Our STN: BL 125745/0

COMPLETE RESPONSE
January 9, 2026

Pierre Fabre Pharmaceuticals Inc.
Attention: Lana Klionsky
500 Plaza Drive, Suite 701B
Secaucus, NJ 07094

Dear Lana Klionsky:

Please refer to your Biologics License Application (b) (4), for tabelecleucel(b) (4), (b) (4). We acknowledge receipt of your amendment dated (b) (4), which constituted a complete response to our January 15, 2025, action letter.

We have completed our review of all the submissions you made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Clinical Deficiencies:

To support this BLA, you submitted the results from the ALLELE study, which evaluated the safety and efficacy of Epstein-Barr virus (EBV)-specific T cell immunotherapy (tabelecleuce(b) (4)), in adult and pediatric (2 years of age and older) recipients of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HCT), with relapsed or refractory EBV-positive post-transplant lymphoproliferative disease (EBV+ PTLD), following prior treatments, with primary endpoint of objective response rate (ORR).

We have concluded that the single arm trial (ALLELE study) is not an adequate and well-controlled study due to deficiencies in study design, conduct and analysis, including choice of external control, unplanned efficacy analysis, high attrition rate, introduction of selection bias, and concomitant treatment interventions which confounded the interpretability of study results. For these reasons, the data from the ALLELE study are insufficient to demonstrate substantial evidence of effectiveness of tabelecleuce(b) (4) to treat relapsed or refractory EBV+ PTLD.

1. Choice of control

   The choice of external control was based on historical estimates and assumptions, with a null hypothesis for ORR of 20%, which was not supported by reference to a specific control population. The lack of robust historical data for a control population that is representative of the study population limits the FDA's ability to assess whether the choice of an external comparator for this study is appropriate. The absence of a high treatment response rate in the intention-to-treat (ITT) population, and uncertainties regarding the balance of known and unknown prognostic factors between the treatment arm and the external control, raise significant concerns about the efficacy of the product.

2. Quality of the ALLELE study

   a. Unplanned efficacy analyses with smaller sample size

      Unplanned changes to the sample size in an ongoing single arm study in your revised statistical plan submitted on (b) (4) , and subsequently revised on (b) (4) , resulted in reduction in sample size from 99 treated subjects (in 3 cohorts) to 44 treated subjects (in 2 cohorts). Due to lack of pre-specification of this analysis and lack of Type I error control, the results within this submission are considered descriptive and not statistically inferential. The unplanned efficacy analyses may have introduced a random chance of a successful primary efficacy outcome in a smaller data set.

   b. High attrition rate

      A substantial proportion of ITT population (n=130) with an available matching cell lot were excluded from treatment with any version of the product (55/130; 42%). A smaller subset of ITT population was treated with the intended product version (44/130; 34%). This high attrition rate further challenged data interpretability. The lack of information about subject disposition impacted our ability to assess the reason for high attrition rate, raising further concerns for introduction of selection bias.

3. Persuasiveness and interpretability of the efficacy data

   a. Limited sample size of complete responders (CR)

      The small number of subjects (12/44 or 27%) who achieved complete response (CR) as the best response post tabelecleucel(b) (4) treatment, limits the certainty of the efficacy data.

   b. Limited durability of partial response (PR)

Although PR was observed in 10 of 44 treated subjects, (23%, 95% CI: 11.5-37.8) and contributed to the ORR of 50%, the short median duration of PR (2.04 months, range: 0.03-11.7 months) was not considered clinically meaningful.

c. Prognostic heterogeneity issues affecting interpretability of the efficacy outcomes

   i. PTLD risk

      Although 30% (13/44) of treated subjects in the study had high-risk PTLD, only 8% (1/13) of this subgroup experienced CR, which suggests that the CRs were observed predominantly in the low-intermediate risk group and not representative of the intended target population.

   ii. Histologic heterogeneity

      The study enrolled subjects with a broad range of PTLD histology, ranging from less aggressive histology, such as follicular hyperplasia, plasmacytoma like B cell type, and marginal zone lymphoma to diffuse large B cell lymphoma, with differing prognostic characteristics, limiting the ability of a small single-arm study to demonstrate treatment effect of your product.

d. Potential confounders from treatment interventions

   Concomitant treatment interventions, including reduction in immunosuppression and proximity of rituximab therapy to study entry, affected the interpretability of the efficacy results.

It may be challenging for a single arm study to provide robust efficacy data because relapsed or refractory PTLD presents as a prognostically heterogeneous population. We acknowledge inherent confounding factors related to proximity of prior therapies and reduction in immunosuppression are necessary elements of patient care. Nevertheless, these factors carry the potential to confound the assessments for establishing treatment effect of your product. Therefore, a randomized controlled study may be necessary to minimize bias and confounding effects.

We look forward to collaboratively working with you on study design considerations that adequately minimize the confounding from these factors and reduce the likelihood of biases. We will review and provide comprehensive tailored feedback on study design, including appropriate choice of control, if you were to submit a detailed draft protocol under the existing Investigational New Drug (IND) application.

ADDITIONAL COMMENTS

In addition to the deficiencies that were the basis for not granting approval, we have the following observations on supporting clinical data.

Clinical

1. EBV assessments

   A postulated mechanism of tabelecleucel(b) (4) is to target and lyse EBV infected or positive cells. However, a significant number of subjects had missing EBV data at baseline and some had no data after exposure to study treatment. This was further compounded by the assay methodology, which was changed during the ALLELE study, making the submitted EBV data uninterpretable. These issues precluded the use of EBV data as a supportive biomarker for regulatory decisions.

2. Cytokine data

   The level of analyzed cytokines during the ALLELE study either remained below the lower level of quantification (LLOQ) (IL-1β, IL-2) or remained stable at multiple time points evaluated (IL-6 and TNF-α) for efficacy assessments, in most subjects. Therefore, the submitted cytokine data could not be used as supportive evidence for regulatory decisions.

3. Dosage rationale

   Dosing regimen for the ALLELE study was selected based on previous clinical experience (Study 95-024 and Study 11-130). Conventional dose response analysis was not conducted, as the same dose (2×10^6 cells/kg) was administered to all subjects in the ALLELE study. However, the number of dosing cycles was based on clinical response, as determined by investigator. The observed variability in dosing cycles made it challenging to assess dose response relationship.

Chemistry, Manufacturing, and Controls

4. We completed a follow-up inspection of (b) (4) in (b) (4), and determined that inspectional issues at this facility have been adequately addressed. The deficiency comment in our Complete Response letter dated January 15, 2025, has been satisfactorily resolved.

We reserve additional comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed draft final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (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. 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 Type A post-action meeting within 3 months of the date of this letter. Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm.

If you have any questions regarding the above, please contact the (b) (4)

Sincerely,

(b) (4)

Center for Biologics Evaluation and Research