CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761183Orig1s000

OTHER ACTION LETTERS

BLA 761183

COMPLETE RESPONSE

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, submitted under section 351(a) of the Public Health Service Act for PRV-031.

We also acknowledge receipt of your amendments dated April 15, April 28, May 18, May 27, June 7, and June 25 (eCTD #56), 2021, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

(1) The results of the pharmacokinetic (PK) bridging study PRV-031-004[1] in healthy volunteers failed to show PK comparability between the PRV-031 product used in TN-10[2] and the planned commercial product. Study PRV-031-004 revealed considerable differences in the total area under the time-concentration curve extrapolated to infinity ($AUC_{0\text{-}inf}$) between the two products, with the planned commercial product providing an approximately (b) (4)% lower $AUC_{0\text{-}inf}$, despite a comparable C_{max} after a single intravenous infusion. As PK remains the primary endpoint for demonstration of comparability between the two products, you will need to establish PK comparability appropriately between the intended commercial product and the clinical trial

[1] A Phase 1, Randomized, Double-Blind, Parallel Group, Single-Dose Study in Healthy Subjects to Evaluate the Bio comparability of Teplizumab (PRV-031) Manufactured at Two Sites
[2] Anti-CD3 mAb (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus

product, or provide other data that adequately justify why PK comparability is not necessary.

PRODUCT QUALITY

(2) Results of your ongoing real-time stability studies demonstrate unacceptable charge variation measured in PRV-031 drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions. For instance, (b) (4) these data preclude the ability to assign a shelf-life for either drug substance or drug product, not only because of the unacceptable degree of change, but also because stability behavior is not consistent between drug product lots manufactured using AGC material. This degree of change also prevents a determination as to whether there is a problem with product stability, the method, or both. Finally, the possibility that this variation arises from method variability also introduces uncertainty into the reliability of all results generated with this method, including the analytical comparability assessment, highlighted by the difference in stability behavior between AGC lots and lots manufactured by Eli Lilly. To address these deficiencies:

a. Provide data and information regarding the source of the variability of the PRV-031 drug product and drug substance charge profile on stability as measured by the CEX-HPLC assay.

b. Address and remediate the source of the charge variation of PRV-031 manufactured at AGC.

c. Address the differences in PRV-031 stability behavior between clinical material manufactured at Eli Lilly and proposed commercial material manufactured at AGC Biologics.

d. If changes are made to the CEX-HPLC assay as a result of the investigation, provide data and information to support that these changes to the CEX-HPLC assay do not impact the data to support this application. This should include, but not be limited to, batch release data, stability data, in-process testing, process characterization studies, and the comparability assessment between the clinical material manufactured at Eli Lilly and the proposed commercial material manufactured at AGC Biologics.

(3) No information was provided in Section 3.2.S.2.3 regarding your plans to monitor Master Cell Bank (MCB) and Working Cell Bank (WCB) stability. To correct this deficiency, provide cell bank requalification protocols for the MCB and WCB to include, but not be limited to, the frequency of testing, a justification for this frequency, number of vials proposed to be tested at each testing timepoint, tests proposed/parameters to be evaluated, and appropriately justified acceptance criteria.

(4) The protocol provided in your submission dated March 31, 2021, for requalification of the primary reference standard (PRS) is deficient. The requalification protocol should ensure that the PRS remains stable over time and remains suitable for its intended purpose. In order to accomplish this, address the following:

[redacted] (b) (4)

(5) Insufficient information was provided regarding the levels and types of leachates in PRV-031 derived from its container closure and the risk to patients from any leachates that are potentially present in the drug product during its shelf life. To address this deficiency, provide sufficient data from a leachable study to evaluate the filled drug product container closure systems when stored inverted under the recommended conditions. Perform testing at regular intervals through the end of shelf-life to include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS).

FACILITY INSPECTIONS

(6) During a recent inspection of the [redacted] (b) (4) (FEI: [redacted] (b) (4)) manufacturing facility for this application, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[5]

[3] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[4] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated January 22, 2021, which addresses the proposed proprietary name, Tzield. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Clinical

(1) We were not able to confirm your exploratory analysis of the relationship between ADA status at Month 3 (positive, negative, or missing) and efficacy in TN-10. We note that your SAS code for TN-10 CSR Figure 2.5.4.1 contains the relevant code, which utilized SDTM.PC as the source dataset. To facilitate our analysis, please provide the following:

- A description of the derivation algorithm for this variable,
- A SAS code that is used to generate this variable, and
- A SAS dataset that contains the variable.

Clinical Pharmacology

(2) Characterize the immunogenicity potential for the proposed commercial product manufactured by AGC Biologics, including but not limited to assessments of the titers of anti-drug antibodies and neutralizing antibodies to PRV-031. Compare the immunogenicity potential of the AGC product to the clinical trial product and provide justification for any differences noted.

Product Quality

(3) Determine the extinction coefficient for PRV-031 experimentally to ensure that the concentration of PRV-031 is determined correctly in release and stability testing.

(4) In your submission dated March 29, 2021, you provided data to demonstrate that oxidation of (b) (4) affects PRV-031 potency (Section 3.2.S.7.1, Table 19 and Figure 12). Because limited data were available to demonstrate that the gene reporter assay has adequate and consistent sensitivity to oxidation of (b) (4) of PRV-031, an analytical method should be developed for release and stability testing of PRV-031 drug substance and drug product that can accurately assess and control levels of

(b) (4) oxidation with adequate acceptance criteria for these purposes. Provide the final method validation report, analyses, and justification to support the proposed acceptance criteria.

(5) Perform and provide results of potency by CD3 binding assay using stressed PRV-031 samples to demonstrate the stability-indicating capability of the assay.

(6) Product-specific validation data were missing from the validation reports of multiple methods to control process-related impurities in the PRV-031 drug substance manufacturing process. For methods to quantify host-cell protein, host-cell DNA, (b) (4) and (b) (4) perform product-specific validation to demonstrate acceptable accuracy, repeatability, intermediate precision, specificity, quantitation limit, linearity, and range of each method for its intended purpose. Provide the corresponding validation reports, data, and analyses.

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OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/

ELLIS F UNGER
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