

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761183Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 100262

MEETING MINUTES

Provention Bio, Inc.
Attention: Sharon Rowland PhD, RAC
SVP Regulatory Affairs
308 Foster Knoll Drive
Joppa, MD 21085

Dear Dr. Rowland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRV-031.

We also refer to the teleconference between representatives of your firm and the FDA on January 25, 2022. The purpose of the meeting was to discuss and obtain agreement on your proposed clinical pharmacology data package as well as the clinical contents for the BLA 761183 resubmission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Supendeeep Dosanjh, Regulatory Project Manager, at 301-837-7649.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy Director
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: January 25, 2022, 12:30-2:00pm EST
Meeting Location: ZoomGov

Application Number: IND 100262
Product Name: PRV-031
Proposed Indication: Treatment of newly diagnosed type 1 diabetes mellitus (T1DM)
Sponsor Name: Provention Bio, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Lisa B. Yanoff M.D.
Meeting Recorder: Supendeeep Dosanjh Pharm.D.

FDA ATTENDEES:

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN),

Lisa B. Yanoff, M.D.	Deputy Director
<i>Division of Diabetes, Lipid Disorders, and Obesity (DDLO)</i>	
John Sharretts, M.D.	Director (acting)
Michael Nguyen, M.D.	Clinical Team Lead
Justin Penzenstadler, Pharm.D., MSc	Clinical Reviewer
Lauren Wood Heckman, M.D.	Clinical Reviewer

Office of Regulatory Operations

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Callie Cappel-Lynch, Pharm.D., RAC	Chief, Project Management Staff
Supendeeep Dosanjh, Pharm.D.	Regulatory Project Manager

Office of Translational Sciences (OTS), Office of Clinical Pharmacology

Division of Cardiometaabolic and Endocrine Pharmacology

Shirley Seo, Ph.D.	Division Director
Jaya Vaidyanathan, Ph.D.	Associate Director for Therapeutic Review
Harisudhan Thanukrishnan, Ph.D.	Clinical Pharmacology Reviewer

Division of Pharmacometrics

Justin Earp, Ph.D.	Pharmacometrics Team Lead
Elyes Dahmane, Ph.D.	Pharmacometrics Reviewer

OTS, Office of Biostatistics

Division of Biometrics II

Yoonhee Kim, Ph.D.

Yu (Jade) Wang, Ph.D.

Statistical Team Lead (acting)

Statistical Reviewer

SPONSOR ATTENDEES

Provention, Bio, Inc

Ashleigh Palmer, Chief Executive Officer

Eleanor L. Ramos, M.D., Chief Medical Officer

Francisco Leon, M.D., Ph.D.; Chief Scientific Officer

Wei Tian Ph.D., Vice President Biostatistics

Paul Dunford, Vice President Translational Science

Ann Andre, Senior Vice President Clinical Operations and Project Management

Randy Anderson, Senior Vice President Biometrics

Sharon Rowland, Ph.D., RAC, Senior Vice President Regulatory Affairs

Shobha Gopalakrishnan, Ph.D., Vice President Regulatory Affairs

Consultants for Provention, Bio, Inc

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1.0 BACKGROUND

BLA 761183 was submitted on October 31, 2020, and received on November 2, 2020, for PRV-031 for the proposed indication of the delay of clinical type 1 diabetes in at-risk individuals.

On June 30, 2021, a general advice letter was issued to the Applicant to provide written comments and additional recommendations on the questions contained in the May 18, 2021, briefing package related to the pharmacokinetics/pharmacodynamics (PK/PD) data from the PROTECT study.

On July 2, 2021, a complete response (CR) letter was issued for BLA 761183 because of clinical pharmacology and product quality issues. In particular, the PK bridging study, PRV-031-004, failed to show PK comparability between PRV-031 product used in the TN-10 study and the planned commercial product.

On July 27, 2021, the Sponsor submitted an amendment to IND 100262 containing the statistical analysis plan (SAP) for the PK/PD substudy in the ongoing PRV-031-001 (PROTECT) study. The Agency replied with an Advice/IR letter on August 6, 2021, in which we strongly recommended the population pharmacokinetic (popPK) model and analysis plan be pre-specified before unblinding of PK data. Furthermore, the Agency

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strongly suggested that all data from the Protégé study, TN-10 study, and PROTECT study be built in a single (joint) popPK model. Lastly, the Agency asked the Sponsor to specify their plan to address the issues raised in our general advice letter from June 30, 2021, and strongly suggested to submit the joint PK model before finalizing the SAP and releasing PROTECT PK data to QuantPharm.

On August 17, 2021, the Sponsor submitted a proposed BLA PK/PD data package and anticipated timelines to support comparability in response to our August 6, 2021, Advice/IR letter. The Sponsor sent a follow up email on August 25, 2021, seeking agreement to proceed with data transfer of unblinded PK data to the (b) (4)

A subsequent Advice/IR letter was issued on September 1, 2021, stating review expectations and providing comments and recommendations on the SAP and modeling and simulation analysis plan. The Sponsor responded over email on September 1, 2021, requesting a 1-hour informal tcon for clarification purposes. The Agency granted this request, and a teleconference was held on September 3, 2021, from 2:30-3:00pm EST.

Following the September 3, 2021, informal tcon, the Sponsor sent a follow up email on September 8, 2021, to confirm the Agency's recommendation on the amended two-stage PK/PD model design as discussed at the tcon. On September 9, 2021, the Agency confirmed agreement with the proposed approach via email.

On October 1, 2021, the Sponsor formally submitted a request for a 1-hour type A meeting. On October 7, 2021, the Agency granted the type A meeting to take place on November 18, 2021, from 2:00-3:00pm EST. The purpose of this meeting was to discuss and obtain agreement on the FDA-requested Stage 1 popPK model in order to advance to the Stage 2 model.

The Agency sent Preliminary Comments to Provention Bio, Inc. on November 12, 2021. Subsequently, the Sponsor sent responses to the Preliminary Comments via email on November 16, 2021. A follow up email was sent to the Sponsor on November 17, 2021, indicating that the Agency would be unable to comment on this additional information as it required further review. The Agency requested that this information along with the information below be included in a future type B meeting request:

1. Stage 2 full PK datasets
2. Population PK analyses codes and output
3. A full population PK report
4. A detailed answer to all the Type A Meeting preliminary comments

The email also requested that the background information be submitted at the same time as the meeting request, if possible.

On November 29, 2021, the Sponsor formally submitted a 90-minute type B meeting request. On December 8, 2021, the Agency granted the type B meeting to take place

on January 25, 2022, from 12:30-2:00pm EST. The purpose of this meeting was to discuss and obtain agreement on the Sponsor's proposed clinical pharmacology data package as well as the clinical contents for the BLA 761183 resubmission.

FDA sent Preliminary Comments to Provention Bio on January 21, 2022.

2.0 DISCUSSION

The Sponsor's questions are repeated below in regular text and the FDA's response to each question are **bolded**. Following that is the Sponsor's response provided by email on January 24, 2022, in *italics* followed by the meeting discussion which is underlined. Any post meetings comments are shown in **bold and underline**.

Provention Bio Introduction:

We thank the Agency for the preliminary comments to our briefing package. We understand the Agency's position with regard to the differences in PK parameters between the clinical (Eli Lilly) and planned commercial product (AGC Biologics). We agree to propose an alternative dosing regimen for the AGC Biologics product to match the PK parameters of Eli Lilly, using PK modeling. We also agree to explore whether infusion rate modification is necessary to control for C_{max}. We request clarification on certain Agency comments, as noted below, to facilitate our BLA resubmission as soon as feasible.

Question 1: Does the Agency agree that the proposed data package is adequate to address the comparability deficiency noted in the Complete Response Letter (CRL) to allow for a BLA resubmission? Does the Agency have any initial impressions of the data it might like to share in advance of possible BLA resubmission and review?

FDA Response to Question 1:

No, we do not agree that your proposed package is adequate to address the comparability deficiency and allow for BLA resubmission. You propose to submit the model used to derive the primary PK parameters for comparability along with comparisons of the trough concentrations, CD3 coating, concentration versus CD3 coating, and immunogenicity using sparse samples from the PROTECT sub-study. The predicted primary parameters are indicative of a lower exposure for both AUC_{inf} and C_{max} with the AGC product and do not adequately support PK comparability.

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An average PK model simulation (using typical population PK parameters instead of individual PK parameters) estimated about 40% higher model-predicted AUC_{inf} and 60% higher model-predicted C_{trough} for the Lilly product, compared to the AGC product.

Sponsor's Response to Preliminary Comments Question 1:

We would like to request the Agency for clarification on the values presented in Table 1 and how they were derived. In our submission for this meeting, we already corrected for the replicate observations and doses for ID#893. For example,

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Meeting Discussion on Question 1:

No discussion occurred.

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Sponsor's Response to Preliminary Comments Question 1a:

We agree to replace the duplicated observations as requested and provide the updated dataset in the BLA resubmission.

Meeting Discussion on Question 1a:

See "Meeting Discussion on BLA resubmission Question 1a" below.

- b. In PROTECT study PK, 11 subjects in the Lilly arm had 1 to 2 missing doses (ID # [REDACTED] (b) (6)). Please clarify whether these subjects actually missed their doses or not and correct the PK data accordingly.

Sponsor's Response to Preliminary Comments Question 1b:

We agree to provide clarification as requested and provide the updated dataset, if applicable, in the BLA resubmission.

Meeting Discussion on Question 1b:

No discussion occurred.

- c. In PROTECT study, 10 subjects (8 in Lilly arm and 2 in AGC arm) received body surface area (BSA) based dosing that either constantly or occasionally deviated from PROTECT study regimen. Please verify the accuracy of the reported doses.

Sponsor's Response to Preliminary Comments Question 1c:

We agree to verify the accuracy of the reported doses and provide clarification in the BLA resubmission.

Meeting Discussion on Question 1c:

No discussion occurred.

For BLA resubmission, further quality control of the PK data, PK modeling, and PK comparability results are needed.

For the purpose of BLA resubmission, we recommend the following:

- a. Propose an alternative full 14-day dosing regimen to match the AUC_{inf} and/or C_{trough} exposures between the Lilly and AGC products, using PK simulations from the PROTECT study typical (average) and individual PK parameters of the model 362 (after addressing comments b and c below). Modification of the duration of infusion of PRV-031 may be needed to control C_{max} levels. Provide safety justifications for the modified full 14-day dosing based on previous studied higher dose regimens, as applicable.

Sponsor's Response to Preliminary Comments BLA resubmission Question 1a:

Provention Bio Response: We would like to discuss the following at the meeting. In accordance with the Agency's recommendation, we will focus our BLA resubmission on an alternative 14-day regimen predicted by the PK model to match exposure to the Eli Lilly product, and we will provide the safety justification. We would appreciate clarification on the following:

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Sponsor's Response to Preliminary Comments BLA resubmission Question 1c:

We would like to discuss the following at the meeting. In order to address this, we would appreciate if the Agency can provide the NONMEM ID of the 10 subjects (also requested via email on 21 January 2022).

Meeting Discussion on BLA resubmission Question 1c:

No discussion occurred.

- d. **Indicate the dosing regimen and infusion duration used for the provided PK comparability results.**

Sponsor's Response to Preliminary Comments BLA resubmission Question 1d:

For the proposed alternative 14-day dosing regimen we will provide the infusion duration in the BLA resubmission.

Meeting Discussion on BLA resubmission Question 1d:

No discussion occurred.

- e. **Of the 33 patients that received dosing with AGC product, data for anti-PRV-031 antibodies (anti-drug antibodies (ADA)) are available from only 3 patients, on Day 56. Clarify the reason for the lower number of samples in the AGC arm that are provided for the comparison of immunogenicity. Provide an overall assessment of the impact of ADA on efficacy and safety.**

Sponsor's Response to Preliminary Comments BLA resubmission Question 1e:

We will provide clarification on the number of samples in the AGC arm in the BLA resubmission.

As the PROTECT study is still an ongoing blinded study, we cannot assess the impact of ADA on efficacy or safety at this time. We did however present the evaluation of the effect of ADA on safety and efficacy in the Integrated Summary of Immunogenicity, which was included in the original BLA submission. The results found no impact of ADA on efficacy or safety.

We appreciate the Agency's preliminary comments. We will implement all your recommendations and plan to proceed with the BLA resubmission. Does the Agency agree?

Meeting Discussion on BLA resubmission Question 1e:

No discussion occurred.

Post-Meeting Comment on BLA resubmission Question 1e:

As the PROTECT study is an ongoing blinded study, it is acceptable that an overall assessment of the impact of ADA on efficacy or safety conclusions from

the PROTECT study cannot be performed at this time. The Agency cannot agree whether or not the immunogenicity evaluation is complete until we receive the clarification regarding the number of samples in the AGC arm for the PROTECT substudy.

Question 2: Does the Agency agree that the information in the safety update is adequate for BLA resubmission?

FDA Response to Question 2:

For the safety update, we recommend that you provide analyses that use the same definition of hypoglycemia as used in the original BLA submission to assess the safety population in the update, in addition to analyses using revised definition(s). You should clearly indicate what hypoglycemia definition is being used for what analysis. In your safety update, you should also include updated exposure information for the clinical studies/trials in person-time. Otherwise, the proposed safety update is adequate for review.

Sponsor's Response to Preliminary Comments Question 2:

We will provide the requested information and analyses in the BLA resubmission.

Meeting Discussion on Question 2:

No discussion occurred.

Question 3: Does the Agency agree that the BLA resubmission content list provided in the briefing document is complete and adequate to move forward with the BLA resubmission?

FDA Response to Question 3:

No. Refer to response to Question 1 for additional content required for BLA resubmission. We also have the following requests that are not required for BLA submission, but would facilitate our review:

- a. The PK-PD dataset for the PROTECT sub-study should be formatted for NONMEM and include all PD markers relevant to the pharmacological profile of PRV-031.
- b. Confirm that the raw dataset for PK-PD from PROTECT sub-study will be available for review at the time of resubmission.
- c. Perform the concentration-CD3 occupancy analysis as indicated in the population PK analysis plan. Consider CD3 subtypes as covariates, if applicable.

- d. **Provide a comparison of demographic characteristics, ADA levels, baseline lymphocytes levels and other available PD markers (by age and disease status when applicable) between the studies (n=5), including the Encore study that showed 40% difference in exposure compared to the Protégé study.**
- e. **Provide an explanation for the difference in exposure between the Encore and Protégé study, as no explanation was provided previously.**

Sponsor's Response to Preliminary Comments Question 3:

With regard to the requests that are not required for the BLA submission, we acknowledge your requests and will comply.

Meeting Discussion on Question 3:

No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.¹

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information² and Pregnancy and Lactation Labeling Final Rule³ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of

¹ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁴ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁵. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical*

⁴ <https://www.fda.gov/media/84223/download>

⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

*Specifications.*⁶

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor to submit BLA resubmission	Provention Bio, Inc	TBD

⁶ <https://www.fda.gov/media/85061/download>

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/

LISA B YANOFF
02/18/2022 08:46:50 AM

IND 102629

MEETING MINUTES

Provention Bio, Inc.
Attention: Sharon Rowland, PhD, RAC
SVP Regulatory Affairs & Quality
308 Foster Knoll Drive
Joppa, MD 21085

Dear Dr. Rowland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRV-031.

We also refer to the teleconference between representatives of your firm and the FDA on August 20, 2020. The purpose of the meeting was to discuss the content and format of the clinical sections of your planned Biologic License Application (BLA).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Elisabeth Hanan, Senior Regulatory Project Manager, at 240-402-0350.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: August 20, 2020, 4:00 PM – 5:00 PM, EDT
Meeting Location: teleconference

Application Number: IND 102629

Product Name: PRV-031
Indication: for delay or prevention of clinical type 1 diabetes in at-risk individuals
Sponsor Name: Provention Bio, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Lisa B. Yanoff, MD
Meeting Recorder: Elisabeth Hanan, MS

FDA ATTENDEES

Office of New Drugs (OND), Office of Cardiology, Hematology, Endocrinology, and Nephrology

Ellis Unger, MD; Director

Division of Diabetes, Lipid Disorders, and Obesity

Lisa B. Yanoff, MD; Director (Acting)

Mitra Rauschecker, MD; Deputy Director for Safety (Acting)

Suchitra Balakrishnan, MD; Clinical Reviewer

Lauren Wood Heickman, MD; Clinical Reviewer

Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology

Federica Basso, PhD; Nonclinical Team Lead (Acting)

Daniel Minck, PhD; Nonclinical Reviewer

OND, Office of Regulatory Operations

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Elisabeth Hanan, MS; Senior Regulatory Project Manager

Office of Biostatistics

Division of Biometrics II

Yun Wang, PhD; Statistical Team Lead

Yu (Jade) Wang, PhD; Statistical Reviewer

Office of Clinical Pharmacology

Division of Cardiometaabolic and Endocrine Pharmacology

Manoj Khurana, PhD; Clinical Pharmacology Team Lead

Sury Sista, PhD; Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products

Division of Biotechnology Review and Research I

Rachel Novak, PhD; Review Chief

Brian Janelins, PhD; Team Lead

Anshu Rastogi, PhD; Reviewer

Office of Scientific Investigations

Cynthia F. Kleppinger M.D., Senior Medical Officer

SPONSOR ATTENDEES

Provention Bio, Inc.

Eleanor L. Ramos, MD; Chief Medical Officer

Sharon Rowland, PhD, RAC; Senior Vice President, Regulatory Affairs & Quality

Shobha Gopalakrishnan, PhD; Senior Director, Regulatory Affairs

Linda Arterburn, PhD; Vice President, Regulatory Affairs

Ann Andre; Senior Vice President, Clinical Operations

Francisco Leon, MD, PhD; Chief Scientific Officer

Ralph Raymond, PhD; Senior Vice President, Biometrics and Clinical Strategy

Ashleigh Palmer; Chief Executive Officer

Paul Dunford; Executive Director, Translational Sciences

Consultants for Provention Bio, Inc.

(b) (4)

1.0 BACKGROUND

IND 102629 for PRV-031 (formerly MGA031) was submitted by MacroGenics, Inc., on December 23, 2009, to investigate the delay or prevention of type 1 diabetes (T1D) in relatives of type 1 diabetics at-risk for developing T1D. PRV-031 is a recombinant humanized anti-human CD3 monoclonal antibody (mAb).

On May 23, 2012, a type C guidance meeting was held to discuss the low enrollment of Study TN-10 (At-Risk), which investigates PRV-031 and is entitled, "Anti-CD3 mAb (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus," as well as to discuss the inclusion of children aged 8-15 years of age. Meeting minutes were issued on June 11, 2012.

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On May 21, 2018, the IND sponsor was changed from MacroGenics, Inc., to Provention Bio, Inc. (Provention Bio).

On March 18, 2019, a type C meeting request was received to discuss the development pathway for PRV-031 for delay or prevention of onset T1D in at-risk relatives of individuals with T1D. FDA granted the meeting as written responses only, which were issued on May 31, 2019.

On August 2, 2019, FDA granted breakthrough therapy designation to PRV-031 for delay or prevention of clinical type 1 diabetes in at-risk individuals.

On November 7, 2019, a type B meeting was held for an initial multidisciplinary discussion of the development program for PRV-031 under the breakthrough therapy program. The meeting minutes were issued on December 6, 2019.

On January 22, 2020, Provention Bio submitted a type B meeting request for written responses to receive feedback on the statistical analysis plan for their proposed C-peptide meta-analysis to support efficacy of PRV-031 for delay or prevention of clinical type 1 diabetes in at-risk individuals. The briefing package was submitted on February 7, 2020, and written responses were issued on March 20, 2020.

On April 17, 2020, a type B meeting was held to discuss the content, including format and data sets, to be submitted in the clinical modules 2 and 5 of their planned biologic license application (BLA). The meeting minutes were issued on May 8, 2020.

On June 10, 2020, Provention Bio submitted a request for a pre-BLA meeting to discuss the content and format of the clinical sections of their planned BLA. The briefing package was submitted on July 20, 2020, and FDA issued preliminary comments August 18, 2020. The sponsor's stated objectives for this meeting are as follows:

- To obtain feedback on the content of a complete clinical package to support filing of the clinical portions of the BLA (Module 5, and Module 2, Sections 2.5 and 2.7)
- To obtain feedback on the adequacy of the clinical pharmacology package to support the BLA
- To obtain feedback on the Office of Scientific Investigations (OSI) package to be submitted in the BLA
- To obtain feedback on the 120-day safety update as well as items that may be submitted within 30 days of the submission of the complete BLA

- To obtain feedback on Provention Bio's plan to not include a risk evaluation and mitigation strategy (REMS)

(b) (4)

IND 100262

(b) (4)

The nonclinical and CMC information for IND 102629 is cross-referenced to IND 100262.

On August 13, 2020, a type B meeting was held with OPQ to discuss the adequacy of the analytical and functional data to demonstrate comparability between the pre-change and post-change drug substance lots. The meeting minutes were issued on September 9, 2020.

On July 24, 2020, Provention Bio submitted a request for a pre-BLA CMC meeting to discuss the content and format of the CMC sections of their planned BLA. The meeting is scheduled to occur on September 24, 2020.

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), the sponsor's responses (italics), and meeting discussion (bolded and italics).

Question 1: A description and listing of the planned Module 5 and Module 2 Sections 2.5 and 2.7 clinical contents is included in the briefing package. Does the Agency agree that the overall clinical contents constitute a complete clinical package to support filing the BLA?

FDA Response to Question 1: Your proposal for Module 5 and Module 2 clinical contents, as outlined in Sections 10.1, 10.2 and 10.3, of your background package, seems acceptable to support the BLA package and initiate review.

Sponsor Response to Question 1: *Thank you for your feedback. No discussion requested.*

Meeting Discussion for Question 1: *None.*

Question 2: A summary of the clinical pharmacology data to be included in the complete BLA package, including study reports and datasets, is included in the briefing package. Does the Agency agree that the studies, data, and supporting reports which constitute a complete clinical pharmacology submission, are adequate to support the BLA package for teplizumab?

FDA Response to Question 2: The studies, data, and supporting reports that you propose to include in the planned submission appear adequate to support the BLA package for PRV-031. Acceptability of the Clinical Pharmacology data will be a review issue.

You had indicated that the original bioanalytical method reports from the Protégé study for both PRV-031 concentrations and ADA concentrations are not available, and therefore abbreviated bioanalytical reports, written by Provention Bio, will be submitted. Clarify if the bioanalytical methods used in Protégé study were validated, and if your abbreviated reports will capture all the required validation parameters. It is expected that the bioanalytical method validation reports submitted be comprehensive in detail to allow for a complete assessment of the suitability of the methods. Since data from the Protégé study constitute a major component of the PopPK and immunogenicity analysis, absence of proper bioanalytical method validation may invalidate the analysis.

Clarify also if data from the TN-10 trial were included in the PopPK analysis, and if so, confirm whether a cross-validation of the sandwich enzyme immunoassay (used in Protégé and Encore) and electrochemiluminescence (MSD-ECL) method used in the TN-10 trial is available.

For additional information, refer to the guidance for industry *Bioanalytical Method Validation*¹ and FDA's website for PopPK data submission model/data format.²

Sponsor Response to Question 2: Thank you for your feedback. We would like to provide clarification on the two points noted above.

Bioanalytical Clarification: The original bioanalytical method validation reports, for both PRV-031 concentrations and ADA concentrations, from the Protégé study are available. The Protégé bioanalytical data reports (study sample analyses) for both PK and ADA are not available. Therefore, we prepared abbreviated bioanalytical data reports for PK and ADA, for Protégé. Both of these method validation and data reports will be submitted to the BLA.

TN-10 Data Clarification: The TN-10 PK data were not included in the PopPK analysis.

Provention Bio would like to confirm the clarifications stated above address the FDA comments.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format>

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Meeting Discussion for Question 2: Provention Bio opened the discussion by describing the history of their acquisition of PRV-031 from MacroGenics, Inc., after that firm had deprioritized the development program. The sponsor stated that they have faced significant challenges with retrieving information from the early portion of the PRV-031 development program. The sponsor described how they have implemented their best efforts to obtain missing information, including multiple interactions with MacroGenics, Inc., laboratories that conducted the analyses, and archive facilities that were contracted to store these data and reports. The sponsor stated that they have prepared the final reports to the best of their ability with the data that they were able to obtain. The sponsor expressed their frustration with the unavailability of certain primary data but they are confident in the validity of the final results.

FDA stated that while we understand that Provention Bio has made its best efforts to compile the necessary data, the bioanalytical method details submitted must substantiate that the data are scientifically accurate. Specifically, the information must confirm that the study actually used the validated method. Further, if any changes were made from the validated method during the conduct of the study, the information should also confirm if there was appropriate documentation of those changes and that the results were analyzed accurately. FDA stated that we are willing to accept the BLA submission for filing without the original reports, but acceptability of these data will be a review issue.

Provention Bio thanked FDA for their feedback and stated they will take this information into consideration to see what can be done to ensure that the data submitted will be acceptable.

Question 3: The contents of the Integrated Summary of Immunogenicity (ISI) to be included in the BLA package is described in the briefing package.

- a. Does the Agency agree that the proposed contents of the ISI are adequate to support the BLA package for teplizumab?
- b. Does the Agency agree that the intended statistical analysis and study timepoints of the ISI as outlined are adequate to support the BLA package for teplizumab?

Additional Information from the Sponsor:

The objective of this ISI is to provide a comprehensive assessment of the immunogenicity profile of teplizumab after intravenous (IV) administration for the various dosing regimens/ courses. The overall proposed contents of the ISI are shown below (Table 3). Additionally, associations of ADA/nAb to PK, PD (lymphocytes change), efficacy (C-peptide following mixed meal tolerance test [MMTT] or oral glucose tolerance test [OGTT], and time to diagnosis of clinical T1D in TN-10) and immune-related safety events will be explored. Analyses will be

performed on a per-study basis. In addition to the tabulation and summary of ADA/nAb results, the ADA/nAb impact assessment will be performed by exploring these 4 key areas of the association:

- Assessment of the effect of immunogenicity on PK using teplizumab serum concentrations (depending on the collection time point, this may not be Ctrough)
- Assessment of the effect of immunogenicity on PD: (absolute lymphocytes CD4+ and CD8+), percent CD25+FoxP3+ (of CD4 and CD8) in Encore and Protégé and total lymphocytes (hematology) in Protégé, Encore and TN-10.
- Assessment of the effect of immunogenicity on efficacy using
 - o The change in C-peptide levels from baseline values following a 4-hour MMTT (Protégé and Encore) or a 2-hour OGTT (TN-10), and
 - o The association of ADA positivity to the time to diagnosis of clinical T1D, for the subset of subjects in the teplizumab-treated group from the TN-10 study
- Assessment of the effect of immunogenicity on patient safety using immune-related treatment-emergent adverse events (TEAE)

Data and collection timepoints vary between the 3 studies (Protégé, Encore and TN-10) for which immunogenicity data exist (refer to Table 4, Protocol-Specified Collection Days for ADA, nAb, PK, C-peptide, and Lymphocytes). The table shows timepoints for which there are available data. Not all subjects have data at all timepoints due to termination of some studies/or cessation of collection of certain samples. ADA data are available for 99-200 subjects depending on the arm of the study for the Protégé study, 11-13 subjects depending on the arm for the Encore study and for 44 subjects in the TN-10 study. For the studies, often the ADA, PK, PD, and safety timepoints are not aligned (on the same day), while for the TN-10 study there is a single ADA timepoint which is not aligned with other study measurements; in addition, there are a limited number of dosed subjects (n=44). Nonetheless we believe there will be sufficient data to understand the immunogenicity related to the administration of a single 14-day course of teplizumab treatment.

Table 3 Proposed ISI Content:

Section	Content
1	Introduction
2	Product Profile
2.1	Molecular Structure
2.2	Mechanism of Action
2.3	Proposed Clinical Indication
3	Immunogenicity Risk Assessment of Teplirumab
3.1	Product Factors
3.2	Mechanism
3.3	Patient Factors
4.	Bioanalytical Methods
4.1	Bioanalytical Strategy
4.2	Description of Assays and Key Performance Characteristics
4.2.1	Anti-Drug Antibody (ADA) Assays
4.2.2	Neutralizing Antibody (nAb) Assays
5	Immunogenicity Assay
5.1	Nonclinical Toxicology Studies
5.2	Clinical Evaluation of Teplirumab
5.3	Clinical Study Design
5.4	Statistical Analysis
5.5	Protege
5.6	Encore
5.7	TN-10
5.8	Immunogenicity Analysis
6	Overall Conclusion: for Clinical Immunogenicity Evaluation and Risk Mitigation
7	Regulatory Feedback and Commitment: (Related to Immunogenicity)
8	References

FDA Response to Question 3: The proposed contents of your immunogenicity summary appear adequate. However, you should clarify how you will handle the effects of missing data in your planned statistical analysis.

Sponsor Response to Question 3: Thank you for your feedback. We will address how we handle missing data in the BLA. No discussion requested.

Meeting Discussion for Question 3: None.

Question 4: The proposed OSI data package is provided in the briefing package.

- Does the Agency agree on the proposed OSI package?
- Does the Agency agree that the OSI Package should be located in Module 5, Section 5.3.5.4?

FDA Response to Question 4: Yes, we agree with the proposed OSI package. We note that for the Section III Site Level dataset, you will not be including site-specific efficacy data due to the small number of subjects per site.

We also agree that the OSI package is to be located in Module 5, Section 5.3.5.4.

In addition, if the definition and handling of protocol deviations is not available in the Statistical Analysis Plan, please include in the application submission the necessary document for review (e.g., Protocol Deviation Plan).

Sponsor Response to Question 4: *Thank you for your feedback. We plan to include the definition and handling of protocol deviations for TN 10 in the BLA. No discussion requested.*

Meeting Discussion for Question 4: *None.*

Question 5: Provention Bio plans to provide the data described below at the 120-day Safety Update. Does the Agency agree with the proposed plan for the 120-day Safety Update?

Additional Information from the Sponsor:

The PROTECT study (PRV-031-001) is a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of teplizumab in children and adolescents with newly diagnosed T1D. The study was initiated in 2Q2019. It is anticipated that for an April 1, 2021 safety update, data cut-off of February 2021 will be provided. The data to be submitted will include:

- Enrollment status: disposition of participants
- Demographics and baseline characteristics
- Extent of study drug exposure
- Adverse Events: serious adverse events (SAEs, including deaths) and adverse events of special interest (AESIs)

FDA Response to Question 5: **Your proposal for the 120-day safety update appears acceptable. You should also provide a status update on PRV-031-002 (Open-Label study to Evaluate the Safety of Teplizumab in At-Risk Relatives Who Develop Type 1 Diabetes), if the study has been initiated.**

Sponsor Response to Question 5: *Thank you for your feedback. The PRV-031-002 study has been initiated. Therefore, in addition to the safety update for the PROTECT study (PRV-031-001), we will also provide a status update for the PRV-031-002 study. No discussion requested.*

Meeting Discussion for Question 5: *None.*

Question 6: Provention Bio does not intend to include a REMS. A justification is included in this briefing document. Provention Bio does plan to prepare a patient medication guide to ensure patient education about the potential risk of side effects of teplizumab. Does the Agency agree with Provention Bio's proposal not to include a REMS in the BLA?

FDA Response to Question 6: We agree with your position of not including a REMS with the BLA submission. However, the final determination of a need for a REMS will be made during the review of the BLA submission.

Sponsor Response to Question 6: Thank you for your feedback. No discussion requested.

Meeting Discussion for Question 6: None.

Question 7: Does the Agency currently foresee that an Advisory Committee meeting will be necessary for teplizumab and if so, what would be the likely timing of the meeting?

FDA Response to Question 7: We have not determined whether an Advisory Committee will be necessary for PRV-031.

Sponsor Response to Question 7: Thank you for your feedback. No discussion requested.

Meeting Discussion for Question 7: None.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the need for a REMS will be determined during the review of this application (refer to the response to Question 6).
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for September 24, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.³ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁴

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the U.S. Food and Drug Administration
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time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁷ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁸. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major

⁷ <https://www.fda.gov/media/84223/download>

⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

8.0 NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

9.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

10.0 ACTION ITEMS

None.

⁹ <https://www.fda.gov/media/85061/download>
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11.0 ATTACHMENTS AND HANDOUTS

The sponsor provided the attached table showing a listing of all the methods and reports that will be used to support their proposed BLA submission. In a submission dated August 28, 2020, the sponsor submitted a corrected version of the table; changes from the version discussed at the meeting are marked.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

LISA B YANOFF
09/11/2020 09:27:11 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 102629
Request Receipt Date	June 3, 2019
Product	Teplizumab
Indication	delay or prevention of clinical type 1 diabetes in at-risk individuals
Drug Class/Mechanism of Action	anti-CD3 mAb
Sponsor	Provention Bio
ODE/Division	ODE2/DMEP
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	August 2, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

For the delay or prevention of clinical Type 1 diabetes mellitus (Type 1 DM) in at-risk individuals.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- ☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response:

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Teplizumab is a 150-kiloDalton (kD) humanized IgG1 monoclonal antibody (mAb) that is purported to bind with high specificity to the CD3ε chain of the T-cell receptor (TCR) complex on human T cells. According to the sponsor, it was engineered to interact minimally or not at all with Fc receptors by modifying its Fc domain to eliminate Fc

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

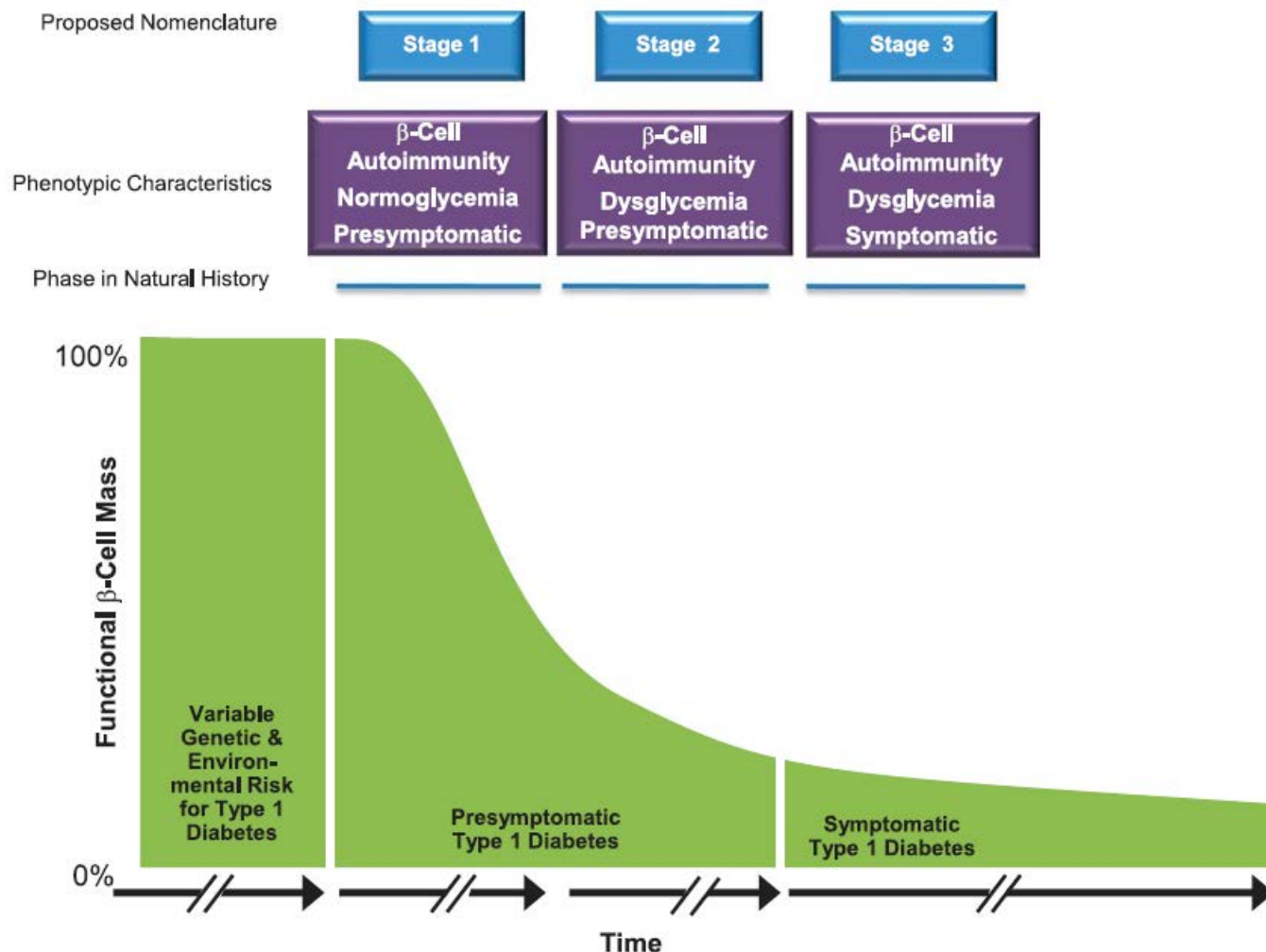
receptor and complement binding and, therefore, limit the likelihood of cytokine release syndrome (CRS). It is being developed as a short-term immunomodulation therapy for the delay or prevention of clinical type 1 diabetes mellitus (Type 1 DM) in individuals at-risk of developing type 1 DM (IND 102,629), (b) (4) IND (IND 100,262).

Type 1 diabetes mellitus (Type 1 DM) results from T-cell mediated autoimmune destruction of insulin producing pancreatic beta cells leading to impaired insulin production and secretion, and impaired glucose metabolism. It is a serious chronic medical condition. Acute life-threatening complications of type 1 DM include diabetic ketoacidosis due to insulin deficiency which can result in cerebral edema and death, while chronic macro- and microvascular complications include cardiovascular disease, peripheral artery disease, retinopathy, nephropathy, and neuropathy.

The vast majority of type 1 DM is diagnosed in children. Although all people are susceptible, relatives of individuals with type 1 DM are at much greater risk for development of the disease. The impact of HLA and non-HLA genetic risk is observed in relatives of individuals with type 1 diabetes, who have a 10-fold to more than 100-fold greater risk than the general population¹.

In an individual with normoglycemia with an increased genetic risk (primarily driven by HLA haplotypes), the natural history of type 1 DM has been described in three proposed stages as shown in the figure below. “Stage 1” represents individuals who have developed two or more type 1 DM– associated islet autoantibodies but are normoglycemic. “Stage 2” includes individuals with two or more islet autoantibodies but whose disease has now progressed to the development of glucose intolerance, or dysglycemia, from loss of functional β -cell mass. Dysglycemia was defined in Diabetes Prevention Trial -1 (DPT-1) as any glucose level after ingestion of oral glucose of > 200 mg/dl and/or a glucose level 2 hours after ingestion of oral glucose of 140-200 mg/dl and/or fasting glucose between 110 – 126 mg/dl during a standard oral glucose tolerance test². The 5-year risk of symptomatic disease at this stage is approximately 75%, and the lifetime risk approaches 100%. “Stage 3” represents manifestations of the typical clinical symptoms and signs of type 1 diabetes, which may include polyuria, polydipsia, weight loss, fatigue, and diabetic ketoacidosis (DKA).

Figure 1: Stages of Type 1 DM



Source: Insel et al, Diabetes Care 2015, Figure 1(Reference 1)

To support the BTDR, the sponsor has submitted the results of the ‘pivotal’ TN-10 study, sponsored by the National Institutes of Health (NIDDK) and the Juvenile Diabetes Research Foundation as well as from a supportive study “PROTÉGÉ” (both studies discussed further below)

8. Information related to endpoints used in the available clinical data:

- Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The sponsor reported a statistically significant delay in the primary endpoint of time of type 1 DM onset (hazard ratio 0.412 [95% CI: 0.216, 0.783], adjusted Cox proportional hazards, $p=0.006$) with median time from 24.4 months (placebo) to 48.4 months (teplizumab) in the TN-10 study.

The sponsor does not plan to conduct any additional studies, but has been advised that an additional confirmatory study to evaluate an alternative dosing regimen (a second cycle of teplizumab treatment at six months or one year) should be considered based on the available data from TN-10 showing attenuation of effect after 1 year⁵.

- Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
 - A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

For investigational products intended for the prevention of type 1 diabetes mellitus in high-risk individuals, a delay in the diagnosis of type 1 diabetes by standardized criteria is acceptable to the Division. An appropriate endpoint to support efficacy can be the proportion of subjects in the treatment groups who develop stage 3 diabetes after a prespecified period of time compared across treatment groups³. In TN-10 the sponsor looked at follow-up out to 5 years.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Preservation of endogenous β cell function (C-peptide response) over time in patients who develop type 1 DM (“stage 3”) after teplizumab treatment could be supportive evidence. C-peptide has been accepted as a marker of residual beta cell function, and T1DM patients who demonstrate preservation and/or maintenance of residual beta cell function, as measured by mean peak C-peptide levels, appear to have a reduction in long-term complications, such as hypoglycemia, diabetic retinopathy, and albuminuria in natural history studies.^{5,6,7} Although the Division has not previously used C-peptide alone for consideration of accelerated approval, it is reasonable to consider C-peptide / beta cell function as supportive of a clinical benefit.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

To date there are no available therapies for delay or prevention of Type 1 DM in at risk- individuals.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation⁴.

Current approved medical therapies for treatment of Type 1 DM include exogenous insulin, along with adjunctive therapy with pramlintide, an amylin-mimetic. Exogenous insulin has known side effects including hypoglycemia, that can be fatal. Both approved therapies can help improve glycemic control, however, they do not alter the underlying pathophysiology of the disease. To date there are no other drugs tested for delay or prevention of Type 1 DM in at risk individuals. There have been other therapies tested for preservation of β -cell function in patients with newly diagnosed clinical Type 1 DM, but none of these have requested breakthrough therapy designation.

11. Information related to the preliminary clinical evidence:

⁴ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁵, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

TN10:

The sponsor conducted a phase 2, randomized, placebo-controlled, double-blind trial of teplizumab (an Fc receptor–nonbinding anti-CD3 monoclonal antibody) involving relatives of patients with type 1 diabetes who did not have diabetes but were at high risk for development of clinical disease⁸.

Participants were identified through the TrialNet Natural History Study (TN01) as which recruited non-diabetic relatives of a proband with Type 1 DM⁹ between 1-45 years at the time of enrollment in TN01 and age ≥ 8 at time of randomization in this trial (TN10). Participants also had to have had two or more diabetes-related autoantibodies detected in two samples obtained within 6 months before randomization. In addition, participants had to have had evidence of dysglycemia during an oral glucose-tolerance test (OGTT), with dysglycemia defined as a fasting glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L) as per inclusion criteria for DPT-1, a 2-hour postprandial plasma glucose level of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L), or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter within 52 days before enrollment. Individuals ≥ 18 years of age at time of randomization must have had two consecutive TrialNet conducted OGTT's demonstrating abnormal glucose tolerance.

Participants were randomly assigned in a 1:1 ratio to receive either teplizumab or placebo. Randomization was stratified according to TrialNet site, age (<18 years or ≥ 18 years), and second oral glucose-tolerance test result before treatment (impaired tolerance, normal tolerance, or diabetes). Participants received a 14-day outpatient course of teplizumab or saline to be administered intravenously in a clinical research center. Teplizumab was given at a dose of 51 μg per square meter of body-surface area on day 0 and titrated upwards to a dose of 826 μg per square meter on each of days 4 through 13.

The primary endpoint was the elapsed time from randomization to the clinical diagnosis of diabetes, determined with the use of criteria from the American Diabetes Association¹⁰. Scheduled oral glucose-tolerance tests were performed 3 months and 6 months after the infusions and every 6 months thereafter. Random screening glucose levels were evaluated at 3-month intervals, and an oral glucose-tolerance test was performed if the random glucose level was higher than 200 mg per deciliter (11.1 mmol per liter) in association with standardized symptoms of diabetes. Oral glucose-tolerance test results that indicated diabetes were then sequentially confirmed, and the date of diagnosis was identified as the time of the first of the two diagnostic tests.

Study Results:

There was a slower-than expected rate of enrollment. The original protocol (which called for the enrollment of 144 participants) was revised to detect a 60% (previously 50%) lower risk in the teplizumab group than in the placebo group (i.e., a hazard ratio of 0.4) with 80% statistical power at an alpha level of 0.025 (one-sided). This update set the goal of enrolling at least 71 participants and following them until 40 participants had received a diagnosis of type 1 diabetes. A total of 112 subjects were screened for eligibility at TrialNet sites. Seventy-six of the subjects were randomized to teplizumab (44) or placebo (32) arms. The sponsor attributed the unequal randomization to study sites with small numbers of subjects. Baseline characteristics are shown in the table below:

⁵ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Table 1: Baseline characteristics:

Table 1. Baseline Characteristics of the Participants.*		
Characteristic	Teplizumab (N= 44)	Placebo (N= 32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti-IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

GAD65 denotes glutamic acid decarboxylase 65, IA-2 islet antigen 2, ICA islet-cell autoantibody, IQR interquartile range, and ZnT8 zinc transporter 8.

† Participants in this category may have had more than one sibling with type 1 diabetes.

‡ Shown are the autoantibodies for which participants were positive at the time of randomization. All participants were positive for at least two autoantibodies before randomization.

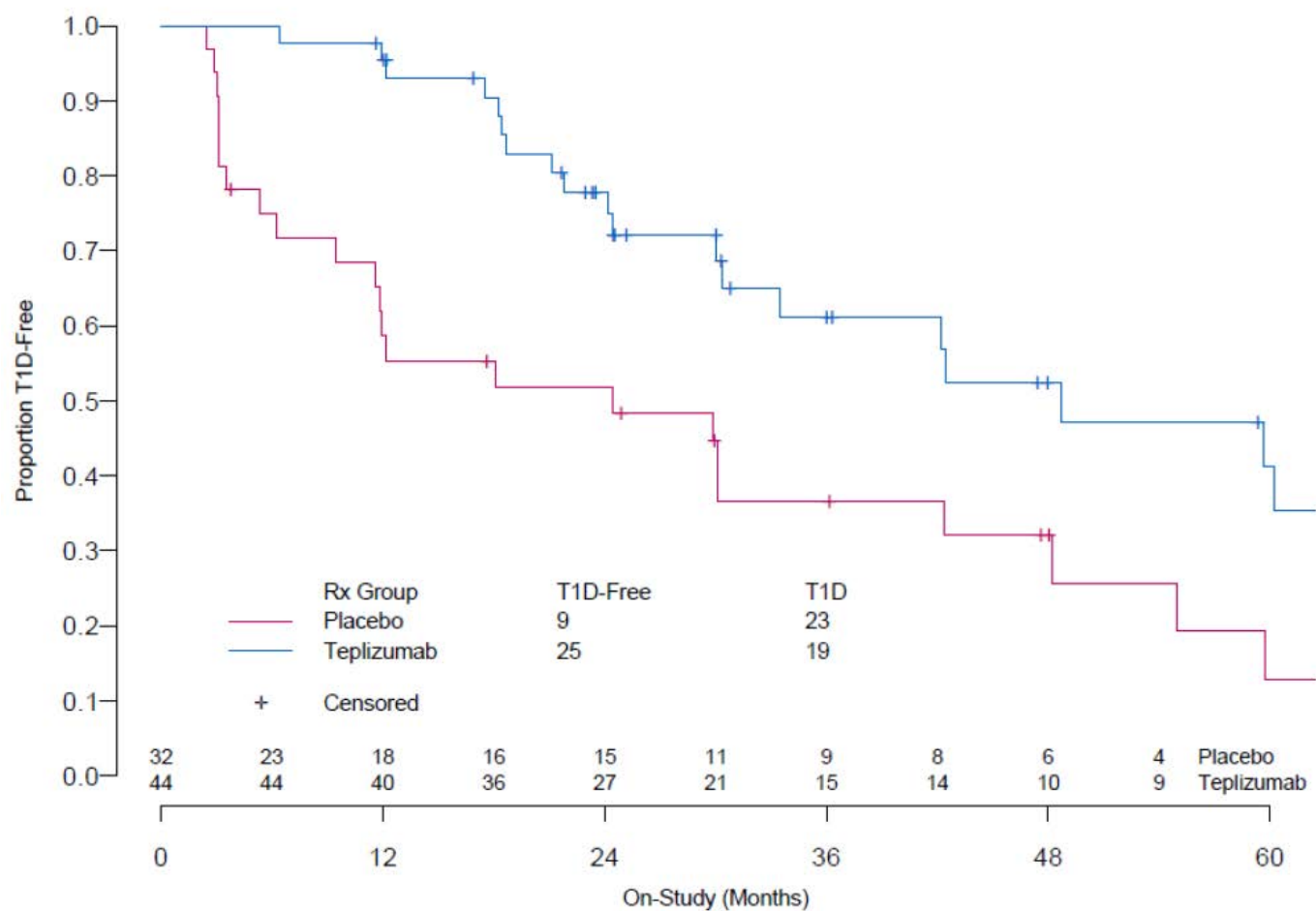
Source: Table1, Reference 8

The majority of participants (55 [72%]) were children (<18 years), most were White, and more than half were siblings of patients with type 1 diabetes. Of the 55 participants who were younger than 18 years of age, 47 had a confirmed

dysglycemic oral glucose-tolerance test result before randomization. Of the participants who underwent randomization after a single dysglycemic test result, 2 had diabetic and 6 had normal oral glucose-tolerance test results on the day of randomization. These participants were included in the intention-to-treat analysis, which was adjusted for the results of the blinded oral glucose-tolerance test before randomization

Treatment with a single course of teplizumab delayed the time to “Stage 3”, or clinical Type 1 DM (see figure below, $p=0.006$): The median times to Type 1 DM was 24.4 months in the placebo and 48.4 months in the teplizumab groups (hazard ratio = 0.412 (95% CI: 0.216, 0.783) $p=0.006$ (2-sided). Nineteen of the 44 (43%) teplizumab treated and 23 of the 32 (72%) of the placebo treated participants developed Type 1 DM. The annualized rates of clinical Type 1 DM development were 14.9% and 35.9% per year, for the teplizumab and placebo groups, respectively.

Figure 2: Effects of teplizumab treatment on development of Type 1 DM



Source: Figure 5 in Sponsor’s submission

The overall rate of progression to clinical T1D was greatest in the first year after entry into the trial ($n=17$, 41%) compared to year 2 ($n=10$, 24%), year 3, ($n=6$, 14%), or year 4 ($n=5$, 12%) (Table 2). Thus, the greatest effect of teplizumab treatment was in the first year: as only 3 out of 44 subjects (6.8%) in the teplizumab group had developed diabetes in contrast to 14 of the 32 subjects in the placebo group. In contrast, 8 subjects (18.2%) in the teplizumab group developed Type 1 DM in year 2, versus 2 subjects (6.3%) in the placebo group (see table below).

Table 2: Frequency of clinical (Stage 3) type 1 diabetes by treatment group and cumulative and interval hazard ratio

Year	No. of T1D*		Chi-square Test†	Hazard Ratio (95%CI)†	
	Teplizumab (%)	Placebo (%)		Cumulative	Interval
1	3 (6.8%)	14 (43.8%)	15.9	0.129 (0.0482, 0.343)	0.129 (0.0482, 0.343)
2	8 (18.2%)	2 (6.3%)	7.55	0.372 (0.169, 0.82)	1.8 (0.473, 6.88)
3	3 (6.8%)	3 (9.4%)	7.77	0.404 (0.198, 0.825)	0.58 (0.11, 3.05)
4	3 (6.8%)	2 (6.3%)	7.05	0.447 (0.23, 0.868)	0.864 (0.14, 5.33)
5	2 (4.5%)	2 (6.3%)	8.24	0.439 (0.233, 0.828)	0.359 (0.039, 3.32)
Total	19 (43.2%)	23 (71.9%)	7.77 [€]	0.419 (0.228, 0.772) [€]	---

Frequency of type 1 diabetes by treatment group and cumulative and interval hazard ratios (95% Confidence Intervals) by year on-study.

* The number of participants developing T1D in each treatment arm during the year interval are shown. In addition, the cumulative HRs and the HR for each year interval were calculated.

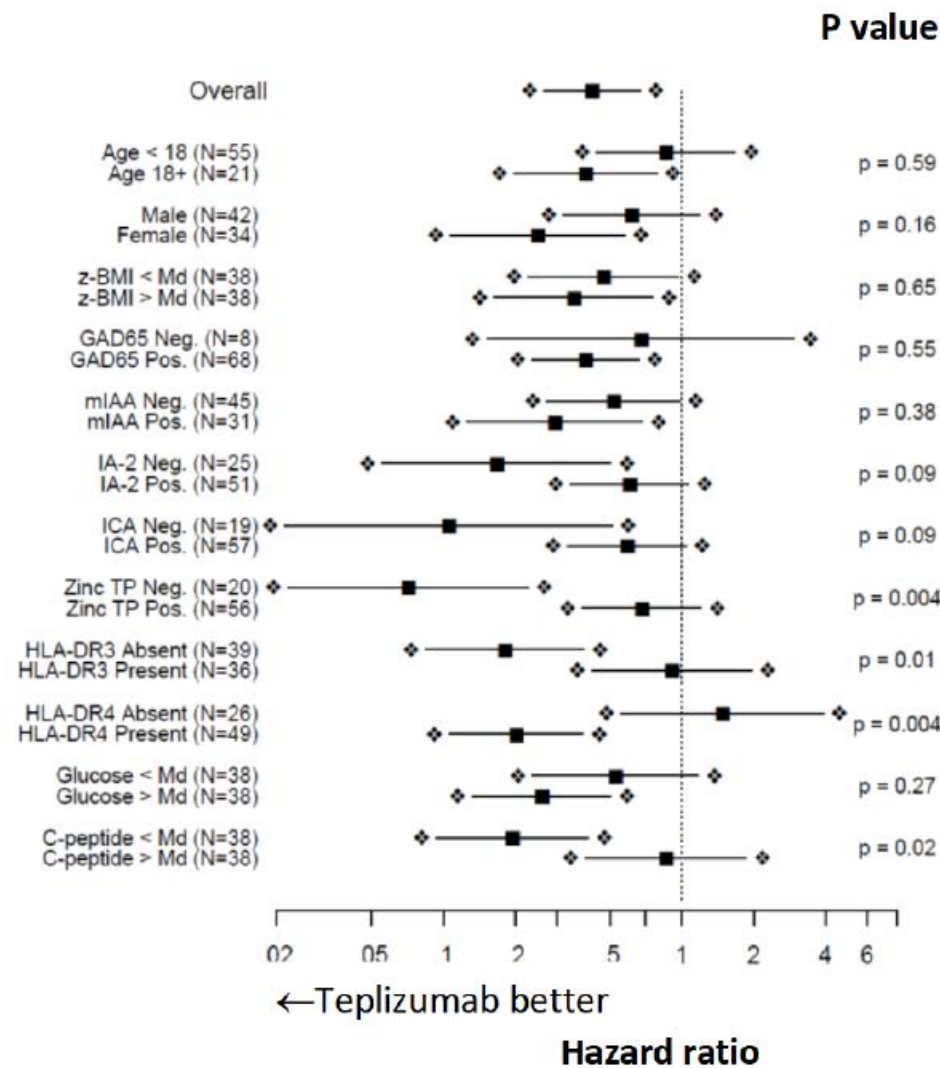
† Mantel-Haenszel method applied to time-to-event data, both chi-square test and hazard ratio estimate.

€ Likelihood ratio test and hazard ratio estimate and 95% CI from the Cox model)

Source: Table 2 in Sponsor's Submission

In pre-specified sub-group analyses, the effects of teplizumab on the primary outcome based on baseline characteristics including age, HLA type, pre-treatment C-peptide and glucose levels during the OGTT, and autoantibodies were evaluated. Participants without anti-ZnT8 antibodies showed a greater response to teplizumab compared with those who did ($p=0.002$). The presence or absence of other autoantibodies was not associated with the clinical response. Forty-nine per cent and 65% of the teplizumab subjects were HLA-DR3 and HLA- DR4, respectively. The presence of HLA-DR4 and absence of HLA-DR3 were associated with a more robust responses to teplizumab ($p=0.004$ and 0.01 , respectively, two-sided tests). The response to teplizumab was also greater in participants whose C-peptide responses to the OGTT at baseline were below the median (1.75 nmol/L).

Figure 3: Demographics and Hazard Ratio



Source: Figure 7 in Sponsor’s submission.

- b. Include any additional relevant information. Consider the following in your response:
- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
 - Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
 - Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.

Assessment of Efficacy data:

As shown in Table 2 and Figure 2, the greatest effect of teplizumab treatment was in the first year: as only 3 out of 44 subjects (6.8%) had developed diabetes in contrast to 14 of the 32 subjects (43.8%) in the placebo group (unadjusted hazard ratio=0.129, 95% CI:0.0482-0.343). However, in year 2, a greater number of subjects in the teplizumab group developed diabetes compared with the placebo group (teplizumab- 8[18.3%], placebo 2 [6.2%]). The interval hazard ratios

for years 2 through 5 do not suggest continued accumulation of benefit, although the benefit accrued in year- 1 appears to have been maintained. Based on the schedule of the OGTT it is reasonable to assume that the response was real and not due to missed or delayed diagnosis in the teplizumab group. Therefore, the data provided can be considered as preliminary clinical evidence of substantial improvement over available therapies.

The findings call into question whether the optimal dosing regimen has been identified and whether a second dose of teplizumab at 6 months or one year of follow-up would have been beneficial.

Supportive data

A multinational, Phase 3 study known as “PROTÉGÉ” (CP-MGA031-01) was initiated in 2006¹¹. Individuals aged 8 to 35 years with Type 1 DM were treated with teplizumab (n=417) or placebo (n=99) within 12 weeks of Type 1 DM diagnosis and followed for 12 months (Protégé) and continued to 24 months (Protégé Extension). This program was halted in 2010 because the Protégé trial failed to demonstrate an effect on the primary outcome of interest (i.e., HbA1c of < 6.5% and a daily insulin dose < 0.5 units/kg/day at 12 months). Exploratory post-hoc analyses conducted at 12 months showed a statistically significant difference in a greater percentage of patients in the 14-day full-dose teplizumab group achieving the HbA1c threshold of <7% at lower insulin dose cutoffs (<0.25U/kg) than in the placebo group, as well as a difference in the median change in C-peptide AUC from baseline. At 2 years, several prespecified exploratory analyses were conducted⁶. Teplizumab treatment (14-day full-dose) yielded a statistically significant reduction in mean change in C-peptide AUC versus placebo (P = 0.027). See Table 3, below. Additional exploratory post-hoc analyses suggest a greater benefit to select subgroups (i.e. patients randomized ≤6 weeks after diagnosis, patients in the U.S., screening HbA1c<7.5%, patients 8-17 years of age, insulin use < 0.4 units/kg/day at baseline, and mean baseline C-peptide AUC ≥0.2 nmol/L at 2 years (see Figure 4). The data from the PROTÉGÉ trial demonstrate preservation of C-peptide levels for the 14-day full dose teplizumab group compared to placebo, and provide additional supportive efficacy data.¹²

Table 3: PROTÉGÉ Outcomes at Year 2

Outcome	14-day full-dose n = 207	P value	14-day low-dose n = 102	P value	6-day full-dose n = 106	P value	Placebo n = 98
Adjusted mean change in AUC of C-peptide from baseline ^{*a}	-0.136	0.027	-0.198	0.968	-0.174	0.312	-0.191
Composite of insulin dose <0.5 units/kg/day and HbA _{1c} <6.5%, ^{*b} n (%)	17 (8.2)	0.775	6 (5.9)	0.402	10 (9.4)	0.859	9 (9.2)
Composite of insulin dose <0.25 units/kg/day and HbA _{1c} <7.0%, ^b n (%)	11 (5.3)	0.070	4 (3.9)	0.183	3 (2.8)	0.339	1 (1.0)
Adjusted mean change in HbA _{1c} from baseline ^{*a} (%)	0.233	0.706	0.220	0.868	0.149	0.606	0.135
Adjusted mean change in insulin use from baseline ^a (units/kg/day)	0.067	0.963	0.010	0.142	0.105	0.861	0.070

Sample sizes shown are at baseline. Patient numbers at each time point are shown in Fig. 1A for AUC mean C-peptide and Supplementary Fig. 1 for insulin use. ^{*}Prespecified end points at year 1. ^aAdjusted mean changes from baseline were calculated using MMRM models adjusted for age-group and baseline values; adjusted means for placebo group were calculated using the placebo vs. 14-day full-dose models. AUC mean C-peptide change from baseline was calculated by: $[\ln(\text{AUC mean C-peptide}_{\text{Day } x} + 1) - \ln(\text{AUC mean C-peptide}_{\text{Baseline}} + 1)]$. ^bP values were calculated using a Mantel-Haenszel test stratified by age-group (8–11, 12–17, and 18–35 years).

Source: Table 1 from reference 7

⁶ Hagopian W, Ferry RJ Jr, Sherry N et al, Protégé Trial Investigators. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. *Diabetes*. 2013;62(11):3901-8. doi: 10.2337/db13-0236. Epub 2013 Jun 25.

Figure 4: Exploratory sub-group analyses at 2 years in the Protégé trial:

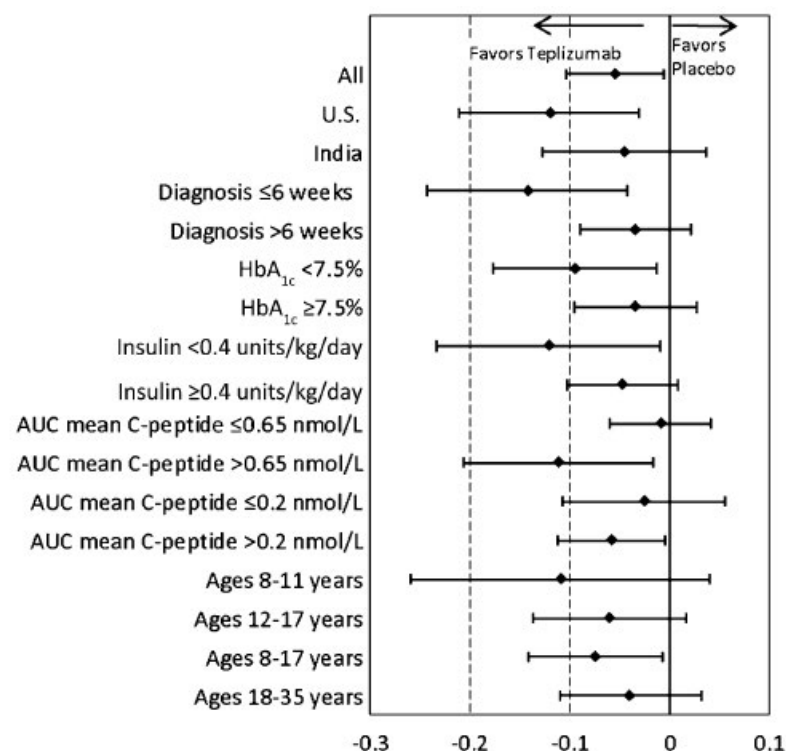


FIG. 2. Adjusted mean difference is shown in AUC mean C-peptide change from baseline at 2 years among subsets at study entry in the 4-day full-dose group vs. placebo. The ♦ indicate least squares means; bars indicate 95% CIs. AUC mean C-peptide change from baseline was calculated using $[\ln(\text{AUC mean C-peptide}_{\text{Day } x} + 1) - \ln(\text{AUC mean C-peptide}_{\text{Baseline}} + 1)]$.

Source: Figure 2 from reference 12

Safety results from Study TN-10 and other studies in patients with established Type 1 DM:

In Type 1 DM, nine studies in 989 (estimated) patients have been conducted. The longest, placebo-controlled exposures and safety data comes from the Protégé trial. In this study, leukopenia/lymphopenia and rash were experienced more frequently (by over 2.5 to 5-fold) teplizumab-treated participants. The rash was reported to be predominantly mild to moderate and usually resolved within one to two weeks. Signs and symptoms of cytokine release syndrome (CRS) occurred in up to 6% of teplizumab-treated patients vs. none with placebo and was reported to be mild to moderate in severity. There were 10 (2.4%) cases of herpes zoster infections in teplizumab-treated patients that were possibly drug-related, and none in the placebo group.

In study TN-10, similar to previous studies with teplizumab in new onset T1D patients (i.e. Stage 3), lymphopenia and rash were the most common safety concerns, however all events spontaneously resolved. There were no reports of cytokine release syndrome (CRS) in this study. Quantifiable EBV and CMV DNA were observed in several subjects, but there were no reports of symptomatic infection.

Division Assessment: The sponsor did exclude patients with leukopenia, thrombocytopenia, and subjects on other immunosuppressive therapy or administered live-attenuated virus vaccination within 8 weeks/killed virus vaccine within 4 weeks of diagnosis. The risk for immunosuppression, infections and CRS is a consideration, which was weighed against the benefits of a delay in Type 1 DM diagnosis.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Type 1 DM is a serious illness with significant morbidity and mortality. To date there are no approved therapies for delay or prevention of Type 1 DM. The sponsor has reported a statistically significant delay in the primary endpoint of time of Type 1 DM onset in clinical trial TN10. Time to T1DM onset is an important Clinical Outcome. Supportive data may be generated from a surrogate endpoint – C-peptide- which may be reasonably likely to predict a clinical benefit.

Some details will need to be discussed further with the sponsor during development of teplizumab. First, the clinical significance of delay in Type 1 DM diagnosis by one year is not established and the risks of teplizumab exposure in this patient population who have not yet developed Stage 3 diabetes should be considered. Note that the Diabetes Control and Complications study (DCCT) showed that the long-term complications could be reduced with near normal control of glucose levels in patients with Type 1 DM¹³ and the 5-year risk of developing Type 1 DM for this patient population is 75%, with a lifetime risk of 100%. However, to what extent an additional year of glycemic control contributes to mitigating long term complications should be addressed by the sponsor.

Consideration should also be given to the fact that majority of patients with Type 1 DM are diagnosed under 14 years of age. Any delay in diagnosis could be meaningful, given the challenges of disease management and insulin therapy for that vulnerable adolescent age-group. The sponsor should define and quantify tangible benefits (disease burden or psychosocial functioning) that may be related to delaying T1DM onset, even for only one year.

The sponsor should also further define the patient population (all patients or only those with certain autoantibodies or HLA haplotypes?) and consider whether an additional dose of teplizumab may confer additional benefit beyond one year.

Despite these remaining questions, the data generated thus far are promising and meet the criteria for Breakthrough Designation.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

See discussion above. The sponsor has been advised that further discussion is warranted prior to the BLA submission to determine if the currently available data is sufficiently robust, any additional analyses that may be required, whether a one year delay in diabetes onset is clinically meaningful or whether it may instead represent an intermediate endpoint for

a potential accelerated approval (rather than a traditional approval) with a confirmatory study of an alternative dosing regimen that may prevent additional cases of new onset Type 1 DM.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Table 1, Insel RA, Dunne JL, Atkinson MA et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38:1964–1974
2. Diabetes Prevention Trial-Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002;346:1685-1691.
3. Final written response for Type C Meeting Request dated May 31, 2019, IND 102629, DARRTs ID 4441932
4. <http://sharepoint.fda.gov/orgs/CDERCommunicationsforGuidanceDocuments/Shared%20Documents/Diabetes%20Mellitus%20Developing%20Drugs%20and%20Therapeutic%20Biologics%20for%20Treatment%20and%20Prevention.pdf>
5. Steffes MW, Sibley S, Jackson M, Thomas W. B-cell function and the Development of Diabetes Related Complications in the Diabetes Control and Complications Trial. *Diabetes Care*. 2003;26:832-836.
6. Sorensen JS, Johannesen J, Pociot F, et al. Residual B-cell Function 3-6 Years After Onset of Type I Diabetes Reduces Risk of Severe Hypoglycemia in Children and Adolescents. *Diabetes Care*. 2013;36:3454-3459.
7. Lachin JM, McGee P and Palmer JP for the DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes*. 2014;63 :739-748.
8. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes, Type 1 Diabetes TrialNet Study Group, June 9, 2019, at *NEJM.org*.
9. Bingley PJ, Wherrett DK, Shultz A, Rafkin LE, Atkinson MA, Greenbaum CJ. Type 1 Diabetes TrialNet: a multifaceted approach to bringing disease-modifying therapy to clinical use in type 1 diabetes. *Diabetes Care* 2018; 41: 653-61.
10. American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2019. *DiabetesCare* 2019; 42: Suppl 1: S13-S28.
11. Sherry N, Hagopian W, Ludvigsson J, et al., Protégé Trial Investigators. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomized, placebo-controlled trial. *Lancet*. 2011;378(9790):487-97.
12. Hagopian W, Ferry RJ Jr, Sherry N et al, Protégé Trial Investigators. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. *Diabetes*. 2013;62(11):3901-8. doi: 10.2337/db13-0236. Epub 2013 Jun 25.
13. DCCTRG-1993. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329:977-986.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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/

MITRA RAUSCHECKER
07/24/2019 02:49:58 PM

LISA B YANOFF
07/24/2019 03:05:00 PM



IND 100262

MEETING MINUTES

Provention Bio, Inc.
Attention: Sharon Rowland, Ph.D., RAC
SVP Global Regulatory Affairs & Quality
308 Foster Knoll Drive
Joppa, MD 21085

Dear Dr. Rowland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for teplizumab.

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2018. The purpose of the meeting was to discuss the clinical, nonclinical, and CMC topics related to phase 3 development and to obtain feedback on any potential BLA filing issues for teplizumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin White, M.S., Regulatory Project Manager at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B (EOP)
Meeting Category: End of Phase 2

Meeting Date and Time: December 13, 2018, 12:00 PM – 1:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 100262
Product Name: teplizumab

Indication: (b) (4)
Provention Bio, Inc.

Sponsor Name:

Meeting Chair: Lisa B. Yanoff, M.D.
Meeting Recorder: Martin White, MS.

FDA ATTENDEES

Division of Metabolism and Endocrinology
Products Lisa B. Yanoff, MD, Director (Acting)
Mitra Rauschecker, MD, Clinical Team Lead (Acting)
Suchitra Balakrishnan, MD, Clinical Reviewer
Todd Bourcier, PhD, Non-Clinical Supervisor
David Carlson, PhD, Non-Clinical Reviewer
Pamela Lucarelli, Chief, Project Management Staff
Martin White, MS, Regulatory Project Manager
Arati Kamath, PhD, Regulatory Project Manager

Office of Biostatistics

Yun Wang, PhD, Statistical Team Lead
Jiwei He, PhD, Mathematical Statistician

Office of Clinical Pharmacology, Office of Translational Sciences

Sury Sista, PhD, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Mei-Yean Chen, Pharm.D., BCOP, Risk Management Analyst

SPONSOR ATTENDEES

Eleanor Ramos, MD; Chief Medical and Operating Officer; Provention Bio, Inc.

Mark Rigby, MD, PhD; VP Clinical Development; Provention Bio, Inc.

(b) (4)

Consultant for Provention Bio, Inc.

(b) (4)

Consultant; Consultant for Provention Bio, Inc.

(b) (4)

Consultant; Consultant for Provention Bio, Inc.

(b) (4)

Consultant; Consultant for Provention Bio, Inc.

(b) (4)

Consultant for Provention Bio, Inc.

Francisco Leon, MD, PhD; Chief Scientific Officer Provention Bio, Inc.

Chantal Petit, PhD; VP Project Management; Provention Bio, Inc.

Sharon Rowland, PhD, RAC; SVP Regulatory Affairs & Quality; Provention Bio, Inc.

Ashleigh Palmer; Chief Executive Officer; Provention Bio, Inc.

Attending via Teleconference:

Paul Dumford; Executive Director of Translational Medicine; Provention Bio, Inc.

1.0 BACKGROUND

IND 100262 was submitted on July 25, 2006, by MacroGenics for teplizumab, which is a humanized IgG1 monoclonal antibody, with a proposed indication

(b) (4)

Previous FDA-MacroGenics major meetings/designations:

- On December 20, 2005, a Pre-IND Meeting was held with DMEP under PIND
- On July 25, 2006, IND 100262 was filed for an indication of treatment of recent-onset Type 1 Diabetes.
- On September 29, 2006, orphan-drug designation was granted by the FDA for teplizumab for treatment of recent-onset type 1 diabetes.
- On January 9, 2012, a Type C Meeting was held with DMEP to review data from Protocol CP-MGA031-01 (the Protégé study): *A Phase 2/3, Randomized, Double-Blind, Multicenter, Multinational, 4-Arm, Controlled, Dose- Ranging Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus*. The primary purpose of the meeting was to review Protégé data with FDA and to discuss and seek concurrence with FDA on (1) the plan to conduct a new phase 3 study, (2) a proposed primary endpoint for a new phase 3 trial and (3) a path toward BLA filing for a recent onset T1DM treatment given the results of the Protégé study.

(b) (4)

- [REDACTED] (b) (4)

In May 2018, teplizumab was acquired by Provention Bio, Inc. Provention Bio continues to develop teplizumab for treatment of recent-onset T1D.

The purpose of this meeting is to discuss the clinical, nonclinical, and CMC topics related to phase 3 development of teplizumab and to obtain feedback on any potential BLA filing issues for teplizumab.

FDA sent Preliminary Comments to Provention Bio, on December 7, 2018.

2.0 DISCUSSION

2.1 CMC

Question 1: Provention Bio acquired teplizumab from MacroGenics Inc. in May 2018. As a consequence, Provention Bio plans [REDACTED] (b) (4)

[REDACTED] A draft outline of a comparability plan for the new supply is included in the briefing package.

Does the Agency agree that this plan is acceptable?

FDA Response to Question 1: No, we do not agree.

We recommend that you submit a more detailed comparability protocol for the transfer of the manufacturing processes to the new manufacturing facility once it is available. Ultimately, the acceptability of drug manufacturing processes, manufacturing process controls, compatibility, etc. will be determined upon review of the license application.

[REDACTED] (b) (4)

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Questions 2: Provention Bio may request an End-of-Phase 2 CMC meeting after the details of the new manufacturing facility are arranged in order to confirm the acceptability of the process, specifications, process validation plans and the stability program to support commercial supply and to discuss other potential CMC issues.

Does the Agency agree?

FDA Response to Question 2: Yes, the Agency recommends that you request an End-of-Phase 2 meeting specifically to discuss CMC issues. It may be helpful to schedule this meeting after preliminary data has been generated from your proposed manufacturing process and once the comparability plan is finalized to have a more productive discussion of what will be required to demonstrate comparability of material produced at your new manufacturing sites.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

2.2 Nonclinical Questions

Questions 3: Teplizumab is a monoclonal antibody. The ICH Guideline S6 R(1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals states that standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still

be needed depending upon duration of clinical dosing, patient population, and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.) The need for a product-specific assessment of the carcinogenic potential for biopharmaceutical should be determined with regard to the intended clinical population and treatment duration (see the guidance S1A The Need for Carcinogenicity Studies of Pharmaceuticals.)

Teplizumab falls within the category of biotechnology-derived pharmaceuticals and has several product-specific characteristics that suggest carcinogenicity studies are not warranted: a) the clinical use is expected to be short (b) (4) b) Direct testing of teplizumab in standard rodent carcinogenicity models is inappropriate due to lack of binding of teplizumab to rodent CD3; c) The surrogate anti-murine CD3 antibody used in pre-clinical pharmacology and toxicology studies (251055), has limited utility in chronic dosing due to increased hypersensitivity and anaphylactic reactions observed with long term repeat dosing. Therefore, taken together Provention Bio believes that a carcinogenicity study is not warranted, and this would be consistent with ICH guidelines.

(1) Does the Agency agree?

(2) If the Agency agrees, should Provention Bio submit a formal request for waiver of carcinogenicity studies to the CDER ECAC committee?

FDA Response to Question 3: We agree a carcinogenicity assessment is not needed given the intended duration of drug exposure. As review divisions determine the need for carcinogenicity assessments, a waiver request for the CDER ECAC is not needed.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Questions 4: Due to the limited binding of teplizumab to CD3 in non-human species suitable for reproductive toxicology studies, reproductive toxicity studies were conducted in mice using a surrogate monoclonal antibody (251055) that binds to the murine CD3ε. Does the Agency agree that the completed reproductive toxicity studies are adequate for submission in a BLA?

FDA Response to Question 4: Yes, we agree that the completed reproductive toxicity studies are adequate for submission in a future BLA.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Questions 5: A tabular overview of Provention Bio's nonclinical program for the indication of treatment of recent-onset T1D is provided in the briefing package.

Does the Agency agree that the outlined nonclinical studies are adequate to support the successful filing of a BLA and that no additional non-clinical studies are needed?

FDA Response to Question 5: We agree that no additional non-clinical studies are needed to support filing of a BLA, unless unanticipated issues arise in your program that are addressable by non-clinical approaches.

Discussion:

The sponsor accepted FDA's response.

Additional Nonclinical Discussion:

During the meeting, DMEP asked if there were plans to alter the dosing regimen in the future. Provention Bio responded that only the proposed dosing regimen is being investigated at this time. The Division noted that additional nonclinical evaluation would likely be needed to support a chronic, recurring dosing regimen for teplizumab.

2.3 Clinical Questions

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4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data

requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

5.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of

Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety.

The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

6.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

8.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

9.0 UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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