Provention Bio Receives Complete Response Letter (CRL) to Biologics License Application (BLA) for Teplizumab for the Delay of Clinical Type 1 Diabetes (T1D) in At-risk Individuals

Previously reported pharmacokinetic (PK) drug product comparability considerations remain outstanding

The CRL did not cite any clinical deficiencies related to the efficacy and safety data packages submitted to the BLA

RED BANK, N.J., July 6, 2021 /PRNewswire/ -- Provention Bio, Inc. (Nasdaq: PRVB), a biopharmaceutical company dedicated to intercepting and preventing immune-mediated disease, today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) for the Company's Biologics License Application (BLA) for teplizumab for the delay of clinical type 1 diabetes (T1D) in at-risk individuals.

In the CRL, received late evening on July 2nd, 2021, the FDA stated that a single, low-dose pharmacokinetic/pharmacodynamic (PK/PD) bridging study in healthy volunteers to compare planned commercial product with drug product originating from drug substance manufactured for historic clinical trials had failed to show PK comparability. "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 product or provide other data that adequately justify why PK comparability is not necessary."

The Company expects relevant additional PK/PD data being, or to be, collected from a PK/PD substudy in patients receiving 12-days of therapy in the ongoing Phase 3 PROTECT trial in newly diagnosed T1D patients later this quarter. These data will be analyzed by independent, unblinded third-parties to maintain the integrity of this placebo-controlled trial. Upon review of the results from this substudy, the Company will determine whether to submit these data to the FDA for its review, along with any other relevant data and analyses based on our ongoing discussions with FDA, to support PK comparability or otherwise justify why PK comparability is not necessary.

In the CRL, the FDA cited several additional considerations related to product quality, which the Company believes have either been addressed in amendments already submitted to the BLA or can be addressed in the short-term. The CRL acknowledged that the FDA had not reviewed several amendments already submitted by the Company in response to certain Chemistry, Manufacturing and Controls (CMC) information requests.

The FDA also stated that certain deficiencies conveyed during a recent general inspection, not specific to teplizumab, at a fill/finish manufacturing facility used by the Company will need to be resolved before approval.

The CRL did not cite any clinical deficiencies related to the efficacy and safety data packages submitted to the BLA and confirmed the acceptability of the proposed proprietary name for teplizumab. The FDA

requested that the Company provide a safety update as part of its BLA resubmission. The CRL contained other comments and recommendations that do not impact approvability, as well as general guidance regarding the resubmission process.

"We want to recognize the patients, their families, study investigators, clinicians and T1D champions that have played such a crucial role in the development of teplizumab and thank our partners and our team of dedicated employees and consultants for their outstanding contributions. We also want to acknowledge the efforts of Drs. Yanoff and Unger and the review team at the FDA, who have worked so closely and transparently with us throughout the priority review of our BLA for this Breakthrough Therapy drug," said Ashleigh Palmer, co-founder and CEO of Provention Bio. "We know the T1D community is urgently awaiting therapeutic advancements to address their medical needs and believe our collective passion and committment will continue to drive us forward to meet this goal. We will continue to work collaboratively with the FDA to hopefully secure approval of teplizumab and bring the first disease-modifying therapy for T1D to at-risk patients as soon as possible."

The Unmet Need in Type 1 Diabetes (T1D):

Over 1.6 million Americans have T1D, an autoimmune disease caused by the destruction of beta cells. Diagnosis of T1D usually occurs in children and young adults, but it can happen at any age after symptoms appear when a person cannot make enough insulin. However, T1D starts in the body long before any symptoms and can be detected through a blood test. The psychological impact of T1D is hard to quantify, but a diagnosis is life-altering, and regular monitoring and maintenance can be extremely stressful. T1D typically takes more than a decade off a person's life, and life expectancy is reduced by 16 years on average for people diagnosed before the age of 10. Insulin therapy and glucose monitoring are currently the standard of care for treating clinical-stage T1D, and are necessary to keep T1D patients alive. The constant monitoring and administration of insulin represents a significant life-long burden for patients. No disease-modifying treatments for T1D are currently available.

About Teplizumab (PRV-031):

Teplizumab is an investigational anti-CD3 monoclonal antibody (mAb) being developed for the delay of clinical type 1 diabetes (T1D) in at-risk individuals. In the pivotal TN-10 Study, a single 14-day course of teplizumab delayed insulin-dependent, clinical-stage disease by a median of at least two years in presymptomatic patients with Stage 2 T1D compared to placebo. The observed adverse events were mechanism-based, transient, and predictable, including lymphopenia, transaminase elevations, rash, and cytokine release events. These results were published in the *New England Journal of Medicine* and simultaneously presented at the American Diabetes Association meeting in 2019. More than 800 patients have received teplizumab in multiple clinical studies involving more than 1,000 subjects. In previous studies of newly diagnosed patients, teplizumab consistently demonstrated the ability to preserve beta-cell function as shown by C-peptide, a measure of endogenous insulin production. It correspondingly reduced the need for insulin use. Teplizumab has been granted Breakthrough Therapy Designation by the FDA and PRIME designation by the European Medicines Administration. Provention is currently also evaluating teplizumab in patients with newly diagnosed insulin-dependent T1D (the Phase 3 PROTECT study).

About Provention Bio, Inc.:

Provention Bio, Inc. (Nasdaq: PRVB) is a biopharmaceutical company focused on advancing the development of investigational therapies that may intercept and prevent debilitating and life-threatening immune-mediated disease. The Company's pipeline includes clinical-stage product candidates that have demonstrated in pre-clinical or clinical studies proof-of-mechanism and/or proof-of-concept in autoimmune diseases, including type 1 diabetes, celiac disease and lupus.

Visit www.ProventionBio.com for more information and follow us on Twitter: @ProventionBio.

Internet Posting of Information:

Provention Bio, Inc. uses its website, www.proventionbio.com, as a means of disclosing material nonpublic information and for complying with its disclosure obligations under Regulation F.D. Such disclosures will be included on the Company's website in the "News" section. Accordingly, investors should monitor this portion of the Company's website, in addition to following its press releases, SEC filings and public conference calls and webcasts.

Forward-Looking Statements:

Certain statements in this press release are forward-looking, including but not limited to, statements relating to the medical need in T1D at-risk patients, the potential therapeutic effects and safety of teplizumab in at-risk T1D patients, the timing and ability of the Company to obtain additional PK/PD data from a PK/PD substudy in the ongoing Phase 3 PROTECT trial and other data and analysis relevant to PK comparability, the potential for these data to address the FDA's PK comparability considerations, the Company's belief that the remaining product quality issues cited in the CRL are addressed or can be addressed in the short-term, the FDA review of such data if submitted by the Company, the need for resolution of deficiencies identified at a fill/finish manufacturer used by the Company,and the Company's plans to address the other matters raised in the CRL including plans to continue working collaboratively with FDA to hopefully secure teplizumab approval . These statements may be identified by the use of forward-looking words such as "likely," and "may," among others. These forward-looking statements are based on the Company's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to delays in or failure to obtain FDA approvals for teplizumab or other Company product candidates and the potential for noncompliance with FDA regulations; any inability to successfully work with FDA to find a satisfactory solution to address its concerns in a timely manner or at all, including any inability to provide the FDA with PK/PD data from our ongoing Phase 3 PROTECT study or other data sufficient to support an approval of the BLA for teplizumab; an inability to satisfactorily address other matters cited in the CRL including relating to product quality, fill/finish manufacturer deficiencies identified in a general inspection, safety update required by FDA or any other FDA requirements for an approval of teplizumabthe potential impacts of COVID-19 on our business and financial results; changes in law, regulations, or interpretations and enforcement of regulatory guidance; uncertainties of patent protection and litigation; the Company's dependence upon third parties; substantial competition; the Company's need for additional financing and the risks listed under "Risk Factors" in the Company's quarterly report on Form 10-Q for the quarter ended March 31, 2021 and any subsequent filings with the Securities and Exchange Commission. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Provention does not undertake an obligation to update or revise any forward-looking statement, whether as a result of new information, future developments or otherwise, except as may be required by applicable law. The information set forth herein speaks only as of the date hereof.

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