

| Office of Clinical Evaluation (OCE) Memorandum<br>BLA 125827 (Second Resubmission) |                                                                                                                   |
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| Application Type                                                                   | Biologics License Application (Resubmission)                                                                      |
| Application Number(s)                                                              | BLA 125827                                                                                                        |
| Applicant                                                                          | Replimune, Inc.                                                                                                   |
| Drug Name                                                                          | TUDRIQEV (vusolimogene oderparepvec-wtpg) also known as RP1                                                       |
| Submission Receipt Data                                                            | Original submission: November 21, 2024<br>First resubmission: April 10, 2026<br>Second resubmission: June 2, 2026 |
| PDUFA Goal Date                                                                    | August 2, 2026                                                                                                    |
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**Recommendation on Regulatory Action: Accelerated Approval based on overall response rate and duration of response**

**I. Executive Summary**

BLA 125827 was initially submitted on November 21, 2024, by Replimune, Inc. for vusolimogene oderparepvec-wtpg (also known as RP1), a genetically modified oncolytic viral therapy for intratumor injection, proposed in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed cell death protein 1 (PD-1)–blocking antibody-based regimen. IGNYTE (NCT03767348), an open-label, multicenter Phase 1/2 clinical trial evaluating RP1 administered intratumorally in combination with nivolumab was intended to provide primary evidence of effectiveness. Two Complete Response Letters (CRLs) were issued on July 21, 2025 (initial BLA) and April 10, 2026 (first resubmission) citing the following principal deficiencies: (1) unreliable response assessment methodology that confounded the reported objective response rate (ORR) and duration of response (DOR); (2) inability to establish the contribution of RP1 to the combination with nivolumab in the absence of a concurrent control; 3) heterogeneity of IGNYTE patient population and lack of a well-established historical control limit comparisons of response rate.

The Applicant submitted a second resubmission on June 2, 2026, which included an updated 3-year OS analysis from the IGNYTE Phase 2 anti-PD-1 refractory melanoma cohort (N=140) and did not introduce substantive new efficacy data to resolve the deficiencies articulated in the prior CRLs. Consistent with prior reviews, the current clinical review team with cross-center collaboration has re-evaluated the totality of evidence, including the IGNYTE Phase 2 efficacy dataset, the early interim data from the randomized Phase 3 IGNYTE-03 trial, the Applicant's exploratory analyses, and the deliberations of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) convened on July 30, 2026.

The CTGTAC voted 10 to 3 that the efficacy results from IGNYTE are evaluable and clinically meaningful. The majority of committee members including melanoma oncologists, clinical trial specialists, and patient advocates acknowledged the significant methodological limitations of the IGNYTE study while emphasizing the substantial unmet medical need, the biologically plausible mechanism of action, the observed signal of tumor shrinkage in both injected and non-injected lesions in a population with no other effective options, and the durable nature of responses in a subset of patients.

Having carefully considered the totality of evidence and the advisory committee's input, and exercising the regulatory flexibility afforded under the Accelerated Approval pathway, Office of Clinical Evaluation (OCE) recommends accelerated approval of BLA 125827 for vusolimogene oderparepvec-wtpg in combination with nivolumab, based on ORR and DOR data, for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a PD-1–blocking antibody-based regimen, subject to the post-marketing requirements described later in this memorandum. This recommendation is made with full acknowledgment of the remaining uncertainties and with the explicit expectation that the ongoing Phase 3 IGNYTE-03 trial will provide confirmatory evidence of clinical benefit.

## **II. Disease Setting and Unmet Medical Need**

Advanced unresectable cutaneous melanoma is a serious and life-threatening malignancy representing the fifth most common cancer in the United States, with an estimated 112,000 new diagnoses and 8,510 deaths in 2026 (NCCN 2026). Major advances in systemic immunotherapy over the past decade, most notably the combination of nivolumab and ipilimumab, which achieved a median OS of 71.9 months in the randomized CheckMate 067 trial (Wolchok et al. 2025) have substantially improved outcomes for patients with previously untreated advanced melanoma. Nevertheless, at least 50% of patients treated with frontline anti-PD-1–based regimen experience disease progression within 1 year.

Treatment selection for patients who have progressed on anti-PD-1–based therapy is challenging. Available options include immune checkpoint inhibitor (ICI) rechallenge, BRAF/MEK inhibitors (for BRAF V600–mutant tumors), chemotherapy, talimogene laherparepvec (T-VEC, approved for local treatment only, without demonstrated OS benefit), and lifileucel (granted accelerated approval in 2024 based on a 31% ORR in a heavily pretreated population). Response rates with available therapies following ICI progression are generally low and inconsistently characterized in the literature, ranging from approximately 7% to 54% depending on prior therapy, patient selection, and response criteria. Patients who have progressed on combination anti-PD-1/anti-CTLA-4 therapy representing 43.6% of the IGNYTE study population face a particularly high unmet need, as therapeutic options with demonstrated systemic efficacy are extremely limited. The CTGTAC unanimously affirmed this unmet need, with several committee members noting that the lack of effective salvage options directly contributes to patient mortality and that each additional month of delay in accessing a potentially active therapy is clinically consequential.

### **III. Summary of Efficacy Evidence**

#### **A. IGNYTE Study Design and Population**

The primary efficacy data are derived from the Phase 2 anti-PD-1 unresectable cutaneous melanoma who progressed on anti-PD-1 based regimen cohort of the IGNYTE study (RPL-001-16; N=140), a single-arm, open-label, multicenter trial. Patients had unresectable Stage IIIB–IV cutaneous melanoma with confirmed progression after at least 8 weeks of nivolumab or pembrolizumab received alone or in combination. Treatment consisted of RP1 administered intratumorally every 2 weeks for 8 doses (starting at  $10^6$  PFU/mL, escalating to  $10^7$  PFU/mL) plus nivolumab 240 mg IV every 2 weeks beginning at Cycle 2. The primary endpoint was ORR per RECIST v1.1 by blinded Independent Review Committee (IRC).

The study population was heterogeneous with respect to prior therapy: 43.6% had received prior anti-PD-1 plus anti-CTLA-4 combination therapy; 25.7% had prior anti-PD-1 only in the adjuvant setting; and 40% had received more than one line of anti-PD-1–based therapy. Approximately 29% of patients had Stage III disease and 18.6% had skin-only disease, reflecting a population with potentially more favorable prognostic characteristics than some historical comparators.

#### **B. Efficacy Results and FDA Analysis**

The Applicant reported an ORR of 33.6% (95% CI: 25.8%, 42.0%) including 23 complete responses (CRs; 16.4%) and 24 partial responses (PRs; 17.1%) by IRC per RECIST v1.1, with a median DOR of 24.8 months (95% CI: 14.1, not

reached). The clinical review team identified substantial methodological concerns that affect the reliability of these figures, as described below.

| Analysis           | Evaluable Patients (n) | ORR (95% CI, %)     | Median DOR (months) |
|--------------------|------------------------|---------------------|---------------------|
| Applicant Reported | 140                    | 33.6 (25.8, 42.0)   | 24.8 (14.1, NR)     |
| FDA Analysis*      | 91                     | 24.2 (15.8, 34.3.0) | 14.1 (10.7, NR)     |

*\*91 patients with at least one noninjected lesion, including 2 patients with unknown injection status.*

The FDA's re-analysis identified five categories of methodological concern that artificially inflate the Applicant's reported ORR and DOR: (1) over half of responders (53%) had all target lesions injected or no measurable target lesions at baseline, precluding assessment of systemic antitumor activity per RECIST v1.1; (2) 14 patients were treated beyond investigator-determined progressive disease (PD), with re-injection of new or enlarging lesions that obscured IRC progression determinations; (3) 115 invasive procedures were performed on tumor lesions in responders during the study, including excisional biopsies and resections preceding response assessments; (4) pathological/histological findings were used to reclassify responses in at least 7 patients (15% of responders) beyond what RECIST v1.1 permits for solid tumors outside of rare specific contexts; and (5) multiple consecutive non-evaluable (NE) IRC assessments in 13 responding patients created uncertainty about intervening disease progression and true DOR.

### **C. Assessment of Systemic Effect and Contribution of RP1**

A central concern throughout this review cycle has been whether RP1 contributes meaningfully to the combination effect, given that the single-arm IGYTE study was not designed with a concurrent nivolumab-alone control arm. The Applicant's exploratory lesion-level analysis in 108 patients with both injected and non-injected measured lesions showed a response rate of 28.7% based on non-injected lesion response alone comparable to the 31.5% response rate observed in injected lesions. While interpretation of this analysis is limited by selection bias (non-injected lesions were a highly selected subgroup chosen by investigators, often for reasons of inaccessibility or small size) and temporal misalignment in the injection status classification, the finding is directionally consistent with a systemic immune mechanism. However, the difficulty lies in that a lesion-level analysis allows mixed responses to be confused with objective responses. Although a lesion-by-lesion analysis may provide insights into the biology, it does not provide insight into the clinical impact at a patient level as

measured by objective response. Nonclinical data in murine melanoma and colorectal carcinoma models demonstrated systemic antitumor activity with RP1 plus anti-PD-1 combination that was not observed with either agent alone. Biomarker data from IGYTE showed increases in CPS scores and gene expression signatures associated with CD8+ T cells, dendritic cells, and tumor inflammation scores from baseline to Cycle 4 in responders versus non-responders, consistent with RP1-mediated immune activation.

The CTGTAC majority concluded with appropriate caveats that the observed responses in heavily pre-treated patients (96% had received 12 or more weeks of prior anti-PD-1 therapy before disease progression and enrollment) were most plausibly attributable to the RP1–nivolumab combination. Several committee members noted that the time to response and the plateau in the DOR Kaplan-Meier curve are consistent with a durable immune-mediated response rather than a transient local effect. Committee members also referenced the early IGYTE-03 interim data (23 RP1+nivolumab patients vs. 18 physician's choice control patients; 3 vs. 0 investigator-assessed responses; PFS HR 0.44 at 6 months), acknowledging that while these data are preliminary and uncontrolled for type I error, they are directionally consistent with a treatment effect of the combination.

#### **D. Overall Survival**

The Applicant submitted a 3-year OS analysis (data cutoff March 8, 2026) reporting a median OS of 32.9 months (95% CI: 25.76, 46.03) with 1-, 2-, and 3-year OS rates of 75.3%, 61.5%, and 47.8%, respectively (N=140; 71 deaths [50.7%]). OS data from a single-arm trial are difficult to interpret as evidence of treatment effect, as the absence of concurrent control does not allow differentiation between a potential treatment effect, patient selection factors, natural disease history, or subsequent therapies received after study progression. The IGYTE study enrolled a notably favorable-prognosis subgroup (29% Stage III, 18.6% skin-only disease, low median disease burden) relative to most reported historical comparators. This data are therefore not used as a basis for this approval recommendation but are acknowledged as consistent with a potential signal warranting further investigation.

#### **IV. Consideration of Advisory Committee Discussion**

The CTGTAC convened on July 30, 2026, to evaluate two discussion questions: (1) whether the single-arm IGYTE study, as designed and conducted, allows for a reliable determination of the expected response rate and durability of response; and (2) whether the clinical meaningfulness of the response rate and DOR observed in IGYTE is indicative of systemic antitumor activity attributable to

RP1. The committee voted 10–3 that the efficacy results from IGNYTE are evaluable and clinically meaningful.

The committee's deliberations surfaced several themes highly relevant to this regulatory determination:

- Unmet need and comparative context. Multiple committee members emphasized that for patients who have failed anti-PD-1 therapy, available alternatives with demonstrated systemic benefit are extremely limited. A committee member noted that lifileucel's accelerated approval was based on a 31% ORR achievable only in a small fraction of eligible patients (approximately 100 centers nationally) due to manufacturing and logistical constraints and argued that a double standard should not be applied to RP1.
- Clinical meaningfulness despite methodological limitations. Several committee members voted in favor of clinical meaningfulness while explicitly acknowledging data limitations. They observed that even at the lower FDA-estimated ORR of 15–25%, responses were durable, consistent across subgroups, and in patients with objectively confirmed disease progression on prior therapy. If the true ORR moves from 5% to even 10–15%, that represents a doubling or tripling of patients who derive benefit a meaningful improvement in absolute terms.
- Systemic effect and DOR plateau. A committee member highlighted the Kaplan-Meier DOR plateau at approximately 44% of responders with no subsequent progression events, stating that observing such a plateau in primary refractory melanoma patients was 'very impressive.' Another committee member noted that the absence of new disease development in patients on study was impactful in a disease where systemic spread is the dominant concern. Given the inevitability of undetected micrometastatic disease, the observation of a systemic effect was biologically consistent and clinically credible.
- Need for new response criteria for intratumoral therapies. Several committee members noted that RECIST v1.1 was not designed for intratumoral therapies and that the field including FDA needs to develop better frameworks for evaluating IT agents. A committee member observed that the most compelling evidence was at the lesional level and called for mandating exclusion of certain injected lesions or requiring a minimum number of uninjected target lesions in future IT therapy trials.
- Dissenting views. Three committee members voted against clinical meaningfulness, citing fundamental uncertainty about the true ORR, the impossibility of reliable cross-trial comparisons, and the view that regulatory standards should not be relaxed on the basis of unmet need alone.

The advisory committee's deliberations taken in totality with the full evidentiary record support the conclusion that RP1 in combination with nivolumab demonstrates a clinically meaningful signal of antitumor activity in a population with critical unmet need. The observed ORR, even at the FDA sensitivity analysis estimate of ~24.2% (95% CI: 15.8%, 34.3%), exceeds the generally expected response to nivolumab rechallenge alone (estimated at approximately 7–19% in the most relevant literature) by a meaningful margin. The response rate is reasonably likely to predict clinical benefit as defined under 21 CFR 601.41, provided confirmatory evidence from the ongoing Phase 3 IGNYTE-03 trial is obtained.

## **V. Safety Summary**

The primary safety evaluation is based on 140 patients treated with RP1 plus nivolumab in the Phase 2 anti-PD-1 refractory cohort (median follow-up 20.8 months). The safety profile was generally manageable and consistent with the known toxicity profiles of nivolumab and intratumoral administration. Grade  $\geq 3$  adverse events occurred in 31% of patients; serious adverse events (SAEs) occurred in 35.7%. Treatment discontinuation due to adverse events occurred in 15.7% of patients.

Most common non-laboratory adverse reactions (incidence > 10%) included fatigue, pyrexia, infections, chills, musculoskeletal pain, nausea, diarrhea, injection site reaction, headache, cough, influenza like illness, rash, vomiting, pruritus, arthralgia, constipation, decreased appetite, dizziness, dyspnea, hemorrhage, edema, and abdominal pain. (No Grade 4 adverse reactions were reported in more than 10% of patients. Adverse events of special interest included tumor hemorrhage (n=3), sepsis (n=3), pneumothorax (n=3, associated with visceral lesion injection), herpetic-like infections (n=4), and cytokine release syndrome (n=1). Two deaths were considered possibly related to study treatment: one patient died of multiorgan dysfunction following injection-site infection and E. coli bacteremia on Study Day 39, and one patient died of myocardial infarction within 30 days of the last nivolumab dose.

Several committee members, including Dr. Garcia, noted that the safety profile did not raise alarm sufficient to outweigh the potential for benefit in this population with no effective alternatives. The absence of a concurrent control arm precludes a fully comparative safety analysis. The benefit-risk profile is considered acceptable for accelerated approval in this serious, life-threatening indication, with the caveat that full characterization of the safety-benefit balance requires the confirmatory Phase 3 data.

## **VI. Regulatory Rationale for Accelerated Approval**

Accelerated approval under 21 CFR 601.41 is available for biological products intended to treat serious or life-threatening conditions that provide a meaningful therapeutic benefit over available therapies. Under this pathway, approval may be based on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit, with a post-market confirmatory trial required to verify benefit. Accelerated approval carries the same statutory requirement for substantial evidence of effectiveness as traditional approval; however, FDA has historically exercised flexibility in interpreting this standard when response rate data supported by duration of response reflect a clinically meaningful and plausible treatment effect in a population with critical unmet need.

The significant methodological limitations of the IGNYTE study, including non-uniform RECIST v1.1 application, the absence of a concurrent control, and the inherent challenges of assessing systemic antitumor activity with intratumoral therapies are acknowledged. Nonetheless, the following considerations taken collectively support an accelerated approval determination:

- Biological plausibility. RP1's mechanism of action includes: direct oncolysis, viral antigen release, GM-CSF–mediated dendritic cell activation, and fusogenic GALV-GP-R<sup>-</sup>–mediated cell-to-cell spread provides a credible scientific rationale for systemic immune priming when combined with PD-1 blockade, supported by murine model data and clinical biomarker findings from IGNYTE.
- Magnitude and durability of response signal. Even the FDA's most conservative sensitivity analysis excluding patients without non-injected target lesions yields an ORR of 24.7% (95% CI: 16.2%, 35.0%) with a median DOR of 14.1 months. For a population in which alternative systemic therapies typically yield ORRs of approximately 7–19%, this represents a clinically meaningful signal.
- Advisory committee support. A 10–3 advisory committee vote affirming clinical meaningfulness including oncologists with direct clinical experience managing this patient population constitutes significant expert consensus that the observed signal is clinically relevant and that approval is appropriate pending confirmatory data.
- Manageable safety profile. The adverse event profile is manageable and does not preclude a favorable benefit-risk assessment in a population with no effective remaining options.
- Confirmatory trial in progress. The ongoing randomized Phase 3 IGNYTE-03 study (RP1-104) provides a viable pathway for post-marketing confirmation of clinical benefit, with primary OS data expected in September 2030.

The regulatory risks of approving a product based on imperfect single-arm data are acknowledged. The concerns raised by dissenting committee members and by prior FDA reviewers regarding response assessment reliability, contribution of effect, and the risk of normalizing suboptimal trial conduct are legitimate and are not dismissed. This recommendation is made in the context of a serious, life-threatening disease with critical unmet need, in which the biologically plausible treatment signal, even at its most conservative estimate represents a clinically meaningful advance over available alternatives, and in which a randomized controlled confirmatory trial is already underway.

## **VII. Post-Marketing Requirements and Conditions of Approval**

Consistent with the requirements for accelerated approval under 21 CFR 601.41(b), the following post-marketing requirement is recommended as conditions of this approval:

- IGNYTE-03 Confirmatory Trial (RP1-104). The Applicant is required to complete the ongoing, randomized Phase 3 IGNYTE-03 trial comparing RP1 plus nivolumab to physician's choice therapy in patients with unresectable advanced cutaneous melanoma who have progressed on anti-PD-1 plus anti-CTLA-4 therapy. The primary endpoint of overall survival is expected to be analyzed no later than September 2030.

### **Pediatric Requirements**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The pediatric study requirement for pediatric patients under 12 years of age with melanoma is waived due to the rarity in pediatric patients in this age group.

- Replimune, Inc is required to conduct an assessment of vusolimogene oderparepvec in combination with nivolumab in pediatric patients 12 years of age and older with advanced melanoma who have confirmed disease progression on an anti-PD-1 and anti-CTLA in combination or in sequence to support the identification of the safe and effective dose in this population. The required pediatric assessment will be conducted through the Phase 3 confirmatory IGNYTE-3 (RP1-104) trial (NCT06264180). The following are the required study timelines.

- Final Protocol Submission: August 31, 2026
- Study Completion Date: September 2030
- Final Report Submission: March 2031

#### Labeling Considerations.

- Product labeling (USPI) includes: a description of the single-arm nature of the supporting evidence of the IGNYTE study; a clear statement that approval is based on the objective response rate and duration of response and that continued approval may be contingent on verification of clinical benefit in the confirmatory trial.

### **VIII. Conclusions and Recommendations**

The primary clinical review team does not recommend approval of the BLA because the Applicant did not address the Complete Response Letter deficiencies in this second BLA resubmission. Having considered the totality of evidence from the IGNYTE Phase 2 study, the early interim data from IGNYTE-03, the known safety profile of RP1 in combination with nivolumab, and the deliberations of the CTGTAC on July 30, 2026, OCE recommends accelerated approval of BLA 125827 for TUDRIQEV (vusolimogene oderparepvec-wtpg) in combination with nivolumab, based on the ORR and DOR data, for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a PD-1–blocking antibody-based regimen.

This recommendation reflects the clinical unmet need in this population, the biologically plausible and directionally consistent efficacy signal from IGNYTE, the manageable safety profile, and the substantial expert clinical consensus expressed by the advisory committee. It is made with the explicit requirement that the Applicant fulfill the post-marketing requirement outlined in Section VII, and with the understanding that continued approval will be contingent on verification of clinical benefit in the ongoing IGNYTE-03 confirmatory trial.

The methodological limitations of the IGNYTE study are acknowledged and documented fully in this memorandum and in the prior review record. The regulatory community should work prospectively with sponsors, trialists, and professional societies to establish validated response criteria for intratumoral immunotherapy trials, so that future applications in this class can be evaluated against a more robust and interpretable evidentiary standard.

## **References**

1. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.
2. FDA Briefing Document, BLA 125827, Cellular Tissue and Gene Therapies Advisory Committee Meeting, July 30, 2026.
3. NCCN Clinical Practice Guidelines in Oncology – Cutaneous Melanoma, Version 1.2026. Accessed July 2026.
4. Wolchok JD, et al. Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med. 2025;392(1):11-22.