

Oncology Center of Excellence Memorandum

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Division/Office	Oncology Center of Excellence (OCE)
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Product: Established Name (Trade name)	Vusolimogene oderparepvec-wtpg
Applicant	Replimune INC
Recommended Regulatory Action	Accelerated Approval

1. Executive Summary

BLA 125827 was initially submitted on November 21, 2024, by Replimune, Inc. for vusolimogene oderparepvec-wtpg (RP1), a genetically modified oncolytic viral therapy for intratumoral injection, proposed in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression on a programmed cell death protein 1 (PD-1)–blocking antibody-based regimen. The primary evidence of effectiveness to support the BLA is based on results from the IGYTE study. The IGYTE study (NCT03767348), an open-label, multicenter Phase 1/2 clinical trial evaluating RP1 administered intratumorally in combination with nivolumab.

Two Complete Response Letters (CRLs) were issued on July 21, 2025 (initial BLA) and April 10, 2026 (first resubmission). The Applicant submitted a second resubmission on June 2, 2026, which included an updated 3-year overall survival (OS) analysis from the IGYTE Phase 2 anti-PD-1 refractory melanoma cohort (N=140) but did not introduce substantive new efficacy data to resolve the deficiencies articulated in the prior CRLs.

OCE review identified several trial design, conduct, and data integrity issues, which are described in detail in Section 3 of this memorandum. These issues include, but are not limited to, unreliable response assessment methodology, multiple Applicant inconsistencies identified across regulatory interactions, and concerns regarding the veracity of submitted datasets. This application was discussed at a Cellular, Tissue, and Gene Therapies Advisory Committee (AC) meeting held on July 30, 2026 (1). The CTGTAC voted 10 to 3 that the efficacy results from IGYTE 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 limited effective therapeutic options, and the durable nature of responses observed in a subset of patients.

OCE has carefully considered the totality of evidence and the discussion at this AC, FDA guidance, and statutory language regarding the establishing substantial evidence of effectiveness and determines that the effect of RP1 has been demonstrated and distinguished from “other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation (2).” Upon FDA review, some patients’ tumors do decrease after injection with RP1. Therefore, at minimum, a local treatment effect has been demonstrated. It remains unclear whether there is any systemic effect of the combination therapy attributable to RP1, and the individual contribution of RP1 and nivolumab to the combination has not been established by the Applicant. Some patients with advanced disease may not consider a therapy effective unless it cures them, prolongs their survival, and/or improves their quality of life. Even in cases of substantial unmet need, these patients deserve safe and effective drugs, and a lower evidentiary bar is not appropriate. However, OCE acknowledges that some patients are willing to accept substantial uncertainty given the unmet need and lack of alternative available therapies. Therefore, after consideration of the discussion at this AC, and consistent with FDA guidance and statutory language regarding establishing substantial evidence of effectiveness, we conclude that accelerated approval is acceptable in the context of this uncertainty. Clinical benefit should be verified in confirmatory trial(s). Without confirming clinical benefit, the risk of severe and fatal adverse events would not be acceptable if only a local injection effect is driving the observed results.

The Applicant should meet with FDA to discuss the confirmatory trial, IGNYTE-3. It is unclear if prior concerns regarding the trial design of IGNYTE-3 have been adequately addressed by the Applicant. There may be challenges in enrolling IGNYTE-3 once RP1 is approved. Failure to conduct a trial with due diligence can be grounds for withdrawing approval using expedited withdrawal procedures (3). Upon last communication with the Applicant, they stated that only 10% of IGNYTE-3 was enrolled. Therefore, OCE recommends that the Applicant meet with the primary review team to discuss their plans to confirm benefit as soon as possible because failure to confirm benefit or conduct the confirmatory trial with due diligence may result in withdrawal of this indication.

2. Regulatory Background

For a full regulatory background, see the FDA AC Briefing Document (1).

3. Background and Review of Clinical Data

For full review and details on clinical data, see FDA AC Briefing Document (1).

A. The Advisory Committee

Several issues were raised at the AC that the review team would like to address.

First, the Applicant and certain members of the committee endorsed an expected response rate to checkpoint inhibitor rechallenge in this population of 5-7%. OCE disagrees.

- The cited 5% value is not a historical control. It is an “aim” from a SITC taskforce, whereby the taskforce members’ goal was to identify a population that would be expected to have a response rate to subsequent checkpoint inhibitor rechallenge of 5% or less. The literature, Kluger 2020 (4), specifically notes that this value has not been validated. Therefore, it is a goal of the committee to identify such a population, not an actual historical control rate that can be used to determine nivolumab’s expected monotherapy activity. Notably, the committee member who supported this 5% value is on the SITC taskforce and was a co-author of the SITC 2020 manuscript. A committee member claiming that 5% is a historical rate when the actual manuscript specifically states that this value has not been validated is concerning for bias and lack of objectivity, as it is that committee member’s own estimate rather than a value validated by any data.
- The 7% value is not a historical control. The citation used to support this, Ribas 2018 (5), was itself derived from a pooled analysis published by Beaver 2018 (6). In the Beaver manuscript, the authors identified 500 patients who received checkpoint inhibitor rechallenge after progression on prior anti-PD-1 therapy, and 95 patients responded to rechallenge, yielding a 19% response rate. Ribas and colleagues claimed that the denominator for this calculation should be 1361 (the number of patients in the sample who progressed on prior checkpoint inhibitor) rather than 500 per Beaver et al. However, the other 861 patients that Ribas et al. propose to include in the denominator to determine the expected response to rechallenge either did not receive rechallenge therapy and/or did not have any assessments for response after rechallenge. Addition of these patients results in a population that is not consistent with IGNYTE, and a denominator of 1361 dilutes the response rate to 7% (95/1361). This does not make sense from a clinical perspective, 7% is not a historical control that can be applied to the IGNYTE population, and assuming nivolumab rechallenge would have a 7% response rate is not justified.
- On the Applicant’s slide 33 from the AC (7), they quote NCCN recommendations as follows: “If a patient experienced progression of melanoma during or shortly after a systemic therapy, rechallenge with the same therapy or a therapy of the same class is unlikely to yield a response and is not recommended (8).” However, they omit the next sentence that states “The exception to this rule is for patients who progressed on single-agent immune checkpoint inhibitor therapy...” FDA review notes that 25.7% of patients received anti-PD-1 therapy only as adjuvant therapy in IGNYTE, and several other patients received monotherapy nivolumab or pembrolizumab in the metastatic setting. Of the 47 patients that the Applicant deemed responders, a minimum of 33 patients (70%) were identified as having received only single-agent immune checkpoint inhibitor therapy. Therefore, this is the population that would be expected to have a higher response rate to nivolumab rechallenge than the NCCN population that the Applicant cites.

- The Applicant also cited the RELATIVITY-002 trial that demonstrate response rates ranging from 9-12% in patients receiving checkpoint inhibitors after initial progression on these therapies (9). FDA review notes that these populations are not comparable, as the IGNYTE study population had substantially more favorable prognostic factors, therefore this is not an appropriate historical control (1).
- One committee member cited their expectation of a response rate to rechallenge is in the range of 15%.
- Ultimately, this underscores that the expected response to nivolumab rechallenge is unknown and the Applicant should have conducted a randomized trial against an appropriate standard of care to better elucidate the need for both RP1 and nivolumab. They did not. OCE review finds that the contribution of effect has not been established, and this may result in patients receiving both products and being exposed to severe and fatal toxicities when only one product may be necessary.

Second, the committee noted that these patients all had confirmed progression on prior therapy with 2 scans. However, the IGNYTE trial allowed enrollment for patients whose prior progression was determined by imaging, biopsy results, or clinical judgement.

Third, the Applicant's responses to several committee questions regarding the reported results from IGNYTE do not appear substantiated. This is summarized further in the table below.

B. Applicant Inconsistencies

The Applicant was inconsistent and made several unsubstantiated claims during the course of the reviews for RP1 that led to subsequent challenges in the FDA review. Select cases are summarized below, however this list is not all-inclusive of this issue.

Prior Interaction	Applicant Inconsistency	FDA Review Notes
Multiple interactions	• Applicant claimed randomizing patients to nivolumab monotherapy would not be ethical but allowed nivolumab monotherapy as control arm of their other trial IGNYTE-3.	• Unclear why Applicant was telling FDA they could not enroll a nivolumab monotherapy arm for ethical reasons but were allowing enrollment to this therapy in their other trial. • If unethical, IGNYTE-3 should not be enrolling such an arm, or conversely, if ethical, a randomized trial with nivolumab monotherapy was in fact possible.
Initial FDA Review, information request #44	• FDA noted that a table submitted by the Applicant stated that the median non-injected TL reduction was 53.3% (range 50% to 100%). However, the minimum lesion	• This calls into question the veracity of the Applicant's datasets, as 9% and 50% are vastly different values.

	reduction was 9.1% in the datasets. Applicant confirmed this was an error and that the lower bound of the range was actually 9%, not 50%.	
Applicant CSR and AC Slides	- The Applicant only assessed one fatal event of myocarditis as related to study treatment. - They did not agree with investigators' other death assessments and did not consider death of a patient from tumor hemorrhage days after injection into sites of hemorrhage as related to treatment.	- This calls into question the Applicant's clinical judgement and reporting integrity. - Also, at least 29 patients had a delay in safety reporting, including deaths and serious adverse events. This reflects broader data quality issues in the conduct of the trial. - See FDA AC Briefing book for further details.
Multiple interactions	The Applicant cited several published reports, including Luke 2024 (10), that had authors who either worked for Replimune or received funding from them. For example, Replimune's co-founder and Chief Scientific Officer was an author on a manuscript that the Applicant referenced to FDA multiple times to support various aspects of their development plan. These were not disclosed to FDA during discussions.	- Lack of disclosure of competing interests is concerning, as these citations were used by the Applicant to defend several of their positions with "external expert" opinion. - Several authors received funding or were employees of Replimune, and other citations and references to the patient community also appear to have received funding or sponsorship from the Applicant.
Type A Meeting held 9/16/25	- FDA stated that assessment of lesions previously treated with RP1 is not consistent with RECIST criteria. - Applicant stated that "since prior therapy with an oncolytic therapy was an exclusion criteria, this is not a confounding issue for IGNYTE."	- The issue is not prior therapy before enrollment on IGNYTE but assessment of tumors after prior to RP1 injections. - This response suggests that the Applicant either did not understand RECIST criteria or made a false claim.
Type A Meeting held 9/16/25	FDA noted that patients could be treated beyond progression and this could impact interpretability of results.	FDA review of the datasets found that the Applicant's claim that all responses occurred before progression was not true.

	Applicant confirmed that all responses occurred before progression was determined in IGNYTE.	This was discussed at the AC held on 7/30/26.
Type A Meeting held 9/16/25	- FDA stated that surgical procedures could have impacted response assessments. - Applicant stated that they can confirm this did not lead to a response observed on study.	- FDA review of narratives and patient level data found that the Applicant's claim was not true. - This was discussed at the AC held on 7/30/26.
Type A Meeting held 9/16/25	- FDA asked Applicant whether histology results resulted in a change in the response assessment for patients on IGNYTE. - Applicant stated that they confirm "that this strategy does not apply to the Anti-PD-1 Failed Melanoma Cohort of the IGNYTE Study."	- FDA review found that several patients had their response designation changed based on histology results. - Therefore, this claim previously made by the Applicant is not true.
Multiple interactions	- FDA stated that the primary analysis should be based on RECIST v1.1. - Applicant confirmed they would use RECIST v1.1 without modification.	- FDA review found several modifications whereby the resulting criteria used in IGNYTE were substantially different than RECIST. - This was discussed at the AC held on 7/30/26.
Multiple interactions	Several discrepancies were identified by the FDA review team with respect to the Applicant's datasets and discrepancies in the provided patient narratives.	- This calls into question the veracity of the Applicant's datasets and collection of data on IGNYTE. - This was discussed at the AC held on 7/30/26.
Annotated CR Letter	- Applicant stated that "the requirement for noninjected target lesions in every patient was a new concept introduced only with the April 10, 2026 CRL." - FDA communicated this issue to the Applicant in a meeting held on March 25, 2021. At that time, the FDA stated that it was not clear in the protocol whether target lesions would include both injected and noninjected lesions, and noted that responses in small injected lesions could be attributed to	- FDA stated this to the Applicant before the April 10, 2026 CRL. - The Applicant was either not familiar with the regulatory history of their own product or made a false claim.

	mechanical effects of repeated injections; thus, they recommended that the Applicant measure and track objective responses to both injected and noninjected lesions when reporting ORR. • This was reiterated again in 2024.	
Advisory Committee Meeting	• Applicant stated that 10 patients with noninjected lesions achieved a complete response (CR). • FDA review of dataset AXIR1 notes that only 5 patients denoted as having a CR did NOT have all their target lesions injected (using ATLINJFL flag).	• Unclear where Applicant derived 10 patients from. • Either they are mistaken or the datasets are unclear and/or flawed.
Advisory Committee Meeting	• Applicant agreed with committee members' inquiry by confirming that all patients had repeat imaging scans confirming their progression on prior checkpoint inhibitor. • Patients on IGNYTE did not all have imaging confirmation of PD on prior therapy. Biopsy and clinical assessment could also allow for enrollment on IGNYTE.	• Applicant should have clarified this during their Q&A time but did not.

The extent and nature of these inconsistencies result in uncertainty regarding the veracity of the Applicant's datasets and regulatory communications with the FDA. This may also have impacted the Applicant's derivation of the ORR and DOR upon receipt of the data from their imaging vendor, (b) (4)

4. Recommended Regulatory Action

OCE acknowledges the unmet medical need for patients with unresectable advanced cutaneous melanoma. Upon FDA review, some patients' tumors do decrease after injection with RP1. It remains unclear whether there is any systemic effect of the combination therapy attributable to RP1, and the contribution of RP1 and nivolumab to the combination has not been established by the Applicant.

Some patients with advanced disease may not consider therapy effective unless it cures them, prolongs their survival, and/or improves their quality of life. Even in cases of substantial unmet need, these patients deserve safe and effective drugs, and a lower evidentiary bar is not appropriate.

However, OCE acknowledges that the committee members and public hearing speakers communicated that they are willing to accept substantial uncertainty given the unmet need of patients with this disease.

Therefore, we conclude that accelerated approval is acceptable in the context of this uncertainty. Clinical benefit should be verified in confirmatory trial(s). Without confirming clinical benefit, the risk of severe and fatal adverse events would not be acceptable if only a local injection effect is driving the observed results.

References

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