Our STN: BL 125827

COMPLETE RESPONSE
APRIL 10, 2026

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

Dear Kari Jeschke:

Please refer to your Biologics License Application (BLA) received (b) (4), for vusolimogene oderparepvec, submitted under section 351(a) of the Public Health Service Act. We acknowledge receipt of your amendment dated October 9, 2025, which constituted a complete response to our July 21, 2025, action letter.

We have completed a comprehensive review of all the submissions relating to this BLA for vusolimogene oderparepvec in combination with nivolumab for adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based therapy. We performed a reanalysis of data from study RPL-001-16 along with the review of additional data from study RP1-104. To maintain objectivity and account for potential bias, the review team members for this BLA resubmission were different than those who reviewed the initial BLA. This BLA resubmission primary clinical review team, supervisory leadership in the Office of Therapeutic Products, and subject matter experts from Oncology Center of Excellence unanimously determined data presented are insufficient to conclude substantial evidence of effectiveness of vusolimogene oderparepvec for treatment of unresectable advanced cutaneous melanoma.
FDA advice has remained consistent as evidenced by our communications dating back to March 2021 and subsequent interactions described in this letter.

The deficiencies for each of the studies are outlined here.

For RPL-001-16:

- Inability to isolate the contribution of vusolimogene oderparepvec when administered in combination with nivolumab,
- Heterogeneity of the study population, and
- Uncertainty of response assessments including surgical interventions with potential for confounding response results

For RP1-104

- Limited number of patients treated to date (10% of the planned study population)
- Response assessment performed only by investigator,
- Lack of duration of response data, and
- Difficulty in interpreting progression-free survival data due to lack of pre-specification for this analysis and without adequate type 1 error control.

Therefore, the evidence as presented does not meet the evidentiary standards required for regulatory approval, and the results of the additional exploratory analyses of the RPL-001-16 data do not alter our initial conclusion that the RPL-001-16 trial is not an adequate and well-controlled clinical investigation that demonstrates substantial evidence of effectiveness.

CLINICAL

To support this BLA for vusolimogene oderparepvec in combination with nivolumab for the treatment of adult patients (n=140) with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based therapy, you submitted clinical data on (b) (4) from a single-arm Phase 2 study (RPL-001-16) without a concurrent control or an acceptable historical control for the primary efficacy endpoint of objective response rate (ORR).

As communicated in the Complete Response letter dated July 21, 2025, and described in more detail below, RPL-001-16 is not considered to be an adequate and well-controlled clinical investigation that provides substantial evidence of effectiveness. RPL-001-16 was not designed to isolate the contribution of vusolimogene oderparepvec when administered in combination with nivolumab. Thus, the specific contribution of vusolimogene oderparepvec to the observed response rate in RPL-001-16 cannot be determined. FDA stated that you must conduct and provide the results from an adequate and well-controlled clinical trial(s) which demonstrates substantial evidence of effectiveness.

To support resubmission of the BLA on October 9, 2025, you provided ORR data from an early unplanned analysis from your ongoing, randomized, Phase 3 trial, RP1-104, including 22 patients in the investigational arm of vusolimogene oderparepvec with nivolumab and 18 patients in the control arm (physician's choice of treatment), representing 10% of the planned enrollment of 400 patients. You also provided results from additional exploratory analyses of RPL-001-16, including analyses of patients who had a response to immediate prior anti-PD1 therapy and their subsequent response to the combination of vusolimogene oderparepvec and nivolumab, of progression-free survival, and of response in patients who had both injected and non-injected tumors.

Prior communication

FDA clearly communicated our concerns with the study design in multiple FDA interactions throughout your development program.

Contribution of Effect

- In the Type B meeting dated March 25, 2021 (IND (b) (4)/CRMTS 13148), we stated that "your proposed single-arm study will not enable identification of the contribution of each component of the combination to the overall response rate" and we recommended that "you conduct a randomized controlled trial (RCT) to demonstrate efficacy and safety of the combination and isolate the contribution from each component to the overall treatment effect."

  Additionally, in the pre-BLA meeting dated September 3, 2024 (IND (b) (4)/Meeting ID 20461), we communicated that you must "provide evidence to demonstrate that there is a compelling reason that *both* RP1 and nivolumab *are necessary* to achieve the observed treatment effect."

Primary Endpoint of Objective Response Rate and Magnitude of Clinical Benefit

- In the Type B meeting dated March 25, 2021 (IND (b) (4)/CRMTS 13148), we noted that "your proposed target of 30% to 40% objective response rate (ORR) may not translate into unequivocally improved clinical benefit in this indication." We also expressed concern about "potential issues of interpreting efficacy result due to baseline heterogeneities among study subjects" and reiterated that we "would not recommend that the Sponsor submit a BLA based on the results of a single-arm study". Finally, we noted that "we consider the interpretation of responses in the setting of the intra-tumoral route of administration to be problematic in the lesions which have been injected."

FDA ultimately did not object to the submission of the BLA based on data from RPL-001-16, reflecting FDA's flexibility in disease settings with high unmet need. However, on review of the RPL-001-16 data submitted to support the BLA, the study design concerns previously communicated were not addressed, and the contribution of vusolimogene oderparepvec to the observed response rate in RPL-001-16 could not be determined.

As communicated in the Complete Response letter dated July 21, 2025, RPL-001-16 was not designed to *isolate* the contribution of vusolimogene oderparepvec to the observed response rate when administered in combination with nivolumab. Additionally, the reported response rate from RPL-001-16 could not be adequately interpreted due to heterogeneity of the trial patient population. FDA stated that you must conduct and provide the results from an adequate and well-controlled clinical trial(s) which demonstrates substantial evidence of effectiveness.

In the Type A meeting dated September 16, 2025, FDA also communicated that the response criteria used in RPL-001-16 were not consistent with RECIST v1.1 and may not be comparable to response rates reported in the historical literature. FDA provided recommendations regarding use of data from the ongoing Phase 3 trial to potentially support Accelerated Approval.

Instead, you submitted data from an early unplanned analysis from RP1-104, representing 10% of the planned enrollment, as well as additional exploratory analyses of the RPL-001-16 data, to support BLA resubmission. This data is insufficient to support an efficacy claim. The specific deficiencies are explained in detail as follows:

Issues in response assessment confound efficacy results

1. FDA review identified several issues in the assessment of the reported response rate and duration of response in RPL-001-16, which include application of response criteria that affect the reliability of the reported results and their clinical meaningfulness. Review of the individual patient data also revealed multiple deviations from standard RECIST v1.1 methodology.

    a. **Lack of noninjected target lesions to assess systemic response:** FDA review identified that almost half (49%) of the patients with objective response had all their target lesions injected with vusolimogene oderparepvec. Furthermore, FDA review identified two additional patients deemed responders who did not have any target lesions per independent review at baseline. Thus, over half (53%) of patients with objective response did not have noninjected target lesions to assess systemic anti-tumor activity. When these patients are excluded from the analysis of the primary endpoint of ORR, the resulting response rate decreases markedly from your reported response rate in RPL-001-16. Therefore, the systemic anti-tumor activity of vusolimogene oderparepvec is not well characterized.

    b. **Re-injection and assessment of progression:** We acknowledge that the protocol allowed for retreatment with vusolimogene oderparepvec according to investigator discretion. FDA review identified patients with either new lesions, or existing lesions that were identified as having enlarged, who were selected for retreatment with vusolimogene oderparepvec injections prior to an independent review committee (IRC) determination of progressive disease. This local intervention obscures the determination of response as assessed by the IRC. These patients may have had intervening progressive disease, prior to their best overall response, which in turn would confound both the reported response rate (by counting responses that occurred after progression) and the reported duration of response (by extending the duration beyond progression events).

c. **Confounding effect of surgical procedures:**
Surgical procedures, including excisional biopsies, were performed on target lesions during the treatment period and, in some cases, immediately preceded the next response assessment that determined a partial or complete response. Removal of tumor tissue can impact measurement of tumor lesions, particularly in patients with few or small lesions, as reduction in tumor size may be due to removal of tumor tissue via surgery or excisional biopsy rather than due to the anti-tumor activity of vusolimogene oderparepvec.

d. **Histology assessments:**
Histopathologic assessments were used to assess response, and in some cases, these results changed the radiologic response assessment of best overall response. In RPL-001-16, these histology specimens were not centrally reviewed, there is a potential for sampling bias with respect to biopsy specimens, and it is unclear whether a determination of tumor response based on pathology reflects local treatment effects at the injection site rather than systemic effects of the investigational therapy.

These issues introduce variability and potential bias in the response assessments and the conduct of RPL-001-16 makes assessments of response difficult to interpret. Given these issues, the reported response rate and duration of response from RPL-001-16 were not reliably assessed, could be artifactually increased, and may not be reproducible. Therefore, RPL-001-16 is not considered to be an adequate and well controlled clinical investigation that provides substantial evidence of effectiveness and the FDA review team cannot conclude that the reported results are clinically meaningful.

Heterogeneity of RPL-001-16 patient population and lack of a well-established historical control limit comparisons of response rate

2. As communicated to you in the Complete Response letter dated July 21, 2025, the response rate in RPL-001-16 appears numerically higher compared to the proposed historical control rate from literature reports. However, comparing response rates cross-trial from RPL-001-16 to historical controls is challenging due to the heterogeneity of the patient populations in RPL-001-16 and the historical controls (e.g., the type of prior therapy received, such as single agent anti-PD-1 or combination checkpoint inhibitor, duration of prior therapy, setting of prior anti-PD-1 therapy [adjuvant vs. advanced/metastatic setting], extent of disease at baseline).

   FDA communicated these concerns to you during the Type B meeting on March 25, 2021 (IND (b) (4)/CRMTS 13148), stating “FDA noted potential issues of interpreting efficacy results due to baseline heterogeneities among study subjects” and reiterated that they “would not recommend that the Sponsor submit a BLA based on the results of a single-arm study.”

Given the issues identified in FDA Comment #1, the heterogeneity in the patient population enrolled in RPL-001-16 and lack of a well-established historical control benchmark for response rate and duration of response in a similar patient population further confounds interpretation of trial results and does not allow for a comparative analysis to be conducted between RPL-001-16 and the historical literature for the purposes of establishing that vusolimogene oderparepvec is reasonably likely to predict clinical benefit or provide a meaningful advantage over available therapies per the statutory requirements for Accelerated Approval.

Trial design inadequate to establish contribution of effect

3. RPL-001-16 was not designed to isolate the contribution of vusolimogene oderparepvec when administered in combination with nivolumab.

   The heterogeneity in the patient population enrolled in RPL-001-16 and lack of a well-established historical control benchmark for response rate and duration of response in a similar patient population (as discussed under FDA Comment 2) do not allow for a comparative analysis to be conducted between RPL-001-16 and the historical literature for the purposes of ascertaining nivolumab's expected monotherapy activity in this population.

   As noted under FDA Comment #1, because the response rate and duration of response were not reliably assessed in RPL-001-16, challenges in comparing these data to external, historical control data for the purposes establishing contribution of effect of vusolimogene oderparepvec to the combination of vusolimogene oderparepvec and nivolumab are further confounded. Thus, it remains unclear whether the observed responses in RPL-001-16 are due to nivolumab alone.

Therefore, RPL-001-16 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).

It may be challenging for a single arm study to provide robust efficacy data because patients with advanced/metastatic melanoma who progress on immunotherapy present as a heterogeneous population. We acknowledge inherent confounding factors related to drug development in this disease setting. Nevertheless, these factors carry the potential to confound the assessments for establishing the treatment effect of your product.

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

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. You may request a meeting to discuss if the ongoing RP1-104 study with a revised study protocol and statistical analysis plan can address the deficiencies outlined or propose a new clinical study.

We reserve comments 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