BLA 761183

CORRECTED BLA APPROVAL

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 biologics license application (BLA) dated October 31, 2020, received November 2, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tzield (teplizumab-mzwv) injection.

We also refer to our approval letter dated November 17, 2022, which contained the following errors:

- Licensing location incorrectly stated as (b) (4)
- Manufactured, filled, labeled, and packaged locations were not correctly identified
- Minor formatting errors in the prescribing information (PI)

This corrected action letter incorporates the correction of the error. The effective action date will remain November 17, 2022, the date of the original letter.

We acknowledge receipt of your resubmission dated February 17, 2022, which constituted a complete response to our July 2, 2021, action letter.

We acknowledge receipt of your major amendment dated June 17, 2022, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2170 to Provention Bio, Inc., Red Bank, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Tzield (teplizumab-mzwv). Tzield is indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture teplizumab-mzwv drug substance at [redacted] The final formulated drug product will be manufactured and filled at [redacted] You may label your product with the proprietary name, Tzield, and market it in 2mg/2mL (1 mg/mL) injection.

DATING PERIOD

The dating period for Tzield shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be [redacted] months from the date of manufacture when stored at [redacted]°C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Tzield to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Tzield, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- The PI and medication guide (MG) were revised to reflect the initial date of approval.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761183**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We are deferring submission of your pediatric study for ages 0 to less than 8 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4359-1 Conduct a 12-month single-arm, open-label study to assess the safety and pharmacokinetics (PK) of teplizumab-mzwv in pediatric patients 0 to less than 8 years of age with two type-1 diabetes (T1D)-related autoantibodies

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

and dysglycemia (Stage 2 T1D) [Part A], followed by a 12-month open-label extension [Part B].

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

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocols to your IND 102629, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 8 to 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk for the following adverse reactions: cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders, malignancy, and adverse pregnancy and birth outcomes.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4359-2 Conduct an observational registry study to assess the long-term safety of teplizumab-mzwv in patients with Stage 2 type 1 diabetes. The study should evaluate cytokine release syndrome, serious infections, hypersensitivity reactions, lymphoproliferative disorders and malignancy. The registry should also collect information on women exposed during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant's first year of life. The study design should include a comparator group and monitor patients for at least 10 years after their first course of treatment. The study should enroll at least 150 subjects exposed to teplizumab-mzwv and collect sufficient clinical information to assess for sources of confounding for the target outcomes.

The timetable you submitted on October 19, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	March 2023
Final Protocol Submission:	September 2023
Interim Report Submissions:	January 2024
	January 2025
	January 2026
	January 2027
	January 2028
	January 2029
	January 2030
	January 2031
	January 2032
	January 2033
	January 2034
	January 2035
	January 2036
Study Completion:	January 2037
Final Report Submission:	September 2037

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to provide comparative safety data on the commercial formulation manufactured by (b) (4) versus the TN-10 clinical trial drug product.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4359-3 Provide comparative safety data on the commercial formulation manufactured by (b) (4) versus the TN-10 clinical trial product by submitting the clinical study reports for study PRV-031-001 (PROTECT), and study PRV-031-003 (PROTECT Extension) that seeks to collect an additional 42 months of long-term safety data in participants who complete the PROTECT study.

The timetable you submitted on October 19, 2022, states that you will conduct this trial according to the following schedule:

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

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

Submit clinical protocols to your IND 102629 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to

investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4359-4 To improve or develop a new assay to analyze the [redacted] (b) (4) profile of teplizumab-mzwv with improved precision and repeatability compared to the current assay and to implement this assay in the teplizumab-mzwv drug substance and drug product release and stability programs and qualification/validation of reference materials. The analytical procedure, validation report, proposed acceptance criterion, data used to set the proposed acceptance criterion, and bridging date to the current CEX assay will be provided in the final study report.

The timetable you submitted on October 13, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2023

4359-5 To validate the [redacted] (b) (4) assay for control of teplizumab-mzwv [redacted] (b) (4) profile at drug substance release and analyze all available data from clinical, process performance qualification (PPQ), and commercial drug substance lots, including historical teplizumab-mzwv lots. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

The timetable you submitted on October 13, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2023

4359-6 To confirm suitability of the current host cell protein assay, as defined by [redacted] (b) (4) HCP coverage. Suitability data will be provided in the final report.

The timetable you submitted on October 13, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2023

4359-7 To implement and qualify a new primary reference material and to implement a two-tiered reference material system with a working reference material consistent with principles described in ICHQ6B, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*. Provide the qualification report(s), and requalification protocols for the working reference materials to the BLA.

The timetable you submitted on October 13, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2023

4359-8 To continue investigations into the root-cause of any product quality differences that may account for the pharmacokinetic differences documented between the (b) (4) and Eli Lilly products in the clinical trials. The complete relevant analytical data from your clinical, PPQ, commercial drug substance lots, and Lilly lots, a risk evaluation for potential impact of the differences based on these investigations, and proposed control strategy (if applicable) will be provided in the final investigation report.

The timetable you submitted on October 13, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2023

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Supendeep 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 Researc

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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
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