



Our STN: BL 125827

**COMPLETE RESPONSE**

JULY 21, 2025

Replimune, Inc.  
Attention: Kari Jeschke  
500 Unicorn Park Drive  
Woburn, MA 01801

Dear Kari Jeschke:

Please refer to your Biologics License Application (b) (4),  
for vusolimogene oderparepvec, (b) (4)

We have completed our review of all the submissions you have 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

Your application provides data from RPL-001-16, a single-arm Phase 2 trial of vusolimogene oderparepvec in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody. The prespecified response rate in the RPL-001-16 trial appears numerically higher compared to the proposed historical control rate from literature reports. However, the numerically higher response rate cannot be adequately interpreted due to heterogeneity of the RPL-001-16 trial patient population, including the type of prior therapy received, such as single agent anti-PD-1 or combination checkpoint inhibitor, duration and setting of prior anti-PD-1 therapy, and extent of disease at baseline, and due to the heterogeneity of the patient population reported in the literature. The RPL-001-16 trial was also not designed to isolate the contribution of vusolimogene oderparepvec to the observed ORR when administered in combination with nivolumab. While vusolimogene oderparepvec is not expected to demonstrate significant single-agent activity based on its mechanism of action, its specific contribution to the observed ORR cannot be determined. Therefore, the RPL-001-16 trial is not considered to be an adequate and well controlled clinical investigation that provides substantial evidence of effectiveness as required by the Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505(d), 21 Code of Federal Regulations (CFR) § 314.126, and Section 351 of the Public Health Service Act (PHS Act).

To address this deficiency, you must conduct and provide the results from adequate and well-controlled clinical trial(s) which demonstrate substantial evidence of effectiveness.

#### ADDITIONAL COMMENTS

Chemistry, Manufacturing, and Controls (CMC)

(b) (4)

#### Clinical

2. Several issues that must be addressed have been identified with the RP1-104 trial, which is a Phase 3 multicenter, multiregional, randomized, controlled, open-label trial to evaluate the safety and efficacy of vusolimogene oderparepvec in combination with nivolumab compared with treatment of physician's choice in patients with unresectable advanced cutaneous melanoma who have confirmed disease progression on an anti-PD-1 and an anti-CTLA-4 treatment regime, either in combination or in sequence. The study design may not isolate the contribution of vusolimogene oderparepvec due to the inclusion of single-agent chemotherapy options in the investigator's choice control arm. There also is

inadequate data to support the statistical assumption of a 6-month improvement in the primary endpoint of overall survival. We recommend you submit a revised study protocol that assesses the individual contribution of vusolimogene oderparepvec to the observed ORR and provide a detailed justification for the statistical assumptions that support your primary efficacy endpoints.

3. We reserve additional comment on the proposed labeling until deficiencies described above have been resolved. We may have comments when we review 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 meeting or teleconference with us to discuss the steps necessary for approval.

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