

Application Type	BLA 2 nd Resubmission
STN	125827
CBER Received Date	June 2, 2026
PDUFA Goal Date	August 2, 2026
Division / Office	Division of Clinical Evaluation Oncology/ Office of Therapeutic Products
Clinical Reviewer(s)	Katherine Barnett
Project Manager	Niloofar Kennedy
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
Supervisory Concurrence	John Scott, Ph.D. Director, FDA/CBER/OBPV/DB
Applicant	Replimune, Inc.
Established Name	Vusolimogene oderparepvec (RP1)
(Proposed) Trade Name	TUDRIQEV

Table of Contents

Glossary	2
1. Executive Summary	2
2. Statistical Analyses.....	3
3. Advisory Committee Discussion	3
4. Conclusion and Recommendation	4

GLOSSARY

Abbreviation	Definition
AC	Advisory Committee
BLA	Biologics Licensure Application
CI	Confidence interval
CR	Complete Response
DOR	Duration of response
FDA	Food and Drug Administration
IRC	Independent Review Committee
IND	Investigational new drug
KM	Kaplan-Meier
NR	Not reached
ORR	Objective response rate
OS	Overall survival
OTP	Office of Therapeutic Products
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
US	United States
USPI	United States Prescribing Application

1. EXECUTIVE SUMMARY

This Biologics Licensure Application (BLA) was initially submitted on 11/21/2024, for vusolimogene oderparepvec (RP1), a genetically modified oncolytic herpes simplex virus therapy, seeking an indication in combination with nivolumab for the treatment of adult patients with advanced melanoma who have previously received an anti-PD-1 containing regimen. The primary data supporting this BLA were derived from a Phase 2 cohort of the IGNYTE study, a single-arm, open-label, multicenter, multi-cohort Phase 1/2 study evaluating the safety and effectiveness of RP1 in combination with nivolumab. Two Complete Response (CR) letters have been issued based on the original submission and first BLA resubmission, respectively.

On 06/02/2026, the Applicant submitted a second BLA resubmission, including an updated 3-year overall survival (OS) analysis from the Phase 2 cohort of IGNYTE study. The FDA clinical review team re-evaluated the totality of evidence and identified several key efficacy issues (Refer to FDA clinical review memo). Therefore, the FDA review team re-calculated the objective response rate (ORR) and duration of response (DOR) by excluding responders who had all target lesions (TLs) injected with RP1 or had no TLs at baseline, resulting in an ORR of 15.7% (22/140; 95% CI: 10.1%, 22.8%) and a median DOR of 14.1 months (95% CI: 10.7, not reached [NR]). FDA also conducted a sensitivity analysis by excluding all patients who had all TLs injected or no TLs at baseline from the denominator, resulting in an ORR of 24.2% (22/91; 95% CI: 15.8%, 34.3%) and a median DOR of 14.1 months (95% CI: 10.7, NR).

Study IGNYTE (Phase 2 cohort) did not meet its efficacy objective¹ under FDA's primary analysis and did meet it under FDA's sensitivity analysis. Based in part on advisory committee deliberations, FDA/CBER Office of Therapeutic Products (OTP) leadership is planning to grant accelerated approval, with the primary efficacy conclusions based on FDA's sensitivity analysis described in this memo.

2. STATISTICAL ANALYSES

Table 1 below shows the efficacy analysis of ORR and DOR by FDA adjudicated analysis. By excluding the responders who had all TLs injected with RP1 (n=23) or had no TLs at baseline (n=2), FDA's primary efficacy analysis includes 22 responders, resulting in an ORR of 15.7% (22/140; 95% CI: 10.1%, 22.8%) and a median DOR of 14.1 months (95% CI: 10.7, not reached [NR]). FDA's primary efficacy analysis retains all 140 patients in the denominator to maintain consistency with the prespecified primary efficacy analysis set, following the intent-to-treat (ITT) principle.

FDA also conducted a sensitivity analysis by excluding all patients who had all TLs injected or no TLs at baseline (n=49) from the denominator, resulting in an ORR of 24.2% (22/91; 95% CI: 15.8%, 34.3%) and a median DOR of 14.1 months (95% CI: 10.7, NR). This analysis restricted the population to a subgroup whose response is potentially evaluable according to FDA's adjudicated response definition. This post-hoc analysis has the potential to inflate the Type I error rate.

Table 1. FDA analysis of ORR and DOR: excluding responders/patients who had all TLs injected or had no baseline TLs

	Responders (n)	ORR (95% CI) ^a	Median DOR (months) (95% CI) ^a
FDA Primary Analysis (N=140)	22	15.7% (10.1%, 22.8%)	14.1 (10.7, NR)
FDA Sensitivity Analysis (N=91)	22	24.2% (15.8%, 34.3%)	14.1 (10.7, NR)

(Source: FDA analysis)

^a Kaplan-Meier estimate

Abbreviations: CI, confidence interval; NR, not reached; ORR, objective response rate; DOR, duration of response; TL, target lesion

3. ADVISORY COMMITTEE DISCUSSION

The AC discussion was hosted on 07/30/2026 to discuss the following questions:

(1) Discuss whether the single-arm IGNYTE study, as designed and conducted, allows for a reliable determination of the expected response rate and durability of response in the proposed population; and

¹ The pre-specified ORR under null hypothesis is 15%.

(2) Discuss the clinical meaningfulness of the response rate and duration of response reported in Study IGNYTE and if the observed responses are indicative of systemic anti-tumor activity attributable to RP1.

The committee voted 10-3 that the efficacy results from IGNYTE are evaluable and clinically meaningful. The majority of members also expressed concern about the efficacy issues identified during FDA review. Reasons for yes votes included overall clinical impression that RP-1 was having a systemic effect and the significant unmet medical need in this late-line patient population.

4. CONCLUSION AND RECOMMENDATION

Study IGNYTE (Phase 2 cohort) did not meet its objective under FDA's primary analysis in the ITT population and did meet it under FDA's sensitivity analysis in a post hoc evaluable population. FDA/CBER OTP intends to grant accelerated approval, incorporating AC deliberations, with the primary efficacy conclusions based on FDA's sensitivity analysis described in this memo. The confirmatory evidence of effectiveness will come from the results of the ongoing Phase 3 randomized trial IGNYTE-03, comparing RP1 + nivolumab vs. physician's choice on the primary endpoint of OS.