Cross-Discipline Team Leader Review

Date	Refer to electronic signature
From	Michael D. Nguyen, MD Clinical Team Lead Division of Diabetes, Lipid Disorders and Obesity
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 761183
Applicant	Provention Bio
Date of Submission	Original BLA: November 11, 2021 Resubmission: February 17, 2022
PDUFA Goal Date	November 17, 2022
Proprietary Name	Tzield
Established or Proper Name	Teplizumab-mzwv
Dosage Form(s)	Injection for intravenous use
Applicant Proposed Indication(s)/Population(s)	For the delay of clinical type 1 diabetes in Stage 2 patients (at-risk individuals).
Applicant Proposed Dosing Regimen(s)	Administered by intravenous infusion in a 14 consecutive day course: (b) (4) 1, (b) (4) mcg/m^2 2, 125 mcg/m^2 3, 250 mcg/m^2 4, 500 mcg/m^2 (b) (4) 5 through 14, (b) (4) mcg/m^2
Recommendation on Regulatory Action	Approval of BLA
Recommended Indication(s)/Population(s) (if applicable)	To delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.
Recommended Dosing Regimen(s) (if applicable)	Administer TZIELD by intravenous infusion (over a minimum of 30 minutes) once daily for 14 consecutive days. Day 1, 65 mcg/m^2 Day 2, 125 mcg/m^2 Day 3, 250 mcg/m^2 Day 4, 500 mcg/m^2 Days 5 through 14, 1030 mcg/m^2

Contents

1. Benefit-Risk Assessment

Type 1 diabetes (T1D) is a serious, life-long, autoimmune disease caused by progressive destruction of insulin-producing islets of Langerhans cells leading to insulin deficiency and dependence on exogenous insulin for survival. Approximately 1.6 million Americans have T1D.[1] T1D is associated with significant microvascular (damage to kidney, eyes, nervous system) and macrovascular (cardiovascular disease) complications, and premature death. Disease management is complex, demanding multiple daily insulin injections and intensive monitoring of glucose, diet, and activity levels.

Teplizumab (Tzield, pronounced TEE-zeeld) is a first-in-class, humanized, anti-CD3 monoclonal antibody intended to delay the onset of T1D in individuals who have two or more T1D-related autoantibodies and dysglycemia (Stage 2 T1D, see below for more details on clinical staging). Stage 2 T1D is associated with a 75% risk of progression to a diagnosis of T1D within 4 to 5 years, and a lifetime risk of nearly 100%. If approved, teplizumab would be the first disease-modifying therapy for T1D.

The teplizumab development program has met substantial evidence of effectiveness with persuasive results from an adequate and well controlled study (TN-10) plus confirmatory evidence from 5 clinical trials containing biomarker evidence (C-peptide preservation) that directly relates to the pathophysiology of disease. Reliance on a single adequate and well-controlled trial plus confirmatory evidence is appropriate in light of multiple factors. The trial was highly statistically significant, robust to sensitivity analyses with conservative assumptions, and demonstrated effect on a clinical outcome. There is substantial unmet medical need. T1D is a serious, lifelong condition with no available cure or therapy to delay disease onset, and the typical age of T1D disease onset occurs in a vulnerable pediatric population. Attention to diabetes management pervades nearly all daily activities causing strain on children and families. Patients are at risk of acute complications from under- or overdosing insulin, including hypoglycemia and ketoacidosis, a two-year difference in the median time to diagnosis would allow children critical time to grow and mature before assuming more of the burdens of disease management.

The benefit of teplizumab in delaying the onset of T1D was demonstrated in the TN-10 trial, a randomized, placebo-controlled, event driven trial in 76 patients (ages 8 and older) at risk of T1D who received one intravenous infusion per day for 14 days. After approximately five years of follow-up, 20 (45%) patients in the teplizumab group and 23 (72%) in the placebo group developed laboratory confirmed T1D, demonstrating a statistically significant delay in onset of diagnosis. The median time to diagnosis was 25 months in the placebo group versus 50 months in the teplizumab arm, for a difference of 25 months. With a median follow-up time of 51 months, teplizumab resulted in a statistically significant delay in the development of Stage 3 type 1 diabetes, hazard ratio 0.41 (95% CI: 0.22 to 0.78; p=0.0066). The observed difference is clinically meaningful because it is expected to result in delay of the burdens of disease management, which include the requirement for daily glucose monitoring and insulin therapy, and delay of the risks of insulin therapy (e.g., hypoglycemia).

[1] Centers for Disease Control and Prevention. National Databetes Statistics Report 2020. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Cytokine release syndrome (CRS), serious infections, lymphopenia and hypersensitivity reactions were the most important identified risks and are listed in the Warnings and Precautions section of the proposed labeling. Most CRS cases were mild to moderate in severity and managed with antipyretics. Serious infections were more frequent within first 3 months of teplizumab dosing compared to placebo recipients but did not result in permanent sequelae. A single case of serum sickness occurred but may have been confounded by preexisting autoimmunity. In the clinical development program, the majority of patients developed anti-drug antibodies (ADA) and a possible association between ADAs and rash was observed, the details of which are incorporated into the immunogenicity section of proposed labeling. Lymphopenia and transaminase elevations were predictable and generally self-limited. Uncertainties remain including theoretical risks of lymphoproliferative disorders and the risk of malignancy related to long term immunosuppression.

The overall benefit-risk profile is favorable. Safety for the intended use was demonstrated from data submitted in the first review cycle. Safety data submitted in the safety update with the resubmission did not change the overall safety conclusions. Several required postmarket studies, including a longitudinal observational safety study using a patient registry design will provide additional safety data on longer latency safety outcomes that may not be detected premarketing, e.g. malignancy. A required postmarket pharmacokinetic (PK) study in children aged 0-7 years will also be issued under the Pediatric Research Equity Act (PREA).

In the first review cycle there were no clinical deficiencies; however, the application received a Complete Response (CR) Action Letter because of a lack of PK comparability between the to-be-marketed product and the clinical trial product (see section 2.3). Other issues included product quality deficiencies related to drug substance and drug product stability assessment (including the stability comparison between the to-be-marketed and clinical trial products), and deficiencies related to objectionable conditions observed during the prelicensure inspection of the manufacturing facility. These deficiencies have been addressed in the resubmission.

The CR issue regarding lack of PK comparability was adequately addressed through the submission of new data and the development of a population PK (popPK) model using newly submitted PK data from the ongoing PROTECT study in patients with new onset T1D (PROTECT PK substudy). The PK model also leveraged prior single dose PK data, as well as data from study TN-10. New PK and pharmacodynamic (PD) data were also used to develop a new exposure-matched dosing regimen. The new data suggested the difference in PK between the clincal trial and commercial product after multiple dosing was likely not clinically meaningful because the difference in AUC was small, with 27% less exposure for the AGC product versus the Lilly product (smaller than the difference observed with single dosing). Furthermore, analysis of PD endpoints also suggested no difference in target binding. Although there was consensus that the combination of analytical comparability, small PK differences with multiple dosing, and comparability of PD markers suggest that the drug could be approved without a dose adjustment, there was ultimately agreement that matching PK using an adjusted dosage regimen was reasonable to ensure that exposure achieved with the AGC product would be comparable to the exposure achieved with the Lilly product. Safety

concerns would not be raised because the C_{max} of the new dosing regimen is comparable to the original dosing regimen.

In addition to being scientifically unnecessary, it is likely neither feasible nor ethical to test the new dosage regimen in a prospective clinical trial of stage 3 T1D prevention. TN-10 was a multinational trial that spanned 9 years and recruited only 76 patients. In the absence of universal screening for islet autoantibodies, identifying sufficient subjects would be challenging. For example, in a program of primary care based screening in Germany, only 0.02% (17 out of 90,632) children aged 2 to 5 years who were screened for autoantibodies over a 4-year period were diagnosed with stage 2 T1D.[2] Moreover, we do not believe that clinical equipoise exists to repeat the trial given the positive finding.

In the context of this BLA, exposure matching to achieve PK comparability is scientifically justified. Although we are not aware of prior examples of PK exposure matching to bridge two biological products manufactured at different sites, model-informed exposure matching is commonly used in regulatory decision making (e.g. pediatric extrapolation, new route of administration, dosing in specific populations, such as renal/hepatic impairment). We do not believe that PK exposure matching could be widely leveraged as a general pathway to address lack of PK comparability for investigational drug products seeking FDA approval, as teplizumab is uniquely situated within the logistical and ethical challenges described earlier, as well as the unmet medical need. Furthermore, although the root cause of the differences in PK has not yet been elucidated for teplizumab, FDA will issue multiple postmarket commitments for the applicant to continue to investigate the issue (see Section 3 below). In addition, the statutory requirements for licensure of a biological product as biosimilar to a reference product would preclude use of this approach in that setting.

Although not factored into the benefit-risk assessment of this application, the availability of teplizumab may enable population-based screening and intervention programs for type 1 diabetes to expand beyond research settings.[3] Whether screening is risk-based (e.g., family history) or age-based, enhanced screening could potentially identify a larger proportion of individuals at-risk for developing T1D at an early stage and alter the progression of disease. Studies suggest that early identification of at-risk patients lowers the rate of diabetic ketoacidosis (DKA) to less than 5%, compared to the estimated baseline frequency of DKA

[2] Ziegler AG, Kick K, Bonifacio E, Haupt F, Hippich M, Dunstheimer D, Lang M, Laub O, Warncke K, Lange K, Assfalg R, Jolink M, Winkler C, Achenbach P; Fr1da Study Group. Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany. JAMA. 2020 Jan 28;323(4):339-351. doi: 10.1001/jama.2019.21565. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990943/

[3] Sims EK, Besser REJ, Dayan C, Geno Rasmussen C, Greenbaum C, Griffin KJ, Hagopian W, Knip M, Long AE, Martin F, Mathieu C, Rewers M, Steck AK, Wentworth JM, Rich SS, Kordonouri O, Ziegler AG, Herold KC; NIDDK Type 1 Diabetes TrialNet Study Group. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. Diabetes. 2022 Apr 1;71(4):610-623. https://diabetesjournals.org/diabetes/article/71/4/610/144874/Screening-for-Type-1-Diabetes-in-the-General

between 15-80%.[4,5] The prevention of DKA at presentation potentially avoids the acute morbidity of cerebral edema, shock, neurocognitive impairment and mortality that can have long term consequences.[6,7] Moreover, early identification of at-risk patients would provide critical time for family counseling and education to prepare for insulin therapy.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 1 diabetes mellitus (T1D) is a serious, life-long autoimmune disease that presents most commonly in childhood. T1D affects 1.6 million adults aged 20 years and older and 244,000 children and adolescents less than 20 years of age. • Over time, among individuals at risk for developing T1D, declining production of insulin from autoimmune beta cell injury results in dysregulation of glucose homeostasis and hyperglycemia requiring insulin therapy for survival. • Once patients develop dysglycemia on oral glucose tolerance testing (Stage 2 T1D), the 4- to 5-year risk of T1D is 75%, and the lifelong risk is nearly 100%. • The majority of individuals with T1D (85%) have no family history and are not identified at earlier stages of T1D prior to need for insulin dependence. Therefore, the pool of patients who are currently identified as at-risk for	The clinical consequences of Stage 3 T1D include reliance on insulin therapy for survival. The burden of daily insulin therapy (including intensive glucose monitoring), as well as its acute risks (severe hypoglycemia) contribute to poorer quality of life. The presence of autoantibodies and dysglycemia (Stage 2 T1D) makes an eventual diagnosis of Stage 3 T1D virtually inevitable, and treatments that could delay this progression to Stage 3 would be clinically meaningful because of the burden and risks of insulin therapy. The small pool of at-risk patients makes conducting clinical trials in Stage 2 T1D extremely challenging.

[4] Hekkala AM, Ilonen J, Toppari J, Knip M, Veijola R. Ketoacidosis at diagnosis of type 1 diabetes: Effect of prospective studies with newborn genetic screening and follow up of risk children. Pediatr Diabetes. 2018 Mar;19(2):314-319. https://onlinelibrary.wiley.com/doi/10.1111/pedi.12541

[5] Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. Pediatr Diabetes. 2012 Jun;13(4):308-13. https://onlinelibrary.wiley.com/doi/10.1111/j.1399-5448.2011.00829.x

[6] Cameron FJ, Scratch SE, Nadebaum C, Northam EA, Koves I, Jennings J, Finney K, Neil JJ, Wellard RM, Mackay M, Inder TE; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care. 2014 Jun;37(6):1554-62. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4179516/

[7] Ghetti S, Kuppermann N, Rewers A, Myers SR, Schunk JE, Stoner MJ, Garro A, Quayle KS, Brown KM, Trainor JL, Tzimenatos L, DePiero AD, McManemy JK, Nigrovic LE, Kwok MY, Perry CS 3rd, Olsen CS, Casper TC, Glaser NS; Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study Group. Cognitive Function Following Diabetic Ketoacidosis in Children With New-Onset or Previously Diagnosed Type 1 Diabetes. Diabetes Care. 2020 Nov;43(11):2768-2775. doi: 10.2337/dc20-0187. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7576431/

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	T1D is extremely small.	
Current Treatment Options	• There are no current treatment options for the delay of T1D in at-risk individuals. • Although there are therapies to improve glycemic control in patients with T1D, there are no currently approved disease-modifying therapies.	There are no treatment options to delay T1D available at this time.
Benefit	• In TN-10, a randomized placebo-control trial in at-risk children and adults aged ≥8 years, teplizumab successfully delayed T1D diagnosis. Among 76 patients enrolled, 44 were given teplizumab and 32, placebo. After approximately five years of follow-up, 20 patients in the teplizumab group (45%) and 23 in the placebo group (72%) had been diagnosed with T1D (met the primary endpoint). • The median time to T1D diagnosis was 50 months in the teplizumab group vs. 25 months in the placebo group. In the primary analysis of time to T1D diagnosis, the hazard ratio was 0.41 (95% confidence interval (CI): 0.22 to 0.78, p=0.0066). The treatment effect was statistically significant and robust to sensitivity analyses under a range of conservative assumptions for missing data. **Uncertainties in Benefit** • No evidence of effectiveness in children aged 0-7 years. • No evidence of improved effectiveness with repeat dosing, or effectiveness in other stages of disease (Stage 1 or Stage 3 T1D). • TN-10 was not designed to assess clinical benefit in specific subgroups, such as patients with specific HLA genotypes.	The observed difference in children and adults age 8 and older is clinically meaningful, as it allows the avoidance of insulin therapy and the accompanying risks of insulin therapy, such as iatrogenic hypoglycemia, and is expected to result in reduced disease burden. The Applicant will be required to conduct a postmarket PK study in children 0-7 years of age to bridge the safety and efficacy into the younger age cohorts.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The most important safety concerns were cytokine release, serious infections, lymphopenia, and hypersensitivity reactions, all of which are labeled in the Warnings and Precautions. • Rash was a common adverse event (AE) among teplizumab-treated patients (45%) but was self-limited and all cases resolved without sequelae. **Uncertainties in Risk** • The development program was not designed to assess rare safety events with long latency such as malignancy or lymphoproliferative disease. • No data regarding the safety in pregnancy or in children 0-7 years of age.	Overall, the safety profile has been reasonably well characterized in the relevant population of at-risk patients and a similar population with new- or recent-onset T1D. Safety issues include cytokine release, infection, lymphopenia, and rash, although many of these adverse events were self-limited, mild, or transient (limited to the 14-day dosing period). Uncertainty regarding rare or long-latency risks will be addressed through a required postmarket patient registry study (PMR) that will follow patients exposed to teplizumab for 10 years and compare rates of key adverse events to a comparator.

2. Background

2.1 Applicant Proposal and Product Information

Provention Bio seeks FDA approval for teplizumab (Tzield), henceforth teplizumab, a first-in-class, humanized, anti-CD3 monoclonal antibody. The proposed indication is to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D. Teplizumab is administered by intravenous infusion once daily in a single 14-day course. Teplizumab is thought to interfere with T-cell mediated autoimmune destruction of beta cells by inducing immunologic exhaustion of autoreactive CD8+ T cells and was granted breakthrough therapy designation by FDA in 2019.

2.2 Therapeutic Context

T1D is lifelong illness resulting from T-cell mediated autoimmune destruction of pancreatic beta cells that leads to insulin deficiency. Approximately 1.6 million adults and 244,000 children aged <20 years have T1D in the United States (US).[8] An estimated 64,000 new cases

[8] CDC. Prevalence of Diagnosed Diabtes. https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-diabetes.html

of T1D are diagnosed annually in the US in children and adults ages 0-64 years.[9] Chronic diabetes-related complications include both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disease, peripheral artery disease). Current T1D management focuses on matching exogenous insulin with food intake and daily activities, with the goal of normalizing average blood glucose levels, while avoiding hypoglycemia. Exogenous insulin (administered using basal and mealtime formulations) and pramlintide (an amylin analogue) are the only two approved therapies for treatment of T1D. Both medications reduce hyperglycemia but neither modifies the underlying autoimmune disease process. Moreover, insulin is associated with important safety risks including hypoglycemia and weight gain; pramlintide requires injections before each meal, must be separately injected from insulin at a different site, and requires careful monitoring and patient selection to avoid hypoglycemia, making it a therapeutic option that is not widely used in T1D management.

T1D Stages

T1D is a heterogeneous disorder that progresses through 4 sequential stages defined by the development of autoantibodies and blood glucose levels (see Figure 1). Not all individuals follow this exact sequence and there is wide variation in the rate of progression.

- **Stage 1** is defined as having ≥2 T1D-related autoantibodies, which include glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen 2 autoantibody (IA-2A), insulin autoantibody (IAA), zinc transporter 8 (ZnT8), or islet cell autoantibodies (ICA).
- **Stage 2** is characterized by multiple autoantibodies plus dysglycemia (impaired glucose tolerance or fasting glucose), without overt hyperglycemia.
- **Stage 3** is defined by hyperglycemia with laboratories meeting traditional diabetes diagnostic criteria (glycated hemoglobin, fasting glucose, 2-hour plasma glucose on oral glucose tolerance testing).
- **Stage 4** is established T1D.

[9] Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Med. 2017 Nov 8;15(1):199. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5688827/

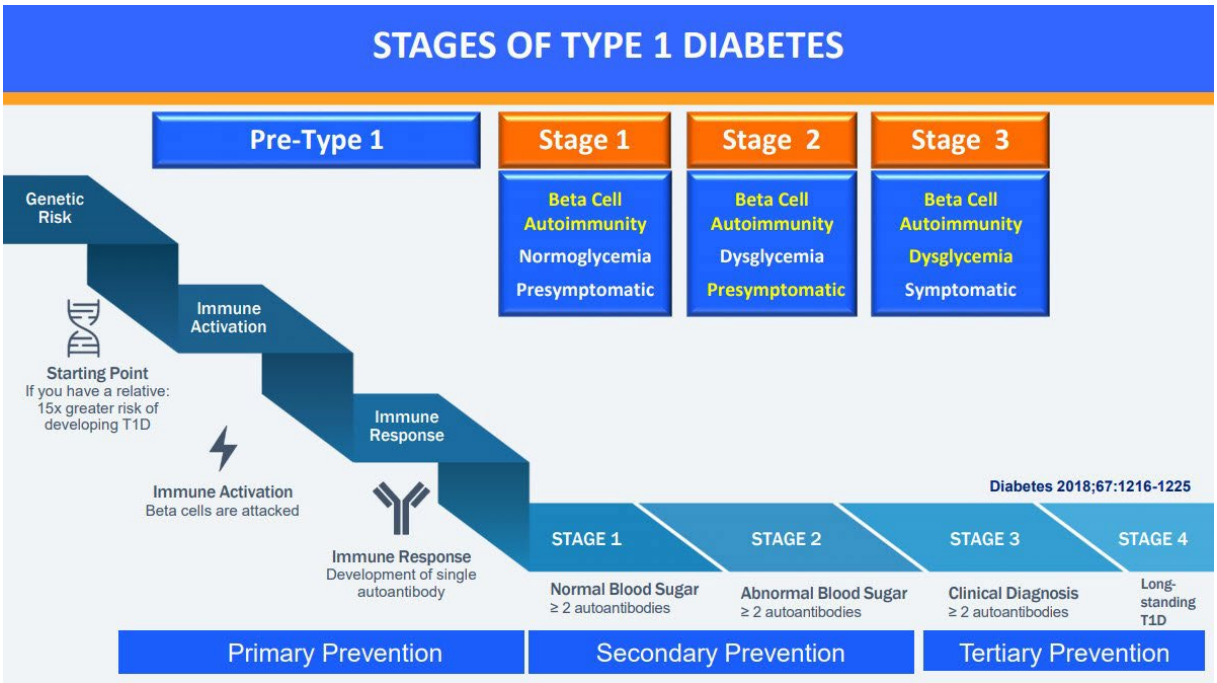


Figure 1 Stages of Type 1 Diabetes – TrialNet

Source: https://twitter.com/t1d_trialnet/status/1111314463179853825, based on Greenbaum CJ et al. Strength in Numbers: Opportunities for Enhancing the Development of Effective Treatments for Type 1 Diabetes-The TrialNet Experience. Diabetes. 2018 Jul;67(7):1216-1225.

Children with only a single islet autoantibody have a ~15% risk of reaching Stage 3 T1D within 10 years. [10] Children with two or more autoantibodies (Stage 1) have a 44% 5-year risk and 80-90% 15-year risk of reaching Stage 3. The 5-year risk of progression is approximately 75%, and the lifetime risk approaches 100%.[11]

At diagnosis, symptoms are usually present (increased thirst and urination, blurred vision, unexplained weight loss, fatigue) and insulin therapy is initiated. However, clinical presentation may range from modest hyperglycemia to diabetic ketoacidosis (40-60%). It is estimated that approximately 60-90% of beta cell mass has been lost by the time of clinical diagnosis.[12]

[10] Besser REJ et al. ISPAD clinical practice consensus guidelines 2022: Stages of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2022 Sep 30. https://onlinelibrary.wiley.com/doi/10.1111/pedi.13410
[11] Insel RA et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 1 October 2015; 38 (10): 1964–1974. https://doi.org/10.2337/dc15-1419
[12] Powers AC. Type 1 diabetes mellitus: much progress, many opportunities. J Clin Invest. 2021 Apr 15;131(8):e142242. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8262558/

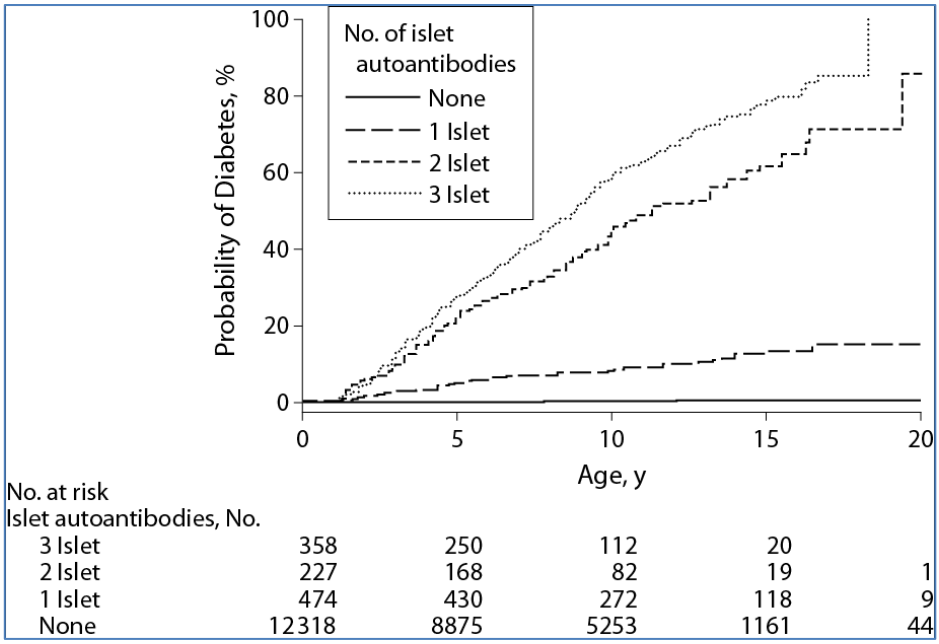


Figure 2. Development of Diabetes in Children Stratified by Islet Autoantibody Outcome

Source: Ziegler AG, Rewers M, Simell O, et al. Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children. JAMA. 2013;309(23):2473–2479.
https://jamanetwork.com/journals/jama/fullarticle/1697963

T1D Incidence and Prevalence

T1D accounts for approximately 80% of diabetes in children, with an estimated incidence of 21.7 new cases of T1D per year per 100,000 population.[13] The typical age of onset has a bimodal distribution, with one peak at ages 4 to 6 years and a second peak at ages 10 to 14. Approximately 30% of patients present after age 18. T1D occurs in all races and ethnicities but is more common among non-Hispanic whites. Relatives of patients with T1D have a 15-fold increased risk of disease compared to those without a relative (0.4% in the general population, 6-7% in patients with sibling with T1D, 6-9% with parent with T1D); however, approximately 90% with new onset T1D do not have a positive family history.[14]

T1D Genetics

Like other immune-mediated disorders, T1D is associated with specific genes located on chromosome 6p encoding human leukocyte antigen (HLA) molecules responsible for antigen presentation. HLA DR and DQ loci confer an estimated 30% to 50% of the genetic risk in T1D. The highest-risk HLA haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 (also

[13] Redondo MJ, Steck AK, Pugliese A. Genetics of type 1 diabetes. Pediatr Diabetes. 2018 May;19(3):346-353. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC5918237&blobtype=pdf

[14] Sims EK, et al.; NIDDK Type 1 Diabetes TrialNet Study Group. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. Diabetes. 2022 Apr 1;71(4):610-623. https://diabetesjournals.org/diabetes/article/71/4/610/144874/Screening-for-Type-1-Diabetes-in-the-General

expressed as DR3-DQ2) and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR4-DQ8).[15] Over 90% of patients with T1D carry DR4, DQB*0302, and/or DR3, DQB*0201. However, the genetics of T1D is complex and polygenic, involving both HLA class I and II genes, as well as non-HLA genes (e.g., INS, PTPN22, CTLA4, IL2RA). Environmental factors are also postulated to contribute to the pathogenesis of T1D, including maternal and intrauterine environment, host microbiome, and viral infections.

Unmet Clinical Need

If approved, teplizumab will be the first disease modifying agent that delays the onset of overt hyperglycemia in T1D by modulating the underlying immunopathology. Although it does not prevent or cure T1D, teplizumab functions as a secondary prevention agent, delaying the onset of clinical diagnosis of diabetes (Stage 3), need for exogenous insulin therapy, intensive glucose monitoring, and the associated safety risks of insulin treatment. This delay is particularly clinically meaningful because the illness presents predominantly in children. Overall 45% of children present before 10 years of age, well before they are able to handle the complex disease management requirements independently and placing the burden on families. Indeed, delaying disease onset allows children to mature and advance in physical dexterity and cognition necessary for self-care.

2.3 Regulatory History: First & Second Review Cycle

The Applicant submitted the original Biologics License Application (BLA) on November 11, 2021. During the first review cycle, the BLA was discussed at the Endocrinologic and Metabolic Drugs Advisory Committee (see Table 1).[16] The advisory committee deliberated upon the overall strength of evidence for approval, clinical meaningfulness of a 2-year delay in disease onset, product safety, and the proposed indication. The committee voted 10 to 7 in favor of approval.

Table 1. Excerpts from the Official Meeting Minutes of the FDA Advisory Committee

Question	Excerpt from Meeting Minutes
1. Discuss the strength of the overall evidence presented herein to conclude that effectiveness has been established for teplizumab for the proposed indication.	• A majority agreed that TN-10 provided adequate evidence of efficacy, although this view was not unanimous. • Several Committee members acknowledged that there was a benefit associated with teplizumab use but were not confident in the magnitude of the observed effect size given the small study size and notable baseline imbalances with respect to age and genetics. • The Committee did not support the use of the C-peptide meta-analysis as confirmatory evidence of effectiveness demonstrated by the Applicant. • Some members argued that the applicant failed to directly link the 2-year delay to clinical benefits, while others argued that a 2-year delay had face

[15] Lambert AP, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EA, Bingley PJ. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinol Metab. 2004 Aug;89(8):4037-43. https://academic.oup.com/jcem/article/89/8/4037/2844654?login=true

[16] https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-agenda-information-may-27-2021-meeting-endocrinologic-and-metabolic-drugs-advisory-committee#event-materials

	validity for clinical meaningfulness because of the obvious burdens of the disease.[17]
2. Discuss the clinical meaningfulness of the observed median 2-year delay of onset of T1D demonstrated in study TN-10.	• Collectively, the Committee agreed that the observed median 2-year delay of onset of T1D demonstrated in study TN-10 was substantially meaningful. • Generally, the Committee members were convinced by the public testimonies that a delayed onset of T1D would improve the quality of life (QOL) for patients and their families. Although one Committee member mentioned that it is unknown whether this 2-year median delay will make an impact on the prevention of long-term complications of type 1 diabetes, more members focused on quality of life than on chronic diabetes-related complications when discussing their views on clinical meaningfulness.
3. Discuss your view of the safety issues identified in the clinical development program and the potential for unobserved, longer latency safety issues (e.g., malignancy) given the mechanism of action of teplizumab. Discuss whether these safety concerns can be adequately mitigated through labeling and/or required post marketing studies.	• The Committee overall thought that the adverse events shown should not prevent the approval of teplizumab. • The concern was noted that patients in TN-10 were not followed for safety after T1D diagnosis. The majority of the Committee thought this deficiency could be addressed with a postmarketing safety study, although one member stated that the lack of data would be difficult to address through labeling. • The rheumatologist on the committee was generally reassured by the breadth of the safety data, noting that there are often smaller safety datasets for immunomodulating therapies used in the pediatric population, and that safety data for patients with stage 3 type 1 diabetes provided a robust quantity of safety data. • If approved, the Committee agreed that there would be a need to establish a rigorous post-marketing registry to monitor long-latency safety issues.
4. Based on available data, discuss how the indicated population should be described to ensure that the expected benefit(s) of teplizumab will outweigh the risks of treatment.	• Collectively, the Committee agreed that based on the data presented, the indication should be restricted to the population that was studied, although several members recommended that the indication not be restricted to relatives of patients with type 1 diabetes but instead should include both non-relatives and relatives meeting the criteria for stage-2 T1D. • Some Committee members also mentioned incorporating HLA DR4 present individuals in the labeling in order to advise patients and families of the most likely patient to benefit from therapy, while others cautioned the Committee about restricting use to patients by subgroup analyses that were not powered to detect treatment effect among groups.

Source: https://www fda.gov/media/151795/download

Substantial Evidence of Effectiveness

In the first review cycle, DDLO concluded that Provention Bio demonstrated substantial evidence of effectiveness of teplizumab for the delay of T1D when administered to patients with Stage 2 T1D based on a single adequate and well-controlled trial (study TN-10), plus confirmatory evidence (see Summary Basis for Regulatory Action memo for further details).[18] Study TN-10 was a multicenter, randomized, double-blind, placebo-controlled trial of 76 patients with Stage 2 T1D. This trial demonstrated a clinically meaningful treatment effect of a delay in Stage 3 T1D with a Hazard Ratio of 0.41 (95% CI 0.22 – 0.78). The results were

[17] From additional meeting notes from FDA staff who attended the Advisory Committee meeting.
[18] Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

robust to sensitivity analyses under a range of assumptions for missing data and baseline imbalances in demographics and disease characteristics.

Confirmatory evidence of effectiveness was provided by a meta-analysis of five trials (Protégé, Encore, Study 1, AbATE, and Delay) that demonstrated a statistically significant reduction in the decline of C-peptide (using pooled data from 4-hour mixed meal tolerance testing) when teplizumab was administered to patients with new or recent onset Stage 3 T1D, a later disease stage than the current indication. C-peptide connects insulin's A-chain and B-chain in the proinsulin molecule and is a measure of endogenous insulin secretion (and by extension, beta cell function) because equimolar amounts of C-peptide and insulin are released into the circulation. The observed reduction in C-peptide decline in patients with Stage 3 T1D was considered compelling mechanistic evidence in the setting of well understood disease pathophysiology, because teplizumab's effect of preserving of beta cells is the same in both Stage 2 and Stage 3 T1D. The benefit-risk profile was favorable with cytokine release syndrome, infections and lymphopenia identified as product risks, all of which were mild to moderate without permanent sequelae.

Complete Response Action

The primary regulatory issue precluding approval in the first cycle was a change in drug substance after clinical studies were completed. A new manufacturing site was developed for the proposed commercial product with nearly identical manufacturing process and cell bank. However, the commercial product was more quickly eliminated than the clinical trial product and had a 50% lower total exposure (as measured by AUC_{inf}), with comparable C_{max} after a single infusion.

On July 2, 2021, FDA issued a Complete Response action letter describing deficiencies related to clinical pharmacology, product quality and facility inspections (see Table 2). The letter also requested a safety update that included data from all clinical studies of the product under consideration and additional comments not related to the approvability of the application.

Table 2. Key Aspects of the FDA Complete Response Action Letter

Category	Deficiency
Clinical Pharmacology	**Issue 1** "The results of the pharmacokinetic (PK) bridging study PRV-031-0041 in healthy volunteers failed to show PK comparability between the PRV-031 product used in TN-102 and the planned commercial product. Study PRV-031-004 revealed considerable differences in the total area under the time-concentration curve extrapolated to infinity (AUC0-inf) between the two products, with the planned commercial product providing an approximately 50% lower AUC0-inf, despite a comparable Cmax after a single intravenous infusion. As PK remains the primary endpoint for demonstration of comparability between the two products, you will need to establish PK comparability appropriately between the intended commercial product and the clinical trial product, or provide other data that adequately justify why PK comparability is not necessary." Refer to the CR letter for the complete text of Issue 1.
Product Quality	**Issue 2**

	"Results of your ongoing real-time stability studies demonstrate unacceptable charge variation measured in PRV-031 drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions… In total, these data preclude the ability to assign a shelf-life for either drug substance or drug product, not only because of the unacceptable degree of change, but also because stability behavior is not consistent between drug product lots manufactured using AGC material. This degree of change also prevents a determination as to whether there is a problem with product stability, the method, or both. Finally, the possibility that this variation arises from method variability also introduces uncertainty into the reliability of all results generated with this method, including the analytical comparability assessment, highlighted by the difference in stability behavior between AGC lots and lots manufactured by Eli Lilly…" **Issue 3** "No information was provided in Section 3.2.S.2.3 regarding your plans to monitor Master Cell Bank (MCB) and Working Cell Bank (WCB) stability…" **Issue 4** "The protocol provided in your submission dated March 31, 2021, for requalification of the primary reference standard (PRS) is deficient…" **Issue 5** "Insufficient information was provided regarding the levels and types of leachates in PRV-031 derived from its container closure and the risk to patients from any leachates that are potentially present in the drug product during its shelf life…"
Facility Inspections	**Issue 6** "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigators conveyed deficiencies to the representative of the facility…"
Safety Update	**Clinical** "When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level…"
Additional Comment (not approvability issues)	**Clinical Pharmacology** "Characterize the immunogenicity potential for the proposed commercial product manufactured by AGC Biologics, including but not limited to assessments of the titers of anti-drug antibodies and neutralizing antibodies to PRV-031. Compare the immunogenicity potential of the AGC product to the clinical trial product and provide justification for any differences noted." Refer to CR letter for items 1, 3-14.

2.4 Scope and Focus of this Summary Review Memo

On February 17, 2022, Provention Bio submitted their response to FDA's Complete Response Action Letter. Contained in Provention Bio's resubmission was information pertaining to the following issues, among other items:

1. Alternative dosing regimen and justification
2. Response to the product quality deficiencies
3. Response to the facility inspections
4. Proposed proprietary name and draft labeling

5. Safety update
6. Immunogenicity and safety data supporting comparability
7. Analytical data supporting comparability

This summary memo focuses on the major review issues pertaining to the second cycle:

- Review Issue #1: Resolution of deficiency: quality of the commercial product
- Review Issue #2: Resolution of deficiency: lack of PK comparability between the clinical trial and commercial products
- Review Issue #3: Autoantibody testing for Stage 2 T1D diagnosis
- Review Issue #4: Safety update

Please refer to the individual review memos from the first review cycle regarding FDA's assessment of product safety and efficacy, facility inspections, QT cardiac safety, clinical pharmacology, statistics, and nonclinical studies (see Table 3). Additionally, please refer to the Summary Basis for Regulatory Action for in depth discussion of the overall benefit-risk assessment as well as FDA's determination of substantial evidence of effectiveness.

Table 3. Key Events in the Review Timeline and FDA Review Memos

Date	Description
8/2/2019	**FDA Grants Breakthrough Designation (IND 102629)**
11/2/2020	**Original BLA submission**
1/14/2021	Proprietary Name Review, Ariane Conrad
2/26/2021	Labeling Review, Ariane Conrad
3/12/2021	Nonproprietary Name Suffix Review, Carlos Mena-Grillasca
3/24/2021	Labeling Review, Ariane Conrad
3/29/2021	Maternal Health Review by the Division of Pediatrics and Maternal Health, Catherine Roca
4/28/2021	Consult Review by the Office of Scientific Investigations (OSI), Cynthia Kleppinger
4/29/2021	Clinical Consult from the Division of Hematologic Malignancies 1 (DHM1), Emily Jen
4/30/2021	Clinical Pharmacology and Pharmacometrics Review, Harisudhan Thanukrishnan / Elyes Dahmane
5/27/2021	**Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting**
5/14/2021	Pharmaceutical Quality Executive Summary, Jennifer Swisher
5/5/2021	Pharmacology/Toxicology Review, Dan Minck
6/25/2021	Interdisciplinary Review Team for Cardiac Safety Studies
6/28/2021	Biostatistics Review, Yu Wang
7/1/2021	REMS Review, Till Olickal
7/2/2021	Clinical Review Memo / Summary Basis for Regulatory Action, Lauren Wood Heickman
7/2/2021	**FDA Complete Response Letter**
9/1/2021	Biostatistics Review Memo Addendum, Yu Wang
2/17/2022	**BLA Resubmission**
5/4/2022	Labeling Review, Ariane Conrad
5/6/2022	Nonproprietary Name Suffix Review, Carlos Mena-Grillasca
5/6/2022	Proprietary Name Review, Ariane Conrad
7/14/2022	Clinical Review Memo, Lauren Wood Heickman
8/19/2022	RPM PLR Format Review, Supendeep Dosanjh
8/24/2022	**Medical Policy & Program Review Committee (MPPRC)**
9/7/2022	**MPPRC Follow Up Meeting**
9/14/2022	Biometrics Review, Wang Yu

10/14/2022	Labeling Review, Ariane Conrad
10/19/2022	Product Quality Review, Rachel Novak
10/20/2022	Clinical Pharmacology Review and Pharmacometrics Review, Harisudhan Thanukrishnan / Elyes Dahmane

3. Review Issue #1: Quality of the Commercial Product

Teplizumab is recombinant humanized monoclonal IgG1 antibody derived from the parent murine monoclonal antibody OKT3 with additional leucine to alanine mutations at positions HC234 and HC235 (AlaAla) that reduces binding to Fc receptors and complement that can result in T cell activation and cytokine release syndrome. Across the teplizumab development program, the drug substance (DS) changed manufacturers over time.

- Macrogenics, 2005 – 2008
- Eli Lilly, 2008 – 2010
- AGC Biologics, 2018 to present

In Study TN-10 the drug substances used in trial subjects were manufactured by Macrogenics and Eli Lilly, while the planned commercial product is manufactured by AGC Biologics.

3.1 Summary of First Review Cycle

In the first review cycle, the product quality team consisted of Deborah Schmiel, Meng-Jung Chiang, and Jennifer Swisher (Team Lead). This team had 3 important conclusions, as described below (please refer to their review memo for further details):

1. **Lots manufactured at Macrogenics and Eli Lilly were analytically comparable**:
   - "ProBio provided comparisons of the manufacturing processes, analytical methods, DS release assay results (both at release in section 3.2.S.4.4 and concurrent testing), some characterization assay results, and stability results for the comparability study. Three MacroGenics lots (QC05021, 060206001, and 060706001) and three Lilly lots (A573775, A573776, and A573777) were assessed in parallel by the following DS release assays: identity, appearance, protein content, pH, potency by CD3 competitive binding assay, SE HPLC, reduced and non-reduced SDS PAGE, charge isoforms by IEF, CHO DNA, host cell proteins (HCP), (b) (4) endotoxin, and bioburden."
   - "Additional characterization assays were used to assess the same six lots from MacroGenics and Lilly that includes molecular mass by LC MS (deglycosylated intact, LC, and HC), free sulfhydryl content, structure by near and far UV CD, N-linked glycan profile, and peptide mapping for primary sequence and posttranslational modifications. The results from release and characterization assays from the MacroGenics and Lilly DS lots supported the comparability of the teplizumab DS manufactured by both processes."

2. **Lots manufactured at Eli Lilly and AGC Biologics were analytically comparable**:

- "The AGC lots appear to be comparable to the Lilly lots by the analytical methods and bioassays. The slight difference in glycan profiles between the AGC lots and the Lilly lots is not likely to impact teplizumab potency or stability."
- "ProBio provided comparisons of the manufacturing processes, analytical methods, DS release assay results (both at release in section 3.2.S.4.4 and concurrent testing), some characterization assay results, and stability results for the comparability study… The results from release and characterization assays from the MacroGenics and Lilly DS lots supported the comparability of the teplizumab DS manufactured by both processes."
- "Although there are significant differences in the N-linked glycosylation pattern in the lots manufactured at Lilly (represented by the [reference standard]) and the commercial lots manufactured at AGC, there should be little impact on teplizumab, in terms of potency or serum half-life, as the product is engineered to reduce Fc effector functions."

3. OBP Recommended a Complete Response Action

- "OBP recommends a Complete Response action for the 351(a) BLA application from Provention Bio for TZIELD (Teplizumab) for intravenous administration due to several deficiencies that preclude the demonstration that the contract manufacturer AGC Biologics can manufacture Teplizumab to historic product quality standards and adequately monitor changes to product quality. Recent stability updates demonstrate results from the CEX HPLC assay are highly variable to a degree that a shelf life cannot be assigned for teplizumab drug substance and drug product. Moreover, the unreliability of the CEX HPLC assay results raises uncertainty in the stability comparison in the comparability study between Lilly and AGC Teplizumab lots."

3.2 Second Review Cycle

In the second review cycle, the product quality team consisted of:

Discipline	Assessor	Branch/Division
Drug Substance/Drug Product	Deborah Schmiel	DBRR I/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facilities and Microbiology, DS	Wendy Tan	DBM/OPMA/OPQ
Microbiology Team Lead	Maxwell Van Tassell	DBM/OPMA/OPQ
Facilities Team Lead	Zhong Li	DBM/OPMA/OPQ
Application Technical Lead	Rachel Novak	DBRR I/OBP/OPQ

In the second review cycle, the OBP had the following conclusions (please refer to their review memo for additional details):

1. All product quality deficiencies listed in the CR letter were adequately addressed and the data submitted are sufficient to recommend approval.

a. "The Office of Biotechnology Products, OPQ, CDER, has completed assessment of STN 761183 for Tzield manufactured by Provention Bio, Inc. The data submitted in this application are sufficient to support a conclusion that the manufacture of Tzield is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. It is recommended that this product be approved for human use under conditions specified in the package insert."

b. "From the product quality perspective, the information and data provided for the CR and additional items in the resubmission were adequately addressed and any remaining residual manufacturing issues will be addressed as post-marketing commitments (PMCs)… For the assay development, the current assays have demonstrated suitability for their intended purpose but require optimization or a full validation exercise. The current reference standard system is one-tier and is considered suitable for testing new DS and DP lots at release and on stability; however, the sponsor is currently developing a two tier system that will be submitted to the BLA in Q3 2023. These items are considered low risk and are appropriate to resolve post-marketing given the expected benefits to patients at risk of developing T1D."

c. "Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy was provided for the (b) (4) This addresses the CR deficiency related to the drug product manufacturing facility.

2. **OPB recommended 5 product quality-related postmarketing commitments (PMCs).**

a. **Continue to investigate the root cause of any product quality differences that can account for the PK differences between the AGC and Lilly products**. OBP concluded that although differences were noted in the analytical comparability assessment between the products manufactured by AGC Biologics and Eli Lilly, those differences were not considered significant or would impact on PK based on current experience. However, the analytical comparability assessment is limited by the attributes assessed, the methods used and their capabilities. To address the residual uncertainty, FDA will issue a PMC to request that the sponsor continue to investigate any product quality differences that could have contributed to the difference in PK between the AGC and Lilly products and investigate additional controls to ensure the product remains consistent.

b. **Optimize or replace the Cation Exchange Chromatography (CEX) charge assay.** Teplizumab manufactured by Eli Lilly has (b) (4)% more basic and acidic variants but this difference was not thought to preclude a determination of comparability. CR issue #2 relates to these acidic and basic variants (impurities) that could result in loss of potency or immunogenicity. The root cause of the method variability was identified and the CEX assay does not appear to demonstrate unacceptable variability. However, the PMC requests that the sponsor continue to optimize the method to reduce variability or to replace the method. Moreover, the deficiencies with the CEX assay that hindered the ability to set shelf life were addressed and the DS and DP storage conditions were established.

c. **Validate the hydrophilic interaction chromatography high-performance liquid chromatography (HILIC HPLC) assay to control glycans at release of the DS and reassess the acceptance criterion for release**. (b) (4)

[redacted] (b) (4) at DS release and a PMC was issued to validate the HILIC HPLC method.

d. **Validate a product-specific Host Cell Protein (HCP) assay**. Host cell proteins are process-related impurities that potentially affect safety and immunogenicity. The sponsor has demonstrated adequate clearance of HCPs [redacted] (b) (4) While this assay has been shown to be suitable for release testing of the DS, the sponsor was asked to generate product specific HCP antibodies for the assay to ensure that the coverage of HCPs is complete. Therefore, a PMC will be conveyed for the sponsor to generate an HCP method that utilizes product-specific HCP antibodies.

e. **Implement and qualify a working reference standard**. The sponsor is currently using a single-tier system consisting of a primary reference standard (PRS) bank only. The PRS is intended to be used to qualify future PRSs and working reference standards (WRSs). The deficiencies described in CR item #4 regarding the PRS requalification protocol were adequately addressed. While the current PRS is considered suitable for its intended purpose, there does appear to be some degradation of the PRS. The sponsor is working to qualify a new PRS to be submitted to the BLA in a prior approval supplement, if approved. In addition, a PMC will be conveyed for the sponsor to implement a two-tiered system. The sponsor stated that the WRS would be implemented by Q3 2023.

4. Review Issue #2: Lack of PK Comparability between the Clinical Trial Product and the Commerical Product

The composition of the review team from the Office of Clinical Pharmacology (OCP) was the same for both review cycles and included Drs. Harisudhan Thanukrishnan and Elyes Dahmane.

4.1 Summary of the First Review Cycle

In preparation for commercial launch, Provention Bio implemented a new manufacturing process at AGC Biologics, [redacted] (b) (4). Although no significant differences affecting safety or efficacy were noted in analytical comparability studies, a single-dose PK study (PRV-031-004) conducted in healthy subjects compared drug exposure following a single subtherapeutic dose (207 mcg/m^2, equivalent to ~2.3% of the therapeutic dose) and found that the AGC Biologics product had 51.5% lower $AUC_{0\text{-}inf}$ (geometric mean ratio [90%CI] = 48.5% [43.6 - 54.1]) despite having comparable C_{max} (see Table 4). Thus, the to-be-marketed drug manufactured by AGC Biologics was not comparable to the drugs used in the trial TN-10 manufactured by Eli Lilly and Macrogenics based on the standard bioequivalence criterion (0.8 – 1.25). Thus, the OCP review team recommended a complete response action. In the first review cycle, OCP also concluded:

- The proposed body-surface area (BSA) based 14-day dosing regimen administered as a once a day infusion over 30 minutes is appropriate. Less than 10% of the total dose is given on the first 4 days of ramp-up as a precaution to avoid adverse reactions (e.g.,

cytokine release syndrome). Exposure to teplizumab after BSA-based regimen was found to be independent of age and body weight.

- No dose modifications are necessary based on intrinsic and extrinsic factors.
- Across all studies, a majority (~60-70%) of study subjects developed anti-drug antibodies (ADA) to teplizumab in response to the single 14-day course. The impact of ADA on exposure is predicted to be minimal, as the time for onset and increase in ADA levels (> Days 28 post-first dose) lagged behind the maximal teplizumab serum concentrations (< Days 28 post-first dose), thereby minimizing the overlap of PK and ADA following the proposed single 14-day dosing regimen.

In the CR letter, the Applicant was asked to establish PK comparability between the intended commercial product and the clinical trial product or provide other data to justify why PK comparability is not necessary.

Table 4. Summary of Pharmacokinetic Parameters and Statistical Analysis of Cmax and AUCs (PRV-031-004) [Clinical Pharmacology Review Memo]

	Teplizumab Test Product			Teplizumab Reference Product			Test versus reference
Parameter (units)	n	GLSM	90% CI of GLSM	n	GLSM	90% CI of GLSM	Ratio of GLSMs (90% CI)
C_{max} (ng/mL)	51	38.9	(36.0, 42.1)	49	41.2	(38.0, 44.6)	94.5 (84.5, 106)
$AUC_{0\text{-}24}$ (h*ng/mL)	51	314	(297, 331)	49	396	(374, 419)	79.2 (73.2, 85.7)
$AUC_{0\text{-}48}$ (h*ng/mL)	51	452	(429, 475)	49	598	(568, 629)	75.5 (70.3, 81.2)
$AUC_{0\text{-}last}$ (h*ng/mL)	51	540	(495, 588)	49	1050	(960, 1140)	51.5 (45.6, 58.2)
$AUC_{0\text{-}inf}$ (h*ng/mL)	37	706	(654, 762)	37	1450	(1350, 1570)	48.5 (43.6, 54.1)

Abbreviations: CI, confidence interval; GLSM, geometric least squares mean; n, number of subjects with valid observations; Cmax, maximum concentration; AUC, area under curve

Source: Table 14.2.1-3, PRV-031-004 Study Report

4.2 Second Review Cycle

4.2.1 PROTECT Substudy

In response to the CR letter, the Applicant submitted results from the PK substudy of the ongoing PROTECT trial, a randomized, double blind, multinational placebo controlled study of children aged 8-17 years with newly diagnosed T1D. The ongoing PROTECT parent trial seeks to enroll approximately 300 subjects randomized 2:1 to received two 12-day treatment courses administered six months apart of teplizumab or placebo with the goal of evaluating whether treatments slow the loss of beta cells (as measured by C-peptide AUC after a mixed meal tolerance test at Week 78). The submitted PROTECT substudy results included all data on only the first course of treatment for patients who received teplizumab (AGC, N=33 or Eli Lilly, N=138) as of August 2021. The substudy data augments the prior single-dose PK study results and prior popPK model by providing:

- **PK data (AUC, Cmax, Ctrough)** from a clinically relevant 12-day multiple-dose regimen with sparse PK sampling (the 12-day course had a 2 day ramp-up, phase instead of 4-day ramp up)
- **PD biomarker data**:
  - CD3 receptor occupancy (on CD3+, CD4+CD8- and CD4-CD8+)
  - Activation status of T-cells (anti-CD69 positivity on CD3+, CD4+ and CD8+ T cells)
  - Total lymphocyte counts
- **Anti-drug antibody data**
  - Incidence
  - Titer values

4.2.2 Population PK Model: PK Comparability

The new joint PK model consisted of the following studies to characterize the PK of teplizumab from 3 different products used during clinical development, see Table 5 below.

Table 5. Studies and Drug Products Contributing to Joint Population PK Model

	Macrogenics	Eli Lilly	AGC Biologics
Protégé (dose ranging study)	442*	0	0
TN-10	16	9	0
Single Dose PK Bridging Study (PRV-031-004)	0	49	51
PROTECT Sub-study	0	137	32

**Divided into 3 different dosage regimens*

OCP's evaluation concluded that the Applicant's joint PK model adequately described the observed concentrations from all studies, dosing regimens and products, and that it could be used to assess PK comparability of the products. The revised joint popPK model still revealed that the AGC Biologics product was not comparable to the clinical trial product in terms of total drug exposure. The model estimated that the total exposure had 27% lower AUC_{inf}, 22% lower C_{trough} and the 90% confidence intervals fell outside the standard equivalence margins (despite having similar Cmax).

4.2.3 Investigating Causes of PK Differences: Immunogenicity

OCP conducted additional investigation of the root cause of the PK differences, in collaboration with the Office of Biotechnology Products. They identified no product quality differences upon structural and functional analytical assessments that could fully explain the observed PK differences. Although minor differences in [redacted] (b) (4) were identified, they were not considered to be the source of the observed PK differences.

Additionally, OCP evaluated whether immunogenicity was a factor contributing to the observed PK differences but determined that it was unlikely to explain the difference in clearance between the teplizumab products. In both the single dose study and the PROTECT substudy, the emergence of anti-drug antibodies (ADAs) occurred beyond the time point when differences in serum drug concentrations were observed. In PROTECT, ADAs mainly appeared on Day 8 to Day 12 after treatment initiation, peaking at Day 56 to 91. Although ADAs were a statistically significant covariate in PK modeling and were estimated to increase drug clearance by 11-33% at the highest titer levels, the highest ADAs titers occurred after the full 14 day course in the PROTECT substudy, when teplizumab concentrations were relatively low (see Table 6 below). Similarly, ADA titers in the single dose study (PRV-031-004) appeared after Day 5 to Day 8, when teplizumab concentrations (from the AGC Biologics and Eli Lilly products) were already very low or below the quantifiable limit (see Table 7 below). The median half-life of the AGC Biologics product was 4.5 days (range 4.2 – 5 days).

Table 6. Summary of ADA Titers in PROTECT Substudy

	PROTECT sub-study							
	Day 1 (predose)*		Day 12		Day 28		Day 56	
	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)	AGC product (N=32)	Lilly product (N=138)
Ln(ADA titers)								
Mean (SD)	0.405 (1.31)	0.114 (0.666)	4.17 (2.42)	3.29 (2.76)	6.29 (3.38)	4.13 (3.56)	6.38 (3.11)	3.78 (3.79)
Median [Min, Max]	0 [0, 5.48]	0 [0, 4.79]	4.79 [0, 8.25]	4.09 [0, 9.64]	6.17 [0, 11.7]	4.79 [0, 11.0]	6.52 [0, 11.7]	4.09 [0, 11.7]
Missing	0 (0%)	36 (26.1%)	1 (3.1%)	37 (26.8%)	5 (15.6%)	39 (28.3%)	4 (12.5%)	42 (30.4%)
ADA category*								
Missing	0 (0%)	36 (26.1%)	1 (3.1%)	37 (26.8%)	5 (15.6%)	39 (28.3%)	4 (12.5%)	42 (30.4%)
Null	30 (93.8%)	101 (73.2%)	9 (28.1%)	46 (33.3%)	5 (15.6%)	38 (27.5%)	4 (12.5%)	47 (34.1%)
Value ≥ Ln(30)*	2 (6.3%)	1 (0.7%)	22 (68.8%)	55 (39.9%)	22 (68.8%)	61 (44.2%)	24 (75.0%)	49 (35.5%)

* Day 1 (predose) represent baseline (control) ADA collected before initiation of the study treatment. The ADA titer threshold value is 30 in the ADA assay. All titers below the threshold are considered as zero.
Note: On Day 28, the neutralizing antibodies (NAb) represented 45% (10/22) and 28.4% (25/88) for the AGC product and the Lilly product, respectively. On Day 56, the NAb represented 57.1% (4/7 samples) and 53% (44/83 samples) for the AGC product and the Lilly product, respectively.
Source: FDA reviewer (based on the population PK dataset)

***Source**: Clinical Pharmacology Review Memo, Table 11, page 34 of 62*

Table 7. Summary of the ADA Titers in the Single Dose PK Bridging Study (PRV-031-004)

	PRV-031-004 study											
	Day 1 (predose)		Day 2		Day 3		Day 5		Day 8		Day 15	
	AGC (N=51)	Lilly (N=49)	AGC (N=51)	Lilly (N=49)	AGC (N=51)	Lilly (N=48)	AGC (N=51)	Lilly (N=47)	AGC (N=50)	Lilly (N=48)	AGC (N=49)	Lilly (N=48)
Ln(ADA titers)												
Mean (SD)	0.0939 (0.670)	0.0694 (0.486)	0.0939 (0.670)	0.0694 (0.486)	0.0939 (0.670)	0 (0)	0.254 (1.08)	0 (0)	1.20 (2.01)	0.430 (1.26)	4.89 (4.07)	4.29 (3.69)
Median [Min, Max]	0 [0, 4.79]	0 [0, 3.40]	0 [0, 4.79]	0 [0, 3.40]	0 [0, 4.79]	0 [0, 0]	0 [0, 6.17]	0 [0, 0]	0 [0, 6.87]	0 [0, 4.79]	5.48 [0, 11.0]	4.79 [0, 11.0]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)
ADA positivity *												
Negative	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (100%)	48 (94.1%)	46 (97.9%)	36 (72.0%)	41 (85.4%)	17 (34.7%)	17 (35.4%)
Positive	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0%)	3 (5.9%)	1 (2.1%)	14 (28.0%)	7 (14.6%)	32 (65.3%)	31 (64.6%)
Neutralizing ADA												
no ADA	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (98.0%)	50 (98.0%)	48 (100%)	48 (94.1%)	46 (97.9%)	36 (72.0%)	41 (85.4%)	17 (34.7%)	17 (35.4%)
Positive	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)	1 (2.0%)	0 (0%)	5 (10.0%)	1 (2.1%)	15 (30.6%)	13 (27.1%)
Negative	0 (0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0%)	0 (0%)	2 (3.9%)	1 (2.1%)	9 (18.0%)	6 (12.5%)	17 (34.7%)	18 (37.5%)

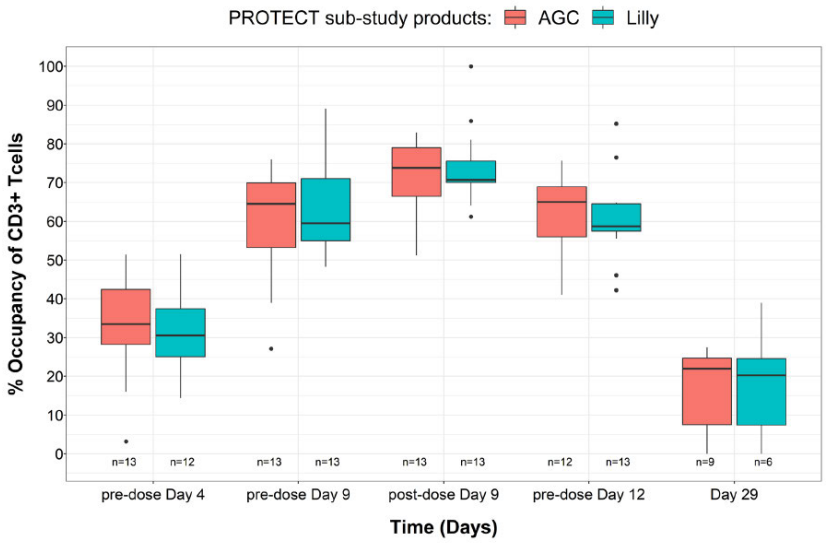
* Day 1 (predose) represent baseline (control) ADA collected before the single dose administration. ADA positivity is for the confirmatory step of a three-tiered approach.

Source: FDA reviewer (based on the Immunogenicity Safety Analysis Dataset: adis.xpt)

***Source**: Clinical Pharmacology Review Memo, Table 12, page 35 of 62*

4.2.4 Population PK-PD Model: PD Biomarker

To facilitate the comparability assessment of the products, exploratory in vivo PD marker results from the PROTECT substudy were submitted as orthogonal markers to the PK information consisting of CD receptor occupancy (including occupancy in T cell subsets) and post-exposure total lymphocyte counts. Both products from AGC Biologics and Eli Lilly showed similar receptor occupancy when examined on different days of the regimen, suggesting comparable target engagement (see Figure 3). A similar trend of comparable coating for both products was also observed in the T-cell subsets CD4+CD- and CD4-CD8+ (data not shown). Moreover, OCP found that CD3 receptor occupancy increased in parallel with higher serum teplizumab concentrations after repeated dosing, indicating it is sensitive to changes in serum drug levels, despite being upstream in the mechanism of action for teplizumab (see Figure 4). Indeed, the relationship between CD3 occupancy and serum drug concentrations was similar between the two products across a broad range of concentrations.



Note: the last planned sampling day for CD3+ occupancy assessment was variable and was restricted to sampling times ranging for Day 29 to Day 30 for adequate comparison.

Source: FDA reviewer (based on the lasted combined PD dataset pkpdnonmemprotect17feb22.xpt)

Figure 3. Teplizumab Occupancy (%) on CD+ T Cells by Product in the PROTECT Substudy

***Source**: Clinical pharmacology review memo, Figure 18, page 61 of 61.*

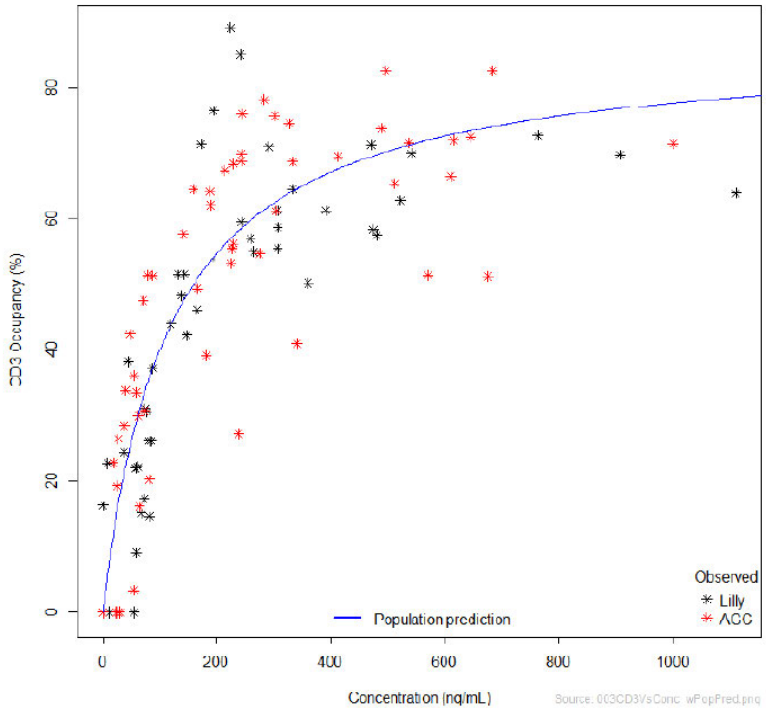
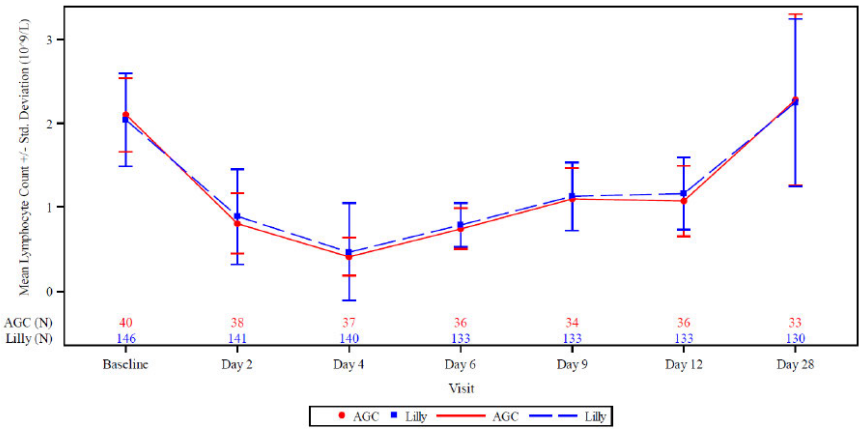


Figure 4. Scatter Plot of Serum Teplizumab Concentration vs. CD3 Receptor Occupancy by Product in the PROTECT Substudy

***Source:** Clinical Pharmacology Review Memo, Figure 6, page 24 of 62.*

Similarly, although not a primary PD marker of interest, the overall profile in the decline and recovery of lymphocyte counts was also superimposable for both products (see Figure 5).



Source: Applicant's PK/PD Substudy Report, Figure 11, page 34.

Figure 5. Mean (SD) of Lymphocyte Counts Baseline to Day 28 By Product in the PROTECT Substudy

Source: *Clinical Pharmacology Memo, Figure 7, page 25 of 62*

4.2.5 Population PK Model: Adjusted Dosing Regimen

The population PK model was considered reliable to describe the PK and simulate the doses for exposure-matching of teplizumab. Using the model, an alternative exposure-adjusted dosing regimen with a higher cumulative dose for the to be marketed product was developed. The optimal adjusted dosing regimen for the AGC product was identified by the OCP to be: 65 – 125 – 250 – 500 – (1030 x 10 days) $\mu g/m^2$.

Based on the model, OCP also determined that the AGC Biologics product has saturable binding to target CD3 receptors but no target-mediated elimination through intracellular internalization, suggesting the AGC Biologics product has linear non-specific elimination. Thus, the increase in AGC Biologics product dosage necessary for the purposes of exposure-matching is not expected to saturate the elimination of teplizumab. Indeed, both teplizumab products have comparable median half-lives (4.5 and 4.4 days for the AGC and clinical trial product, respectively).

4.2.6 Discussion and Conclusion

The original international multicenter trial experienced significant challenges in recruiting subjects and issued protocol changes to reduce its target sample size and address barriers to recruitment, largely due to the absence of routine autoantibody screening and low prevalence. Thus, attempting to replicate the trial with the commercial drug product would result in substantial delay and is potentially not feasible. Given the substantial unmet medical need and positive TN-10 trial results, clinical equipoise would not exist to start a second trial, raising concerns about the ethics of initiating such a trial.

Although an option might be to not approve the current BLA, and wait for the results of the PROTECT study to inform the safety and effectiveness of AGC Biologics, it was determined to be unnecessary because of the persuasiveness of the existing trial results. Reliance on PROTECT would also introduce additional complexities, as the study is conducted in a different population and addresses a different scientific question (preservation of beta cell function using a C-peptide concentration endpoint). Additionally, the trial has a slightly different dosing regimen. If PROTECT were unable to demonstrate statistical efficacy in Stage 3 population, it would not necessarily mean that AGC manufactured teplizumab is not effective in Stage 2 as there may be other possible explanations (e.g., inadequate statistical power, greater drug effects in Stage 2 vs. Stage 3).

Although in discussions there was consensus that the combination of analytical comparability, small PK differences with multiple dosing, and comparability of PD markers suggest that the drug could be approved without a dose adjustment, there was ultimately agreement that matching PK using the adjusted dose was reasonable to ensure efficacy without introducing new safety concerns.

5. Review Issue #3: Autoantibody Testing for Patient Selection for Treatment with Teplizumab

The sponsor is seeking an indication for the delay of Stage 3 T1D in patients with Stage 2 T1D. In TN-10, subjects with Stage 2 T1D were selected based on the presence of dysglycemia plus two or more positive autoantibodies: Islet Cell Autoantibodies (ICA), Glutamic Acid Decarboxylase 65 autoantibodies (GAD65), Insulinoma-Associated-2 Autoantibodies (IA-2A), Insulin Autoantibodies (IAA), or Zinc Transporter-8 Autoantibodies (ZnT8). All autoantibody tests used in TN-10 were developed by (b) (4) and were CLIA-certified but not FDA cleared. FDA has cleared assays developed by (b) (4) to detect antibodies to four specific islet cell antigens: IA-2A (k (b) (4), 510k approval), GAD65 (k (b) (4), 510k approval), IAA (k (b) (4), 510k approval), ZnT8 (DEN (b) (4), de novo approval). There is no FDA cleared ICA test; however, clinical practice guidelines now recommend screening only for specific autoimmune biomarkers.[19] A key issue in this review is whether the autoantibody tests used in TN-10 are considered in vitro companion diagnostic devices."[20]

Provention Bio articulated several reasons to justify their position that the islet cell autoantibody assays are not consistent with the definition of a companion diagnostic, including

[19] Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, Ludwig B, Nørgaard K, Pettus J, Renard E, Skyler JS, Snoek FJ, Weinstock RS, Peters AL. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2021 Dec;64(12):2609-2652. Erratum in: Diabetologia. 2022 Jan;65(1):255. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8481000/

[20] Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices, August 6, 2014. https://www.fda.gov/files/medical%20devices/published/In-Vitro-Companion-Diagnostic-Devices---Guidance-for-Industry-and-Food-and-Drug-Administration-Staff%29.pdf

the belief autoantibody tests are already part of the current practice of medicine and are commonly used and well understood. DDLO agrees with this rationale and agrees that the autoantibody assays are not companion diagnostics.

All forms of diabetes require assays for patient selection and those assays do not require parallel approval under companion diagnostics (e.g., HbA1c, fasting plasma glucose, oral glucose tolerance test). This is also true of autoimmune disorders other than T1D whose assays do not require companion diagnostics approval. We also believe that clinicians would accurately diagnose Stage 2 T1D with the currently available FDA cleared autoantibody assays and tests for glycemic status. Consensus guidelines establishing the diagnosis of Stage 2 T1D have been in existence since 2015 and continue to be promulgated and updated for both pediatric and adult T1D.[10,11,19] These guidelines have expanded the types of acceptable tests to diagnose dysglycemia to include fasting plasma glucose and glycated hemoglobin A1c, and have also modified which antibody tests should be used to confirm autoimmunity in Stage 2 T1D, indicative of efforts to help practicing clinicians improve their identification of this clinical entity.

DDLO consulted CDRH for advice on this issue. Dr. Jessica Chu authored two review memorandums on the issue dated January 1, 2021, and June 17, 2022. They stated that although FDA cleared autoantibody tests exist that could potentially support labeling, there is insufficient data to support the performance of these tests in the intended use population (Stage 2 T1D). Dr. Chu wrote, "Cleared autoantibody tests were cleared with the intended use of 'aid in the diagnosis of Type 1 diabetes mellitus', which is different from a test used to screen for individuals with Stage 2 T1DM eligible for teplizumab treatment… It is not clear that the sensitivity of the cleared tests would be the same for diagnosed T1D patients (studied in the cleared submissions) vs. stage 2 T1D patients and that the specificity of the cleared tests would be the same in the non-target disease groups (studied in the cleared submissions) vs. patients suspected of Stage 2 T1DM but determined to be ineligible for the drug."[21] However, DDLO noted that Stage 2 and Stage 3 T1D share the same underlying disease process and exist along the same clinical continuum. Thus, FDA-cleared assays approved to "aid in the diagnosis of T1D" are expected to perform similarly in Stage 2 T1D and Stage 3 because the same autoreactive antibodies are identified. Both Stage 2 T1D and Stage 3 T1D are characterized by the presence of two or more antibodies and the presence of dysglycemia. What distinguishes these disease stages is the proportion of remaining islet cells, and the extent of residual beta cell function determines when patients transition from impaired glucose intolerance (Stage 2) to an overt hyperglycemic state (Stage 3).

Please note that assays for specific islet cell antigens (IAA, IA-2A, ZnT8, GAD65) were used to determine eligibility for 39 of the 44 teplizumab recipients and 28 of the 32 placebo recipients in TN-10. A laboratory-developed, CLIA cleared, ICA assay was also used to qualify eligibility for 9 total patients in TN-10: 5 in teplizumab group and 4 in the placebo group. However, the 2021 ADA and EASD consensus guidelines for adults with T1D states, "Islet cell antibody (ICA) measurement is no longer recommended because it is an imprecise biological assay that has been superseded by the direct measurement of single antibodies";

[21] Chu, Jessica. CDRH Consult Review Memo, ICCR00851446, BLA 761183, June 17, 2022.

similarly, pediatric clinical researchers have focused on identifying specific islet cell autoantibodies.[19,22] Thus, use of the ICA antibody is no longer recommended clinical practice.

6. Safety Update

The Applicant provided a 13 month safety update in response to one of the non-approvability issues in the Complete Response letter. The safety updated consisted of adverse event (AE), serious adverse event (SAE), and adverse event of special interest (AESI) data from two ongoing trials and one completed clinical trial. The PROTECT study remains blinded (teplizumab or placebo), limiting the interpretation of results. The Applicant also submitted additional blinded safety analyses comparing safety data between subjects enrolled prior to March 2021 (N=223, Eli Lilly or placebo), and subjects enrolled after March 2021 (N=104, AGC Biologics or placebo). Dr. Lauren Wood Heickman authored the primary clinical review and ultimately concluded, "The integrated assessment of safety is not meaningfully changed with the safety update." I concur with her assessment. Please see her memo for further details.

Table 8. Clinical Trials in Safety Update

	Study Description & Population	Role in Review
Ongoing Trials		
PROTECT PRV-031-001	Randomized, double-blind, placebo controlled trial Patients with stage 3 T1D, aged 8-17 years Treatment: two 12-day courses teplizumab (9mg/m^2) Follow up: 18 months	N=327 total randomized* N=223 Eli Lilly teplizumab or placebo N=104 AGC Biologics teplizumab or placebo 1. Unexpected safety signals 2. Expected events that are rare in the general population (cytokine release syndrome, lymphopenia, infection) 3. Immunogenicity between Eli Lilly and AGC Biologics products
TN-10 Extension PRV-031-002	Open label extension of TN-10 study Patients from TN-10 with Stage 3 T1D Treatment: singe 12-day course teplizumab (9mg/m^2) Follow-up: 18 months	N=4 patients 1. Limited evaluation of SAE, TEAE, AESI of N=4 patients
Completed Trial		
Protégé Extension CP-MGA031-02	3-year long term follow up of Protégé (double blind, placebo controlled study, dose ranging study)	N=32 completed segment 1 (open-label) N=187 completed segment 2 (double-blind) 1. Long latency events (e.g., malignancy)

[22] Rewers M, Bonifacio E, Ewald D, Geno Rasmussen C, Jia X, Pyle L, Ziegler AG; ASK Study Group and Fr1da Study Group. SARS-CoV-2 Infections and Presymptomatic Type 1 Diabetes Autoimmunity in Children and Adolescents From Colorado, USA, and Bavaria, Germany. JAMA. 2022 Sep 27;328(12):1252-1255. https://jamanetwork.com/journals/jama/fullarticle/2795226

	No treatment initiated	

** Subjects randomized prior to March 2021 received Eli Lilly product, while all subsequent participants received AGC Biologics product*

6.1 Deaths

No new deaths were reported in the safety update.

6.2 Serious Adverse Event (SAEs)

A. PROTECT Study [PRV-031-001]

As of the cutoff date, 14 (4.3%) subjects reported a total of 17 treatment-emergent SAEs. Dr. Wood Heickman concluded that the results from the blinded analysis of PROTECT were either expected adverse reactions associated with teplizumab (e.g., CRS, infection) or observed at similar or lower rates than the safety data reviewed in the first cycle.

Table 9. Serious Adverse Events (Teplizumab and Placebo), PROTECT Study

	PROTECT (N=327)		Study Day
Preferred Term	**Count [n]**	**%**	
Cytokine release syndrome	3 [3]	0.9%	2-3
Hypoglycemia	3 [2]	0.6%	149, 172, 219
Infection*	2 [2]	0.6%	
Device-related bacteremia			3
Palpitations (related to viral myocarditis)			77
Anxiety	1 [1]	0.3%	22
Colitis ulcerative	1 [1]	0.3%	323
Concussion	1 [1]	0.3%	498
Dermatitis atopic	1 [1]	0.3%	82
Nephrolithiasis	1 [1]	0.3%	220
Suicidal ideation	1 [1]	0.3%	328
Syncope	1 [1]	0.3%	63
Vomiting	1 [1]	0.3%	3

***Source**: Clinical Review Memo, Table 5, page 30 of 52*

B. TN-10 Extension [PRV-031-002]

No SAEs reported in the TN-10 Extension study.

C. Protégé Extension [CP-MGA031-02]

Thirteen (7.2%) teplizumab subjects and none of the placebo subjects reported a total of 20 SAEs in the Protégé Extension study. All SAEs for the long-term noninterventional Protégé Extension follow-up study were reported, at the earliest, approximately 2 years after enrollment. Dr. Wood Heickman concluded that no unexpected pattern of clustering of preferred terms was observed, and no new safety concerns were identified. I concur with her assessment.

Table 10. Serious Adverse Events, Protégé Extension Study

	Protégé Extension Teplizumab (N=181)		Protégé Extension Placebo (N=38)		Study Day (for isolated events)
Preferred Term	**Count [n]**	**%**	**Count**	**%**	
Diabetic ketoacidosis	6 [4]	2.2%	0	0	811-1008
Angina pectoris	1 [1]	0.3%	0	0	761
Appendicitis perforated	1 [1]	0.3%	0	0	915
Coronary artery disease	1 [1]	0.3%	0	0	761
Death	1 [1]	0.3%	0	0	980
Diabetes mellitus inadequate control	1 [1]	0.3%	0	0	987
Appendicitis perforated	1 [1]	0.3%	0	0	915
Gastritis	1 [1]	0.3%	0	0	801
Gastroenteritis	1 [1]	0.3%	0	0	729
Hypoglycemic seizure	1 [1]	0.3%	0	0	868
Iritis	1 [1]	0.3%	0	0	793
Peritonitis	1 [1]	0.3%	0	0	915
Spinal compression fracture	1 [1]	0.3%	0	0	868
Spontaneous abortion	1 [1]	0.3%	0	0	814
Varicella	1 [1]	0.3%	0	0	746

Source: *Clinical review memo, Table 5, page 31 of 52.*

6.5 Adverse Events of Special Interest (AESI)

The AESI included infections, acute mononucleosis-like illness, lymphomas or other malignancies, hypoglycemia, liver function abnormalities, thrombocytopenia, hypersensitivity reactions, rash, cytokine release syndrome (CRS), severe lymphopenia (<500 mm^3 for ≥7 days).

A. PROTECT Study [PRV-031-001]

In PROTECT, 60 (18.3%) subjects had at least one AESI as shown in the table below.

- Although major hypoglycemia was commonly reported, the occurrences are secondary to the study population of PROTECT which contains Stage 3 T1D subjects and these events are not expected in Stage 2 T1D patients.
- While 8 subjects had lymphadenopathy, none were had positive CMV or EBV PCR tests.
- Five subjects had an AESI of EBV test positive; all of which were asymptomatic, transient EBV reactivations.
- Dr. Wood Heickman reviewed the blinded data on liver function abnormalities and concluded, “For cases of liver function test abnormalities, the current discontinuation criteria proposed in the labeling (ALT or AST >5x ULN and total bilirubin >3x ULN) appear to be appropriately protective, with the resolution of all cases of ALT/AST/bilirubin elevations following discontinuation at this threshold.”
- Dr. Wood Heickman noted that, “There were no SAEs of rash in the safety update. Rash was noted as one of the common AEs for the PROTECT study 81/327 (24.8%), consistent with previous observations in the clinical program.”

Table 11. Adverse Events of Special Interest

AESI Category Preferred Term	**N=327 n (%)**
Subjects with at least one AESI	60 (18.3)
Major hypoglycemia	**29 (8.9)**
Hypoglycemia (≥Grade 3)	29 (8.9)
Acute mononucleosis-like illness	**16 (4.9)**
Lymphadenopathy	8 (2.4)
Epstein-Barr virus test positive	5 (1.5)
Epstein-Barr viraemia	1 (0.3)
Epstein-Barr virus infection	1 (0.3)
Infectious mononucleosis	1 (0.3)
≥Grade 3 liver function abnormalities	**6 (1.8)**
Alanine aminotransferase increased	4 (1.2)
Aspartate aminotransferase increased	3 (0.9)
Blood bilirubin increased	1 (0.3)
≥Grade 3 neutropenia	**5 (1.5)**
Neutropenia	5 (1.5)
≥Grade 3 rash	**4 (1.2)**
Rash	3 (0.9)
Dermatitis atopic	1 (0.3)
Lymphocyte count <500 mm3 for 7 days or longer	**3 (0.9)**
Lymphopenia	3 (0.9)
Lymphomas or Other Malignancies	**2 (0.6)**
Skin papilloma	2 (0.6)
≥Grade 3 Infections	**1 (0.3)**
Cellulitis	1 (0.3)

B. TN-10 Extension [PRV-031-002]

As of the cutoff date, no AESIs had been reported.

C. Protégé Extension [CP-MGA031-02]

In the Protégé Extension study, 5 (2.3%) subjects had an AESI; 4 (2.2%) subjects in the teplizumab group and 1 (2.6%) subject in the placebo group. The AESIs included EBV infection (1 teplizumab subject and 1 placebo subject); hypoglycemic seizure on Day 868 after teplizumab assessed not to be drug-related; and appendicitis perforated on Day 915 after teplizumab assessed not to be drug related and resolved without sequelae.

6.6 PROTECT Study: Safety of AGC Biologics vs. Eli Lilly Product

The Applicant submitted blinded safety data from PROTECT to assess the safety of the AGC Biologics vs. Eli Lilly product. The PROTECT study was initiated in 2019 with the Eli Lilly product and transitioned to the AGC Biologics product in March 2021, resulting in a shorter study follow-up period for subjects who received the AGC Biologics product. To compare the 2 products, the Applicant evaluated safety during the first 30 days after the first course of treatment (data lock 24 Nov 2021). Since the PROTECT study is ongoing and blinded, the data represents events from subjects who either received teplizumab or placebo for both AGC Biologics and Eli Lilly.

- Patients in the AGC Biologics/placebo group had fewer SAEs and overall AEs than patients in the Eli Lilly/placebo group (Table 12).
- Among commonly reported adverse events, patients receiving AGC Biologics/placebo reported slightly more vomiting, pyrexia and neutropenia. However, patients in this treatment group also reported less lymphopenia, hypotension, and cytokine release syndrome.
- Although there were a slightly greater proportion of subjects with AESI in the AGC Biologics/placebo group compared to the Eli Lilly/placebo group, the imbalance was driven largely by hypoglycemic events that are related to the study population of Stage 3 T1D and not likely to occur in the indicated population (Table 14).

Overall, the safety profile is comparable in both groups, and no new risks were identified in subjects in patients in the AGC Biologics/placebo group, although the safety assessment is limited by study blinding.

Table 12. Summary of Treatment Emergent Adverse Events in PROTECT by Product (Course 1, Days 1-30)

Subjects with at least one	**AGC Biologics Teplizumab or Placebo N=103**	**Eli Lilly Teplizumab or Placebo N=223**
	n (%)	**n (%)**
Treatment-emergent AE	85 (81.7%)	205 (91.9%)
Treatment-emergent AESI	12 (11.5%)	22 (9.9%)
Treatment-emergent SAE	1 (1.0%)	5 (2.2%)
TEAE leading to death	0	0

Source: *Provention Bio Section 5.3.5.3 Safety Profile Eli Lilly vs AGC Biologics, Table 3, Page 6 of 12.*

Table 13. Summary of Commonly Reported Adverse Events (≥5% of Subjects) in PROTECT by Product (Course 1, Days 1-30)

System Organ Class Preferred Term	**AGC Biologics Teplizumab or Placebo N=104**	**Eli Lilly Teplizumab or Placebo N=223**
	n (%)	**n (%)**
Metabolism and nutrition disorders		
Hypoglycemia	42 (40.4)	85 (38.1)
Gastrointestinal disorders		
Nausea	26 (25.0)	55 (24.7)
Vomiting	22 (21.2)	37 (16.6)
Diarrhea	9 (8.7)	17 (7.6)
Abdominal pain	3 (2.9)	21 (9.4)
Abdominal pain upper	8 (7.7)	13 (5.8)
Skin and subcutaneous tissue disorders		
Rash	23 (22.1)	51 (22.9)
Rash maculo-papular	4 (3.8)	18 (8.1)
Nervous System Disorders		
Headache	22 (21.2)	54 (24.2)
Investigations		

Lymphocyte count decreased	15 (14.4)	53 (24.8)
White blood cell count decreased	12 (11.5)	39 (17.5)
Neutrophil count decreased	8 (7.7)	20 (9.0)
Alanine aminotransferase increased	7 (6.7)	17 (7.6)
Blood and lymphatic system disorders		
Lymphopenia	13 (12.5)	25 (11.2)
Neutropenia	11 (10.6)	13 (5.8)
Leukopenia	11 (10.6)	12 (5.4)
Combined lymphocyte count decrease and lymphopenia	**28 (26.9)**	**78 (34.9)**
Combined neutrophil count decreased and neutropenia	**19 (18.3)**	**32 (14.3)**
Combined white blood cell count decreased and leukopenia	**23 (22.1)**	**51 (22.9)**
Vascular Disorders		
Hypotension	2 (1.9)	21 (9.4)
General disorders and administration site conditions		
Pyrexia	13 (12.5)	20 (9.0)
Immune System Disorders		
Cytokine release syndrome	1 (1.0)	16 (7.2)

Source: *Provention Bio Section 5.3.5.3 Safety Profile Eli Lilly vs AGC Biologics, Table 4, Page 7 of 12. Original table modified with follow up data from a response to an FDA information request submitted under sequence number 75.*

Table 14. Summary of AESI in PROTECT by Product (Course 1, Days 1-30)

	AGC Biologics Teplizumab or Placebo N=104	**Eli Lilly Teplizumab or Placebo N=223**
AESI Category Preferred Term	**n (%)**	**n (%)**
Subjects with at least one AESI	12 (11.5)	22 (9.9)
Acute mononucleosis-like illness		
Lymphadenopathy	1 (1.0)	6 (2.7)
Epstein-Barr virus test positive	0	4 (1.8)
Infectious mononucleosis	0	1 (0.4)
Major hypoglycemia		
Hypoglycemia (≥Grade 3)	4 (3.8)	3 (1.3)
≥Grade 3 liver function abnormalities		
Alanine aminotransferase increased	1 (1.0)	3 (1.3)
Aspartate aminotransferase increased	2 (1.9)	1 (0.4)
Blood bilirubin increased	0	1 (0.4)
Lymphocyte count <500 mm^3 for 7 days or longer		
Lymphopenia	1 (1.0)	2 (0.9)
≥Grade 3 neutropenia		
Neutropenia	2 (1.9)	1 (0.4)
≥Grade 3 rash		
Rash	0	3 (1.3)
≥Grade 3 Infections		

Cellulitis	1 (1.0)	0

Source: *Provention Bio Section 5.3.5.3 Safety Profile Eli Lilly vs AGC Biologics, Table 6, Page 9 of 12.*

7. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. FDA deferred submission of the pediatric study for ages 0 to less than 8 years for this application because teplizumab is ready for approval for use in adults and the pediatric study has not been completed. The deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study and described in Section 10 of this memo.

8. Labeling

- **INDICATIONS AND USAGE**
  - DDLO expanded the indication to include all patients with Stage 2 T1D, rather requiring patients to have a first-degree relative with T1D as the safety and effectiveness of the teplizumab is not expected to vary based on family history.
- **DOSAGE AND ADMINISTRATION**
  - DDLO specified that an oral glucose tolerance test (OGTT) was recommended for patient selection. If an OGTT is not available, another validated method was determined to be acceptable.
  - (b) (4)
  - DDLO incorporated the TN-10 laboratory eligibility criteria.
  - (b) (4)
- **WARNINGS AND PRECAUTIONS**
  - Five safety risks were incorporated into Section 5 of labeling, going beyond what the Applicant originally proposed: cytokine release syndrome, serious infections, lymphopenia, hypersensitivity reactions, and vaccinations.
- **ADVERSE REACTIONS**
  - DDLO anonymized the study population in the pooled safety database and replaced all mentions of (b) (4) with "unapproved population" as recommended by DMPP to focus the label only on the indicated population.
- **CLINICAL STUDIES**
  - Section 14 of labeling focused on the results of TN-10 only and did not describe the confirmatory evidence consisting of the meta-analysis of trials using the C-peptide endpoint.

- The actual dosing regimen in TN-10 was described in the following manner to address the new dose-adjusted dosage regimen: “Patients in the TZIELD group had a total drug exposure that was comparable to the total drug exposure achieved with the recommended total TZIELD dosage [*see Dosage and Administration (2.2)]*.”

9. Postmarketing Recommendations

The following postmarket requirements were issued.

4359-1

Conduct a 12-month single-arm, open-label study to assess the safety and pharmacokinetics (PK) of teplizumab in pediatric patients 0 to less than 8 years of age with two type-1 diabetes (T1D)-related autoantibodies and dysglycemia (Stage 2 T1D) [Part A], followed by a 12-month open-label extension [Part B].

Draft Protocol (Part A and Part B) Submission: November 2022
Final Protocol (Part A and Part B) Submission: May 2023
Part A Study Completion: October 2025
Part A Final Report Submission: April 2026
Part B Study Completion: October 2026
Part B Final Report Submission: April 2027

FDA determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk for the following adverse reactions: cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders, malignancy, and adverse pregnancy and birth outcomes. Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. Therefore, based on appropriate scientific data, FDA determined that the Applicant is required to conduct the following studies:

4359-2

Conduct an observational registry study to assess the long-term safety of teplizumab in patients with Stage 2 type 1 diabetes. The study should evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders, and malignancy. The registry should also collect information on women exposed during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant’s first year of life. The study design should include a comparator group and monitor patients for at least 10 years after their first course of treatment. The study should enroll at least 150 subjects exposed to teplizumab and collect sufficient clinical information to assess for sources of confounding for the target outcomes.

Draft Protocol Submission: March 2023
Final Protocol Submission: September 2023
Interim Report Submissions: January 2024
January 2025

January 2026
January 2027
January 2028
January 2029
January 2030
January 2031
January 2032
January 2033
January 2034
January 2035
January 2036
Study Completion: January 2037
Final Report Submission: September 2037

4359-3

Provide comparative safety data on the commercial formulation manufactured by AGC Biologics versus the TN-10 clinical trial product by submitting the clinical study reports for study PRV-031-001 (PROTECT), and study PRV-031-003 (PROTECT Extension) that seeks to collect an additional 42 months of long-term safety data in participants who complete the PROTECT study. The additional safety data from the PROTECT and PROTECT extension study will provide valuable additional data regarding the safety of the commercial formulation in a randomized setting, compared to the product used in the original teplizumab clinical trial. This additional data should help address the residual uncertainty regarding the minor structural differences that were noted in analytical studies to ensure there are no unexpected safety issues with the commercial formulation. The extension study will also provide longer term safety data (see PMR/PMC development template for additional details).

PRV-031-001 PROTECT
Study Completion: May 2023
Final Report Submission: November 2023

PRV-031-003 PROTECT Extension
Study Completion: Nov 2026
Final Report Submission: May 2027

10. Recommended Comments to the Applicant

All comments were already issued to the Applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHAEL D NGUYEN
11/17/2022 02:06:13 PM

JOHN M SHARRETTS
11/17/2022 02:57:48 PM

LISA B YANOFF
11/17/2022 03:00:15 PM