1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

May 26, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments Submitted to Docket No. FDA-2021-N-0270 for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting on May 27, 2021; Notice of Meeting; Establishment of a Public Docket; Request for Comments

Sidney Wolfe M.D., Public Citizen's Health Research Group

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments to the Food and Drugs Administration (FDA) regarding the biologics license application (BLA) 761183, for teplizumab intravenous infusion, submitted by Provention Bio, Inc. The proposed indication is for the delay of clinical type 1 diabetes mellitus in at-risk individuals.

A. Failure to meet required FDA approval standard for efficacy

TN-10, the only randomized trial upon which teplizumab approval is being considered, was both small and unaccompanied by acceptable "confirmatory evidence," legally required in addition to TN10 because there is no second randomized trial.[1] The post hoc analyzed C-peptide levels in several studies other than TN-10, submitted as such confirmatory evidence "is not a validated surrogate biomarker for clinical benefit, as the quantitative relationship between improvement in C-peptide and delay of T1D is not well defined."[2] Further, "because there were only three studies, and because of nonignorable variation in effects between studies, the estimation of the overall [C-peptide] treatment effect was associated with a large variance and the 2-year overall treatment effect, 0.09 (95% CI: -0.04 to 0.22), was not statistically significant."[3]

[1] Section 115(a) of Food and Drug Administration Modernization Act (FDAMA), which amended 21 U.S.C. § 355(d).
[2] Food and Drug Administration. FDA briefing document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, May 27, 2021; teplizumab BLA 761183. https://www.fda.gov/media/149388/download. Accessed May 26, 2021. PDF p. 12.
[3] *Ibid.* PDF p. 38

B. Safety concerns

The overall safety analysis if TN-10 and the other five studies found 18 cases of diabetic ketoacidosis in patients receiving teplizumab, none in patients receiving placebo. Although none were seen in the more carefully monitored TN-10, the 18 cases, as FDA stated, are "unlikely to be a chance finding."[4] The high rate of other serious adverse events is also cause for concern, especially in light of the flimsy basis for proving the efficacy of teplizumab.

C. Lack of equivalence of the version of teplizumab

Finally, the formulation of teplizumab studied in TN-10 and the other clinical trials is significantly faster in its clearance than the one produced for commercial distribution. "The Applicant conducted a single-dose PK bridging study in healthy volunteers that evaluated the biocomparability of the commercial drug product with the clinical trial drug product. The study failed to demonstrate PK comparability between the two products…"[5]

In summary, the required evidence for the efficacy of teplizumab is lacking, and the drug's risks, such as diabetic ketoacidosis, must be considered in this context. Unlike the previous studies, any future clinical trials for possible approval must be conducted with the same version intended for commercial use.

If, upon patent expiration of any drug, the potential generic manufacturer produced a version that was significantly less bioavailable than the original drug, this would be automatic grounds for FDA rejection.

[4] *Ibid.* PDF p. 43
[5] *Ibid.* PDF p. 19