BLA 761183/S-010
BLA 761183/S-014

ACCELERATED APPROVAL
SUPPLEMENT APPROVAL

Provention Bio, Inc
Attention: Gargi Lakhwani
Regulatory Strategist – Associate Director, Global Regulatory Affairs
100 Morris Street
Morristown, NJ 07960

Dear Gargi Lakhwani:

Please refer to your supplemental biologics license applications (sBLAs), received July 21, 2025, for S-010, and December 23, 2025, for S-014, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tzield (teplizumab-mzwv) injection.

We acknowledge receipt of your major amendment dated November 24, 2025, which extended the goal date by three months for S-010. We also acknowledge receipt of your major amendment dated April 16, 2026, which extended the goal date by two months for S-014.

The Prior Approval sBLA, S-010, provides for updates to the Prescribing Information (PI) and Medication Guide (MG) to add an indication to delay the decline in endogenous insulin production in pediatric patients age 8 to 17 recently diagnosed with Stage 3 type 1 diabetes (T1D) and other information based on trial PRV-031-001 entitled, *A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed T1D (PROTECT).*

The Prior Approval sBLA, S-014, provides for updates to the PI to introduce alternative in-use syringe administration and provide updated compatibility information.

APPROVAL & LABELING

We have completed our review of these sBLAs, as amended. S-010 is approved under the provisions of accelerated approval regulations (21 CFR 601.41), and S-014 is also approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the PI and MG) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct a further adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 8, 2026. This requirement is listed below.

4921-1 Complete study EFC18241, a randomized, double-blind, placebo-controlled trial to describe and verify the clinical benefit of teplizumab-mzwv in patients with Stage 3 type 1 diabetes (T1D). The trial should be

[1] 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.

adequately powered to detect a treatment effect on the endpoint that will be used to describe and verify the clinical benefit.

Final Protocol Submission: August 2026
Trial Completion: June 2029
Final Report Submission: December 2029

Submit clinical protocols to your IND 100262 for this product. 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 clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open clinical trial required under section 506(c). One report will be a standalone submission, and the other report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval of the original BLA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761183/S-010 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval of the original BLA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that you provide detailed analyses of events of bone fracture reported from clinical study and post-marketing reports in your periodic safety report [i.e., the Periodic Adverse Drug Experience Report (PADER) required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format]. These analyses should show cumulative data relative to the date of approval of Tzield (teplizumab-mzwv) as well as relative to prior periodic safety reports.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Supendeep Dosanjh, Regulatory Project Manager, at Supendeep.Dosanjh@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mahtab Niyyati, M.D.
Associate Director of Therapeutic Review (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

MAHTAB NIYYATI
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