sustaining therapy.

In Canada, there are no available therapies that modify the disease progression of T1D. As such, insulin therapy is required for the treatment of T1D when patients are diagnosed at Stage 3. The goal of insulin treatment is to maintain blood glucose levels within a target range to avoid the symptoms of hyperglycemia, and to prevent the acute and chronic complications of diabetes. Acute complications, such as diabetic ketoacidosis (DKA), are life-threatening consequences of insulin deficiency that can result in severe dehydration, metabolic imbalances, and death. In the long term, achieving stable glucose control is crucial to reducing the chronic complications of diabetes including microvascular (diabetic retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular disease, stroke, and peripheral artery disease). Beyond glycemic control, treatment goals also include reducing the burden of disease management, improving overall well-being through individualized therapy, diabetes education, and psychosocial support.

Intensive insulin therapy is the recommended regimen for treating T1D (5,6). As a result, management of T1D is complex requiring glucose monitoring, lifestyle modifications, and specialized education so that optimal glycemic control can be achieved while minimizing the risks associated with insulin therapy. Intensive insulin therapy includes basal-bolus insulin therapy (multiple daily injections) or continuous subcutaneous insulin infusion (CSII) via an insulin pump**.** Insulin regimens must balance glycemic control with the avoidance of hypoglycemia**,** particularly nocturnal hypoglycemia, through careful dose adjustments. Glucose monitoring is essential for effective diabetes management, with continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) recommended over blood glucose monitoring (fingerstick testing) for individuals not meeting glycemic targets. Hybrid closed-loop insulin delivery systems further enhance glycemic control by automating insulin dosing based on real-time glucose readings. Structured education and psychosocial support play a critical role in empowering individuals with diabetes to self-manage their condition**,** including insulin dose adjustments, carbohydrate counting, and managing physical activity.

Adjunctive therapies, including SGLT2 inhibitors, GLP-1 receptor agonists, and metformin, which are primarily used for the treatment of type 2 diabetes, have been explored as potential additions to insulin therapy in adults with T1D (6). However, they are not part of routine care and are considered off-label.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

It is widely known that T1D is an autoimmune condition whereby progressive beta cell destruction occurs. Yet autoimmunity is only peripherally considered in the clinical management of T1D. This disconnect reflects the current lack of approved disease modifying therapies for T1D. Additionally, rapid advances in insulin technology have obscured the fact that insulin is a treatment and not a cure for T1D.

Without disease-modifying therapies, the initial presentation of T1D is often sudden and severe, with many patients experiencing significant metabolic decompensation and requiring urgent medical intervention. In Canada, an estimated 25% of children present with diabetic ketoacidosis (DKA) at diagnosis (7), a potentially life-threatening complication that remains the leading cause of death among children with T1D. By delaying the clinical onset of T1D, the risk of acute complications such as DKA may be reduced.

Furthermore, postponing the onset of significant hyperglycemia can lower the risk of long-term diabetes microvascular complications, as each additional year of preserved glycemic control decreases the likelihood of developing chronic diabetes-related complications (8,9).

Exogenous insulin therapy does not fully replicate physiological insulin secretion and as a result is associated with glycemic variability and risk of hypoglycemia which make achieving tight glycemic control challenging. Advances in diabetes technology, have contributed to modest improvements in glucose control, however, disparities in access persist and remain a barrier to widespread benefit (10,11). Data from the T1D Exchange registry show that only 17% of youth and 21% of adults with T1D meet recommended glycemic targets with particularly poor glycemic control observed in adolescents and young adults (12,13). Similarly, in Canada it has been shown that only 23% of adults with T1D achieve an A1C of ≤7.0%, with disparities based on income, geographic location, and access to specialized diabetes care (14).

Hypoglycemia is the most common and feared complication of insulin therapy and it remains the primary limiting factor in achieving optimal glucose control in T1D. Hypoglycemia occurs when blood glucose levels drop below normal (<3.9 mmol/L) leading to symptoms such as shakiness, confusion, sweating, and, in severe cases, seizures, loss of consciousness, or death (15). Recurrent episodes of hypoglycemia can lead to a loss in the body's own protective responses resulting in impaired hypoglycemia awareness and increased risk of future episodes. CGM and automated insulin delivery systems have reduced the risk of hypoglycemia, but they have not fully eliminated the risk; in a recent study among individuals using these technologies, approximately 20% experienced at least one dangerous episode of hypoglycemia in the past year**,** and over 30% reported impaired awareness of hypoglycemia (16).

Hypoglycemia has profound consequences on the quality of life of individuals with T1D often leading to isolating behaviors (17). The fear of experiencing a hypoglycemic episode can result in avoidance of social activities, limited spontaneity, and a sense of constant vigilance. Some individuals employ compensatory strategies, such as maintaining higher blood glucose levels to prevent hypoglycemia leading to sub-optimal glycemic control. Ongoing demands of managing T1D and the associated emotional burden it carries can also reduce quality of life. Diabetes distress refers to the psychological stress that arises from the relentless self-care requirements, fear of complications, and feelings of frustration, anxiety, and burnout related to diabetes management. In a recent large population study of individuals living with T1D, 22% of individuals reported a high level of diabetes distress (18). Notably, CGM use was associated with higher distress indicating that while technology can be useful in diabetes management, it may also contribute to the burden of self-management (18). Diabetes distress is also prevalent among Canadian adolescents who additionally report experiencing diabetes-related stigma leading to decreased quality of life (19).

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Immunotherapies are a promising complement to existing T1D treatments by targeting autoimmune destruction of pancreatic beta cells**,** which insulin therapy alone does not address. Teplizumab is the first approved disease modifying therapy in T1D. Teplizumab is a humanized monoclonal antibody to CD3 on T cells thought to attenuate activated autoreactive T-cell mediated beta cell destruction. It has been shown to preserve endogenous insulin secretion in newly diagnosed T1D (20) and in the pivotal TN-10 trial to change the progression of autoimmunity in T1D delaying the onset of stage 3 T1D in adults and children with stage 2 disease (21).

The indication for teplizumab is to delay the onset of stage 3 T1D in adults and children (≥ 8 years) with stage 2 T1D. As no other disease modifying therapies are approved in T1D, teplizumab would be used alone as the first-line treatment for this indication. Given the progressive nature of beta cell loss in T1D early intervention is preferred to preserve as much insulin production as possible and deferring treatment is not advisable.

The addition of immunotherapy could shift the treatment paradigm from solely managing blood glucose levels to modifying the underlying disease process. Delaying the onset of stage 3 T1D may offer significant clinical and psychosocial benefits. By allowing individuals a longer period without requiring insulin therapy, they may benefit from having more time to adjust to and receive diabetes education which may help alleviate anxiety and allow for smoother transition to insulin therapy and potentially less risk of hyperglycemic emergencies such as DKA. Additionally, preservation of beta cells and endogenous insulin production may provide long term clinical benefits even after insulin therapy is initiated: 1) individuals may achieve tighter glycemic control with insulin therapy, but with lower risk of hypoglycemia and 2) protection against chronic end-organ complications of diabetes (22).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients most likely to respond to and in most need of teplizumab are adults and children (≥ 8 years) with stage 2 T1D to delay on the onset of stage 3 T1D. At this time, the use of teplizumab should be limited to stage 2 T1D which is characterized by the presence of two or more islet autoantibodies and dysglycemia. There is no evidence that teplizumab is effective at earlier stages of T1D. There is evidence that teplizumab preserves beta cell function and slows the loss of endogenous insulin production, as measured by C-peptide, in newly diagnosed stage 3 T1D (23,20). However, the use of teplizumab in stage 3 T1D is beyond the scope of the current application.

Patients most suitable for teplizumab treatment are identified through autoantibody screening and glucose tolerance testing. Specifically, individuals with stage 2 T1D, defined as 1) the presence of two or more positive islet autoantibodies (glutamic acid decarboxylase autoantibody (GADA), insulinoma-associated-2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A), or insulin autoantibody (IAA)) and 2) evidence of dysglycemia without overt hyperglycemia.

Although we are not making recommendations on the diagnostic criteria for stage 2 T1D, our clinician group would like to bring attention to key differences in the definition of dysglycemia without hyperglycemia between the TrialNet TN-10 study and the FDA label for teplizumab. The TN-10 trial defined dysglycemia based on fasting plasma glucose (≥ 6.1 mmol/L and < 7.0 mmol/L) OR 2-hour glucose (≥ 7.8 mmol/L and < 11.1 mmol/L), or glucose levels at 30, 60, or 90 minutes (≥11.1 mmol/L) on an oral glucose tolerance test (OGTT). Notably, repeat confirmation testing was required for individuals over 18 years of age.

In contrast, the FDA defines dysglycemia based on OGTT results or an alternative method if OGTT is unavailable, without specifying what those alternatives entail. Some members of our group have major concerns with this broader definition, particularly because:

1. Alternative methods for diagnosing dysglycemia are not clearly defined, and current evidence is lacking to support this approach.
2. This less stringent definition may lead to inappropriate teplizumab treatment, either too early in the disease course or in individuals who do not actually have stage 2 T1D—such as those over 18 years old with only a single abnormal fasting plasma glucose or OGTT value.

Diagnosing stage 2 T1D presents challenges because autoantibody screening is not widely available (particularly IA-2 and ZnT8 autoantibodies) with resulting underdiagnosis and missed opportunities for early intervention. However, approval and reimbursement of teplizumab may lead to changing clinical practice and would benefit from establishment of national screening program for which pilot work is underway. CanScreen T1D website

Post-hoc exploratory analysis of TN-10 suggest some patients are more likely to respond to teplizumab treatment (21) . However, based on current evidence, it is not yet possible to identify patients most likely to respond to teplizumab treatment.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The primary outcome for teplizumab treatment is delay in progression from stage 2 to stage 3 T1D. This outcome is aligned across clinical practice and the typical outcomes used in clinical trials. It is a clinically meaningful response to treatment as the clinical diagnosis of T1D requires initiation of insulin therapy and is an outcome that is unlikely to vary across physicians.

Progression to stage 3 T1D should be assessed by symptom review (common symptoms of T1D include polyuria, polydipsia, weight loss and vision changes) and recommended screening tests for diabetes (i.e. fasting plasma glucose, OGTT or hemoglobin A1c) every 3-6 months.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Discontinuation of teplizumab should be considered under the following circumstances (24):

1. Severe or persistent adverse events, including cytokine release syndrome lasting more than two days or requiring hospitalization, persistent lymphopenia, neutropenia, anemia, or thrombocytopenia that does not resolve within seven days, liver enzyme elevations where alanine aminotransferase or aspartate aminotransferase levels exceed five times the upper limit of normal or bilirubin levels reach three times the upper limit of normal, and severe hypersensitivity reactions such as anaphylaxis, angioedema, or serum sickness requiring medical intervention.
2. Disease progression, such as the patient progressing to stage 3 T1D during or shortly after treatment.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Teplizumab administration requires via a multidisciplinary team with expertise in the treatment and monitoring of patients with T1D, including an endocrinologist, in a controlled healthcare setting with the capability for intravenous infusions over 14 consecutive days (with no breaks on weekends or holidays). Outpatient infusion centers, hospital-based infusion clinics, or specialty pediatric endocrine or diabetes centers are preferred. These locations must have the necessary infrastructure to monitor patients for adverse effects.

6. Additional Information

Dr. Anna Lam, Case examples:

A 40-year-old male newly diagnosed with T1D two years ago, expressed concern about the risk of T1D in his three school-aged sons. We discussed that, given his positive family history, his children had a 15-fold increased risk of developing diabetes compared to the general population. While antibody screening in his children is an option, it was not pursued due to the lack of available disease-modifying therapy and concerns about the anxiety associated with positive screening results without available intervention. The approval and reimbursement of teplizumab could reopen this discussion, potentially playing a critical role in delaying the onset of T1D in one or more of his children.

Additionally, in the past six months, I have cared for four female patients with T1D who have become pregnant or recently given birth. For their children, access to T1D screening and teplizumab could have significant implications.

Dr. Seth Marks, Case example:

A 9-year-old boy presents with a family history of type 1 diabetes in his older brother who was followed in an interprofessional pediatric diabetes clinic, and his father. Parents have been concerned about type 1 diabetes onset in this 9-year-old. Home glucose monitoring and serum biochemistry indicates glucose levels in the prediabetes/impaired glucose range. He is asymptomatic. Parents are interested in disease modifying therapy.

Dr. Peter Senior, Case example:

36-year-old female found to have diabetes in first pregnancy (initially assumed to have gestational diabetes). Anti-GAD antibodies positive and lean habitus suggested that subclinical T1D more likely. Postpartum OGTT, off any treatment, indicates impaired glucose tolerance (i.e., stage 2 T1D). Treatment with teplizumab to prevent stage 3 T1D would allow a second pregnancy to proceed with much greater safety for mother and infant than if she develops stage 3 T1D and then seeks pregnancy.

Dr. Nadine Vaninetti, Case Example:

32-year-old male in the Armed Forces found to have mild hyperglycemia (stage 2) on routine labs. Subsequent work up revealed positive antibodies. Over the next 6 months, he progressed to stage 3 and was started on multiple daily injections of insulin. This ultimately led to him being medical discharge from the military due to the impact of the disease on his ability to perform his duties. This case highlights the impact early intervention with disease-modifying therapy could have to help delay or reduce the severity of the disease, potentially preserving this patient's health and ability to continue his military service.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Anna Lam
Position: Assistant Professor, University of Alberta
Date: 25/02/2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Vertex	x			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr Seth Marks
Position: Associate Professor, University of Manitoba
Date: 23-02-2025
I have no conflict of interest.

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Peter Senior
Position: Professor, University of Alberta
Date: 25-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sanofi		x		
Canscreen	$0			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Diane Wherrett
Position: Pediatric Endocrinologist, Hospital for Sick Children, Professor, University of Toronto
Date: 26-02-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Nadine Vaninetti, MD, PhD, FRCPC
Position: Assistant Professor, Division of Endocrinology, QE2 Health Sciences Centre, Halifax
Date: 02-FEB-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

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