Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 27, 2021

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants will be joining this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed the safety and efficacy of biologics license application (BLA) 761183, for teplizumab intravenous infusion, submitted by Provention Bio, Inc. The proposed indication is for the delay of clinical type 1 diabetes mellitus in at-risk individuals.

These summary minutes for the May 27, 2021 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting of the Food and Drug Administration were approved on August 23, 2021

I certify that I attended the May 27, 2021 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/

Thomas J. Weber, MD
Chairperson, EMDAC

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 27, 2021

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 27, 2021. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Provention Bio Inc. The meeting was called to order by Thomas J. Weber, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 1090 people online. There were eighteen Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The Committee discussed the safety and efficacy of biologics license application (BLA) 761183, for teplizumab intravenous infusion, submitted by Provention Bio, Inc. The proposed indication is for the delay of clinical type 1 diabetes mellitus in at-risk individuals.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Michael Blaha, MD, MPH; Elizabeth Chrischilles, PhD, MS; James de Lemos, MD; Susan S. Ellenberg, PhD; Marvin A. Konstam, MD; Anna McCollister (*Consumer Representative*); David M. Nathan, MD; Connie Newman, MD; Thomas J. Weber, MD *(Chairperson)*; Jack A. Yanovski, MD, PhD

Endocrinologic and Metabolic Drugs Advisory Committee Member Not Present (Voting): Rita R. Kalyani, MD, MHS

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-Voting): Gary Meininger, MD *(Industry Representative)*

Temporary Members (Voting): Mara L. Becker MD, MSCE; Erica Brittain, PhD; David W. Cooke, MD; Cecilia C. Low Wang, MD; Kashif Munir, MD; Martha C. Nason, PhD; Carling Skvarca (*Patient Representative*)

FDA Participants (Non-Voting): Ellis Unger, MD; Lisa Yanoff, MD; Harisudhan Thanukrishnan, PhD; Yu Wang, PhD; Justin Penzenstadler, PharmD, MS; Lauren Wood Heickman, MD

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers: Claire Wirt; Tim Ryan; Jeremy Pettus; Sean M. Oser, MD, MPH; Catherine Price; Angie Platt; Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation (JDRF)); Elizabeth Keckler; Mark Atkinson, PhD; Kory K. Hood PhD; Louise Philipson, MD, PhD, FACP; Madison Buff; Kimber Simmons, MD, MS; Nicholas B. Argento, MD, FACE; Kelly L. Close (Close Concerns); Christina Roth (College Diabetes Network (CDN)); Nina Zeldes (National Center for Health Research (NCHR)); Jeff Hitchcock

The agenda was as follows:

Call to Order	**Thomas J. Weber, MD** Chairperson, EMDAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**Justin Penzenstadler, PharmD, MS** Clinical Reviewer, Division of Diabetes, Lipid Disorders, and Obesity (DDLO), Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Provention Bio Inc.**
Introduction	**Eleanor Ramos, MD** Chief Medical Officer Provention Bio Inc.
Unmet Need	**Colin Dayan, MD, PhD** Professor of Clinical Diabetes and Metabolism Cardiff University School of Medicine
Efficacy and Safety	**Eleanor Ramos, MD**
Clinical Perspective	**Kevan Herold, MD** Professor of Immunobiology and Endocrinology Yale University School of Medicine
Target Population for Indication	**Eleanor Ramos, MD**
Clarifying Questions to Applicant	
BREAK	
FDA PRESENTATIONS	
Overview of the Clinical Development Program for Teplizumab	**Lauren Wood Heickman, MD** Clinical Reviewer DDLO, OCHEN, OND, CDER, FDA

FDA PRESENTATIONS (CONT.)

Statistical Assessment of Teplizumab Efficacy	**Yu Wang, PhD** Statistical Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clinical Safety of Teplizumab	**Lauren Wood Heickman, MD**

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** The Applicant is seeking approval of teplizumab to delay clinical type 1 diabetes mellitus (T1D) in at-risk individuals. Discuss the strength of the overall evidence presented herein to conclude that effectiveness has been established for teplizumab for the proposed indication.

   Committee Discussion: *The Committee members discussed the merits of the single adequate and well-controlled trial, TN-10, in detail. A majority agreed that TN-10 provided adequate evidence of efficacy, although this view was not unanimous. Several Committee members mentioned that the primary efficacy outcome (the delay of type 1 diabetes in at-risk individuals) held up to multiple analyses by the FDA. 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 (24-month delay) given the small study size and notable baseline imbalances with respect to age and genetics. There were comments about the small study size limiting the ability to assess differential efficacy in subgroups, particularly noting the human leukocyte antigen (HLA) analyses. The Committee did not support the use of the C-peptide meta-analysis as confirmatory evidence of effectiveness demonstrated by the Applicant. One member expressed that C-peptide is not a validated surrogate; another member found the C-peptide data unconvincing because the Protégé study failed on its primary endpoint. Overall, Committee members opined that they considered the C-peptide data to be weakly supportive of teplizumab's efficacy, but also mentioned that they would have considered measures of glycemic control in patients with stage 3 type 1 diabetes supportive in this population as the major effector of complications in patients with type 1 diabetes is related to glycemic control. It was also noted that the*

Applicant failed to define the benefits of the 2-year median onset delay and its association with long-term effects. On the other hand, some members argued that the sample size reflects the difficulty of recruiting patients in a small affected population, and the delay in T1D onset demonstrated in a such small trial, was itself an important outcome. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss the clinical meaningfulness of the observed median 2-year delay of onset of T1D demonstrated in study TN-10.

   Committee Discussion: *Collectively, the Committee agreed that the observed median 2-year delay of onset of T1D demonstrated in study TN-10 was substantially meaningful. However, they were uncertain if this is the true effect size in light of the low precision and wide confidence intervals associated with the estimated median delay of time to T1D onset (2 years). 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. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** 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.

   Committee Discussion: *The Committee overall thought that the adverse events shown should not prevent the approval of teplizumab. Nevertheless, a broad range of opinions were voiced with respect to the safety findings. Overall, these ranged from a concern about the safety of the product in light of rates of serious adverse events (including diabetic ketoacidosis) and inadequate data to assess safety, to a view that the safety database was adequate for approval with postmarketing safety follow-up. 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. While they were reassured that DKA was not observed in TN-10 patients, several Committee members mentioned that the Applicant and FDA should explore the risk of DKA further through continued study in the at-risk population after diagnosis of type 1 diabetes in order to ensure that this population is not at excess risk of DKA (vs. untreated patients). 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. Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION:** The Applicant's proposed indication statement is "Teplizumab is for the delay of clinical type 1 diabetes mellitus (T1D) in at-risk individuals." TN-10 was conducted in individuals ages 8 and older and enrolled relatives of patients with T1D with two or more positive autoantibodies and dysglycemia. 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. If you have any other recommendations for the indication statement, please provide them.

   Committee Discussion: *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. The members agreed that if the Applicant committed to conducting another study, the design of the trial should include a broader population (extended age range, ethnicity, and disease origin [not only relatives]). Please see the transcript for details of the Committee's discussion.*

5. **VOTE:** Does the information provided in the background, documents and presentations by the Applicant and FDA, show that the benefits of teplizumab outweigh the risks in support of approval to delay clinical type 1 diabetes mellitus?

   a. If you voted yes, provide your opinion on the appropriate indication statement and discuss whether you recommend any post-marketing safety studies.

   b. If you voted no, provide your rationale and provide recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of teplizumab.

   Vote Results: **Yes: 10** **No: 7** **Abstain: 0**

   Committee Discussion: *A majority of the Committee members voted "Yes," agreeing that the background documents and presentations provided by the Applicant and FDA show that the benefits of teplizumab outweigh the risks in support of approval to delay clinical type 1 diabetes mellitus. The Committee again agreed that the product should be restricted to populations reflected in the study, with the exception of including non-relatives. The Committee members who voted "Yes" recommended rigorous post-marketing surveillance to observe the efficacy of delayed onset and adverse events such as cytokine release syndrome, DKA, hypoglycemia, etc. The Committee members who voted "No" noted that the anecdotal testimonies from the public speakers were moving and convincing; however, these Committee members were not persuaded by the data in light of the substantial weaknesses of the trial, i.e., small sample size, and narrow benefit-risk profile. Like their colleagues who voted "Yes," they too urged for the Applicant to conduct another study that would include a targeted population that would reflect a real-world setting. In addition, a post-marketing*

registry was also advised to capture adverse events and long-term efficacy (benefits of a 2-year median delay of T1D in patients treated). Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:30 p.m. Eastern Time.