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Summary Basis for Regulatory Action

Date:	August 6, 2026
From:	Bo Liang, PhD, CBER/OTP/OGT
BLA STN:	125827/0
Applicant:	Replimune, Inc.
Submission Receipt Date:	Original submission: November 21, 2024 First resubmission: April 10, 2026 Second resubmission: June 2, 2026
Action Due Date:	August 2, 2026
Proper Name:	vusolimogene oderparepvec-wtpg
Proprietary Name:	TUDRIQEV
Indication:	A genetically modified oncolytic viral therapy indicated 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-based regimen.

Recommended Action: The Review Committee recommends accelerated approval of this product.

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Director, Product Office

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory Project Management • ORMRR RPM	Niloofar Kennedy, MS, CBER/OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Bo Liang, PhD, CBER/OTP/OGT Guo-Chiuan Hung, PhD, CBER/OTP/OGT Wei Wang, PhD, CBER/OCBQ/DMPQBSharmila Shrestha, CBER/OCBQ/DMPQBCarla Lorenzo, CBER/OCBQ/DMPQBTao Pan, PhD, CBER/OCBQ/DBSQCBMarie Anderson, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Katherine Barnett, MD Ching-Hsien Jessica Lee, MD PhD Peter Lenahan, DC, PhD, MPH, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Cong Wang, PhD, CBER/OBPV/DB Melvyn Okeke, MPH, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Parwathy Chandran, PhD,CBER/OTP/OPT
Clinical Pharmacology	Xing Jing, PhD, CBER/OTP/OCE/DCEH
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, PhD, CBER/OCBQ/DCM/APLB Hanah Pham, PharmD CBER/OCBQ/DCM/APLB Kristine Khuc, PharmD CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories: • Consults	Sundeep Agrawal, MD, CDER/OCE Andrey Sarafanov, PhD CBER/OTP/OPPT
Advisory Committee Meeting	Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) convened on July 30, 2026.

Table of Contents

1. Introduction

Replimune, Inc. submitted a Biologics License Application (BLA), STN 125827, to seek Accelerated Approval for vusolimogene oderparepvec-wtpg (also known as RP1), with the proprietary name of TUDRIQEV. TUDRIQEV is a genetically modified oncolytic viral therapy.

IGNYTE (NCT03767348), an open-label, multicenter Phase 1/2 clinical trial evaluating TUDRIQEV 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 TUDRIQEV 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 that limit comparisons of response rate.

The Applicant submitted a second resubmission on June 2, 2026, which included an updated 3-year overall survival (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. 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.

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 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 Therapeutic Products (OTP)/Office of Clinical Evaluation (OCE) recommends accelerated approval of BLA 125827 for TUDRIQEV in combination with nivolumab 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 requirement described under sections 6.a and 11.c of this document. This recommendation is made with full acknowledgment of the remaining uncertainties and with the explicit expectation that the ongoing Phase 3, randomized, controlled confirmatory clinical trial (IGNYTE-3) will need to verify the clinical benefit attributable to this product.

Accelerated approval of this BLA with a Postmarketing Requirement (PMR) confirmatory trial and four CMC Postmarketing Commitments (PMCs) is listed in Section 11.c of this

document. Continuing approval is contingent upon verification of the clinical benefit of TUDRIQEV via IGNYTE-3 to demonstrate the improvement in overall survival in patients treated with TUDRIQEV in combination with nivolumab compared with treatment of physician's choice. Approximately 400 patients 12 years of age and older with unresectable advanced melanoma who have confirmed disease progression on an anti-PD-1 and anti-CTLA-4 therapy, administered either in a combination regimen or in sequence, will be enrolled to the IGNYTE-3 trial.

2. Background

Advanced unresectable cutaneous melanoma is a serious and life-threatening disease. The outcome in patients with this disease depends on the stage at presentation. In recent years, the expected prognosis of patients with advanced/metastatic melanoma has improved considerably compared to historical data. For example, the CheckMate 067 trial (Wolchok et al. 2025) established nivolumab and ipilimumab in combination as a first-line treatment for patients with metastatic melanoma, and long-term outcomes reported 71.9 months median overall survival for the combination (Wolchok et al. 2025). Other commonly used first-line therapies include nivolumab and relatlimab-rmbw combination therapy, nivolumab monotherapy, pembrolizumab monotherapy, and, for patients with B-Raf proto-oncogene serine/threonine kinase (BRAF) V600 mutation positivity, BRAF/ mitogen-activated protein kinase kinase (MEK) targeted therapies. Selection of second-line or later subsequent therapies is challenging due to the lack of prospective, randomized comparisons in this setting. National Comprehensive Cancer Network (NCCN) guidelines state that 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 (NCCN 2026). However, the "exception to this rule" is that, for patients who progressed on a single-agent immune checkpoint therapy, nivolumab and ipilimumab combination therapy is a reasonable treatment option. In select cases, such as late progression or relapse following treatment discontinuation, reinduction with the same agent or same class of agents may be considered. Other professional guidelines (e.g., Society for Immunotherapy of Cancer [SITC]) (Pavlick et al. 2023) have varying recommendations on the management of patients with advanced/metastatic cutaneous melanoma.

Following progression on anti-programmed cell death protein 1 (anti-PD-1) therapy, expected outcomes can vary based on factors such as disease stage, tumor BRAF mutation status, type and setting of prior therapies received, and other factors. The optimal treatment for this population is not well-defined and may include rechallenge with single or dual immune checkpoint inhibitors, BRAF/MEK inhibitors, chemotherapy, the intratumoral oncolytic viral therapy talimogene laherparepvec, or lifileucel (granted accelerated approval in 2024). The expected outcomes following progression on anti-PD-1 therapy, including response rates to therapies such as immune checkpoint inhibitor rechallenge, are poorly characterized in the literature.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	October 17, 2017
2. IND submission	February 23, 2018

3. Breakthrough Therapy designation granted	November 20, 2024
4. Pre-BLA meeting	September 3, 2024
5. BLA 125827/0 submission	November 21, 2024
6. BLA filed	January 27, 2025
7. Mid-Cycle communication	March 19, 2025
8. Late-Cycle meeting	May 15, 2025
9. First CRL	July 21, 2025
10. Type A meeting	September 16, 2025
11. First Resubmission Date	October 9, 2025
12. Second CRL	April 10, 2026
13. Second Resubmission Date	June 2, 2026
14. Target Due Date	August 2, 2026

3. Chemistry Manufacturing and Controls (CMC)

The CMC review team concluded during review of the original BLA that the manufacturing process and associated test methods and control measures can yield a product with consistent quality characteristics. There was no additional information submitted in the two resubmissions.

The CMC review team recommends approval. TUDRIQEV is a genetically modified oncolytic HSV-1 containing functional deletions of ICP34.5 and ICP47-encoding genes and expressing hGM-CSF and GALV-GP-R$^-$. The drug product (DP) contains sterile frozen, preservative free suspension of TUDRIQEV for intratumor injection provided in single-dose borosilicate glass vials. It is stored frozen at -80°C ± 10°C. After product thaw, each vial contains an extractable volume of 1.0 mL.

a. Product Quality

Manufacturing summary
TUDRIQEV is produced by (b) (4) .

To manufacture the drug product, (b) (4) , filter sterilized, and filled into borosilicate glass vials. Each vial of drug product contains an extractable volume of 1.0 mL with a labeled nominal concentration of 10^6 PFU/mL or 10^7 PFU/mL. One (1) mL of drug product also contains disodium hydrogen phosphate dihydrate (7 mg), sodium dihydrogen phosphate dihydrate (1.4 mg), sodium chloride (1.3 mg), Myo-inositol (39 mg), d-sorbitol (19.5 mg), a recombinant human serum albumin (5.1 mg), and water for injection. The filled drug product vials are 100% visually inspected, labeled, and

frozen at -80°C. The frozen vials are packaged individually into cartons in (b) (4) stored frozen at -80°C ± 10°C.

Manufacturing control strategy

Consistency of the manufacturing process is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing with validated methods, (3) validation of the manufacturing process, and (4) validated lot release tests. The manufacturer accepts raw materials based on verification of raw material specifications and routine incoming acceptance tests. Suppliers are qualified and audited according to established supplier qualification programs. Raw materials derived from animals and humans are appropriately qualified to ensure the absence of microbial or viral contamination. The manufacturing process control strategy includes i) setting acceptable limits for process parameters and ii) testing in-process samples, drug substance, and drug product for microbial and viral contaminants, identity, purity, strength, and potency. (b) (4) drug product are each controlled by lot release tests for microbial contaminants, appearance, identity, purity, (b) (4), and potency (Table 2). Potency is assessed with an infectious titer assay which measures the concentration of plaque-forming units, in addition to four other cell-based bioassays that quantify the relative levels of TUDRIQEV-expressed hGM-CSF and GALV-GP-R$^-$ proteins and their biological activities. Product- and process-related impurities are additionally tested for (b) (4) release. Physicochemical properties, particle contamination, excipients, and (b) (4) are additionally tested for drug product release.

Process validation

(b) (4) drug product manufacturing process validation included production of (b) (4) process performance qualification (PPQ) (b) (4) PPQ drug product lots, (b) (4) at 10^6 PFU/mL and (b) (4) at 10^7 PFU/mL labeled nominal concentration at the Replimune Framingham, MA, facility. Criticality of process parameters was determined through a risk assessment based on the impact on product critical quality attributes. The acceptable operation ranges for process parameters (i.e., normal operation ranges and proven acceptable ranges) and acceptable limits for in-process controls were established based on process development and process characterization studies and successful at-scale manufacturing runs. The process parameters and in-process controls were monitored on each PPQ run per process validation protocol. All PPQ batches met pre-defined lot release acceptance criteria. Sanitary processing capability was demonstrated by consistently meeting in-process bioburden and endotoxin acceptance criteria. Additional validation studies were also performed, including aseptic processing simulation and shipping validation studies. Process consistency will continue to be monitored and assessed post-approval according to the continued process verification (CPV) plan.

Stability

The drug substance is stable for (b) (4) when stored (b) (4). The drug product is stable for 48 months when stored frozen at -80°C ± 10°C. Once thawed, drug product with 10^6 PFU/mL and 10^7 PFU/mL can be stored at 5°C ± 3°C for 2 days and 10 days, respectively. In-use stability data to support a maximum hold duration in syringe under the worst-case conditions is not available. A maximum of two hours hold in syringe is set in the United States Prescribing Information (USPI) based on limited data.

A worst-case in-use stability study will be conducted to determine the maximum hold duration in the syringe as a post-marketing commitment (PMC).

Comparability
Throughout clinical trials, the manufacturing process was optimized. Clinical lots used in the IGNYTE trial were manufactured at (b) (4) or Framingham (MA, USA) facilities. The comparability of lots manufactured at (b) (4) and Framingham facilities was adequately demonstrated by analytical and nonclinical studies. The current manufacturing process produces drug product with critical quality attributes that are comparable to those of clinical lots used in the Phase 2 portion of IGNYTE trial.

Manufacturing risks
The risk of product contamination with microbial and viral adventitious agents is minimized by i) ensuring adequate control of raw materials, especially those of biological origin that are used in the (b) (4), and product manufacturing; ii) testing of (b) (4) for microbials and adventitious viral agents; iii) lot release testing of drug substance and drug product for microbials. The risk of extractables and leachables that could originate from the product manufacturing process and the container closure system was analyzed; and the analytical studies and toxicological assessments were sufficient to mitigate this risk.

PMC
Four PMCs are agreed upon by the Applicant, as listed in Section 11c below.

b. Testing Specifications

Table 2. TUDRIQEV Drug Product Release Specification

Test Property	**Test Method**	**Specification**
Identity	(b) (4)	
Appearance - Clarity	(b) (4)	Translucent to opaque solution
Appearance- Visible Particulates	(b) (4)	Essentially free from visible particulates (Meets AQL)
Appearance- Color	(b) (4)	Colorless
(b) (4)		
(b) (4)		
Total Product DNA	(b) (4)	
Volume	Extractable Volume	(b) (4) 1.0 mL
(b) (4)		
Infectious Titer	Plaque Assay	Nominal 1 x 10^7 PFU/mL: (b) (4) Nominal 1 x 10^6 PFU/mL: (b) (4)
hGM-CSF Expression	GM-CSF (b) (4)	

Test Property	Test Method	Specification
hGM-CSF Activity	(b) (4)	
GALV-GP-R- Expression	GALV-GP-R- (b) (4)	(b) (4)
GALV-GP-R- Activity	GALV-GP-R- (b) (4)	
Sterility	(b) (4)	Absence of bacteria and fungi
Bacterial Endotoxin	(b) (4)	
(b) (4)		

The analytical methods and their validations and/or qualifications reviewed for the TUDRIQEV drug substance and drug product were found to be adequate for their intended use, except for an outstanding issue for the (b) (4) Replimune provided a written commitment in Amendment 94 (dated June 17, 2025) and Amendment 119 (dated June 2, 20262, 2026) to resolve this issue as a Postmarketing Study Commitment by July 31, 2028.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA STN 125827/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of TUDRIQEV (vusolimogene oderparepvec) are listed in the table below. The activities performed and inspectional histories are noted in the Table 3.

Table 3. Manufacturing Facilities Table for TUDRIQEV

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Replimune Inc. 33 New York Ave., Suite 100 Framingham, MA 01701 USA *Manufacture of drug substance (DS)* *Manufacture of drug product (DP)* *Labeling and packaging of DP* *Release and stability testing of DP*	3022984544	079185250	PLI	CBER April 2025 VAI
(b) (4)			PLI	CBER (b) (4)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4) *Release testing of DP*				VAI
(b) (4) *Release testing of DP*	(b) (4)		704(a)(4) RRA in lieu of PLI	CBER (b) (4) rNAI
(b) (4) *Release testing of DP*	(b) (4)		Waiver	ORA (b) (4) VAI

Acronym key: DS – drug substance; DP – drug product (prefilled in vials); PLI – Pre-license Inspection; RRA – Remote Regulatory Assessment; CBER – Center for Biologics Evaluation and Research; ORA – Office of Regulatory Affairs; rNAI – Remote No Action Indicated; VAI – Voluntary Action Indicated.

CBER conducted a PLI of the Replimune Inc. facility in April 2025. All 483 issues were resolved, and the inspection was classified as VAI.

CBER conducted a PLI of the (b) (4) facility in (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

CBER performed a 704(a)(4) RRA in lieu of a PLI of the (b) (4) facility between (b) (4) and (b) (4). A "No Observation Letter" was issued, and the RRA was classified as rNAI.

ORA conducted a surveillance inspection of the (b) (4) facility between (b) (4) and (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The TUDRIQEV DP is aseptically filled into pre-sterilized clear Type (b) (4) borosilicate glass vials (b) (4), 13mm, supplied by (b) (4) and stoppered with pre-sterilized stoppers (13mm, supplied by (b) (4) (b) (4) The stoppered DP vial is sealed with pre-sterilized 13mm aluminum seal

(supplied by (b) (4) with color-coded plastic flip-off cap. White caps are for 10^6 PFU/mL, and blue caps were used for 10^7 PFU/mL.

The container-closure integrity testing (CCIT) is performed using a validated (b) (4) method for DP release and stability.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The EA provided an assessment of TUDRIQEV environmental exposure based on the structural characteristics of the HSV-1 parental virus, the genetic modifications in TUDRIQEV, the biodistribution and virus shedding data, and the procedures described in the USPI to prevent environmental dissemination. HSV-1 is a globally endemic human pathogen that does not naturally infect other species and is known to have poor environmental stability. It is transmitted primarily through direct contact. The genetic modifications in TUDRIQEV compared to the parental HSV-1 are not expected to alter the host range or physical stability of the virus. The risk of TUDRIQEV environmental release is assessed based on biodistribution and virus shedding data from clinical studies. In a clinical trial, TUDRIQEV DNA was detected in blood in 20% treated patients and rapidly cleared from blood after injection. TUDRIQEV DNA was rarely detected in urine or oral mucosa samples. Nearly half of treated patients had detectable TUDRIQEV DNA at the injection sites. But live virus was detected in less than 1% of swab samples of the injection sites. TUDRIQEV DNA was also detected on the exterior of occlusive dressing in 20% of treated patients. No live virus was detected in swabs of the exterior of occlusive dressing, indicating that occlusive dressing is an effective barrier to prevent TUDRIQEV release into the environment. The precautions and handling procedures described in the prescribing information and patient medication information can minimize the chance of environment release. Considering the structural and genetic characteristics of TUDRIQEV, the poor environmental stability of HSV-1, the shedding profile of TUDRIQEV in treated patients, and the risk mitigation procedures to prevent contamination during product preparation and administration in the clinic, the overall risk of TUDRIQEV to the environment is negligible. We determined that approval of TUDRIQEV will not result in any significant environmental impact. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies were conducted with various human solid tumor cell lines, including (b) (4) melanoma cells, which demonstrated that the addition of TUDRIQEV resulted in increased tumor cell cytotoxicity compared to an HSV-1 variant lacking GALV-GP-R^-. In vivo pharmacology studies were conducted with a murine surrogate product, mRP1 (identical to TUDRIQEV, except that human GM-CSF is replaced by murine GM-CSF) using syngeneic murine lymphoma, colorectal and melanoma tumor-bearing immunocompetent BALB/c or C57BL/6 mice. Repeat administrations of intratumoral (IT) mRP1 and intravenous (IV) anti-PD-1 monoclonal antibody (mAb) to tumor-bearing mice resulted in synergistic anti-tumor activity with the combination, while administration of mRP1 or anti-PD-1 mAb single agents resulted in limited reduction of injected tumor volumes or no activity, respectively. Ribonucleic acid

sequencing (RNAseq) analysis of mRP1 injected and non-injected murine melanoma tumors showed increased expression of genes associated with immune cell infiltration and inflammation in injected tumors compared to non-injected tumors; expression was further increased in injected tumors administered the combination of mRP1 and anti-PD-1 mAb. Minimal increases in expression of these genes were observed in tumors injected with anti-PD-1 mAb alone compared to the other study groups.

Toxicology studies evaluating TUDRIQEV and mRP1 were conducted in tumor-bearing immunocompetent (b) (4) mice and healthy (b) (4) rats, respectively. The maximum dose level (DL) of mRP1 evaluated following single (b) (4), single (b) (4) and repeat (b) (4) administration in rats was $1x10^7$ plaque-forming units (PFU)/animal/injection, which was the determined no-observed-adverse-effect level for all studies. No adverse findings were observed up to 6 months following repeat (b) (4) administration of mRP1 (16 total doses; up to $1x10^6$ PFU/animal/injection) in healthy (b) (4) rats. Repeat IT administration of TUDRIQEV batches manufactured at two different sites (b) (4) (Phase 1 study production site) versus Framingham (commercial production site)] to tumor bearing (b) (4) mice at DLs up to $5x10^5$ PFU/animal/injection did not show any test article related adverse findings or significant differences in toxicology profiles between the two batches of TUDRIQEV.

Biodistribution (BD) studies were conducted as part of the toxicology studies following (b) (4) (b) (4) IT administration of mRP1 or TUDRIQEV in tumor-bearing (b) (4) mice. Animals were evaluated up to 85 days post-final administration. The results showed mRP1 viral genomes were predominantly present at the injection sites (i.e.,(b) (4) tumor), irrespective of the route of administration. Following single (b) (4) administration in rats, mRP1 DNA was also detected in blood, some perfused organs (heart, lungs, liver and spleen), ovaries and neurologic tissues (brain, trigeminal ganglia, spinal cord and sciatic nerve) up to Day 71 post-final administration without any associated histological findings. mRP1 DNA was detected in ovaries at early time points until Day 29 following single (b) (4) (b) (4) repeat IT administrations in rats and tumor-bearing mice, respectively. Low levels of mRP1 DNA were detected in neurologic tissues including brain, trigeminal ganglia, spinal cord, and sciatic nerve up to Day 29. In a follow-up study, 16 doses (every 3 days for 7 weeks) of mRP1 were (b) (4) administered to healthy (b) (4) rats. mRP1 DNA was not detected in any neurologic tissues and there was no evidence of viral reactivation at any time point up to 6 months post-final dosing, indicating minimal risk of latency and reactivation of mRP1. In an additional study, repeat IT administration (5 total doses) of $5x10^5$ PFU/animal/injection TUDRIQEV manufactured at the two different sites (b) (4) and Framingham) in tumor bearing mice showed that the TUDRIQEV BD profile was not impacted by the change from clinical to commercial manufacturing facilities.

Developmental and reproductive toxicology studies were conducted in pregnant (b) (4) rats following repeat IV administrations of between $9x10^4$ - $1x10^6$ PFU mRP1/animal/injection over gestation days (GD) 4 to 16 corresponding to early- and mid-organogenesis. mRP1 DNA was detected in maternal blood up to 12 hours post-final dosing on GD 16. However, all maternal and fetal blood samples collected at necropsy on GD 18 were negative for viral DNA indicating minimal risk of placental transfer. Additionally, no embryofetal structural abnormalities or adverse effects on embryofetal growth were observed following repeat IV mRP1 administration.

Studies to evaluate the safety pharmacology, genotoxicity, and carcinogenicity of TUDRIQEV were not conducted. These studies are not warranted based on the product characteristics and safety profile. The nonclinical data provided in this BLA submission support the accelerated approval of TUDRIQEV in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a PD-1-blocking antibody-based regimen.

5. Clinical Pharmacology

The clinical pharmacology review team recommends granting accelerated approval for TUDRIQEV 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-based regimen.

The viral shedding of TUDRIQEV was evaluated in clinical studies. Blood, urine, and swab samples (injection site, injection site dressings from TUDRIQEV injected lesions, oral mucosa/saliva) were collected before and during treatment, and at prespecified timepoints after the last dose of the study drug. In addition, all swab samples that tested positive for TUDRIQEV DNA were further tested for the presence of live TUDRIQEV using the tissue culture infectious dose (TCID50) assay.

Overall, across all the studies, TUDRIQEV DNA was detected mainly during treatment and fell below limit of quantification (BLOQ) within 60 days after last treatment. In addition, for TCID50 positive samples, the corresponding dressing samples were eventually determined to be negative for live TUDRIQEV. No HSV-1-related infections were reported among caregivers or close contacts with those patients.

The mechanism of action for TUDRIQEV is direct tumor killing, leading to the release of tumor and viral antigens and proinflammatory molecules and T cell tumor infiltration. In the anti-PD-1 resistant setting, TUDRIQEV in combination with nivolumab may promote anti-tumor immune response.

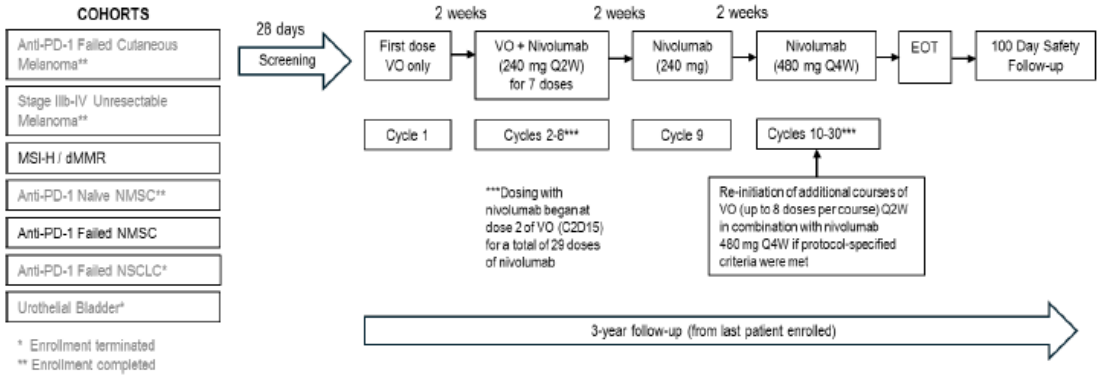
6. Clinical/Statistical

a. Clinical Program

The primary evidence of effectiveness to support this BLA is based on results from IGNYTE, a single-arm, multicenter, Phase 1/2 study. This study was initiated as an exploratory study evaluating TUDRIQEV either as a single agent or in combination with anti-PD-1 therapy for the treatment of a variety of solid tumors. The study was later amended to evaluate TUDRIQEV in combination with nivolumab in a cohort of patients with unresectable advanced cutaneous melanoma who had progressed on anti-PD1 therapy (N=140), rather than being prospectively designed as a pivotal cohort from the study's outset. The study protocol underwent several subsequent amendments that materially changed the cohort's eligibility criteria and conduct.

Figure 1 depicts the IGNYTE schema. The "Anti-PD-1 Failed Cutaneous Melanoma" cohort (N=140) comprises the efficacy-evaluable population. The primary endpoint of IGNYTE is objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), assessed by blinded Independent Review Committee (IRC).

Figure 1. IGNYTE Schema



Source: Adapted from Applicant's Assessment Aid Review Document
Abbreviations: EOT, end of time; NMSC, non-melanoma skin cancer; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; Q2W, every 2 weeks; Q4W, every 4 weeks; VO, vusolimogene oderparepvec

IGNYTE enrolled patients with unresectable Stage IIIB to IV cutaneous melanoma who had confirmed disease progression after at least 8 weeks of anti-PD-1 therapy (e.g., nivolumab or pembrolizumab). Prior therapy may have been administered either alone or in combination with anti-cytotoxic T-lymphocyte Antigen 4 (CTLA-4; e.g., ipilimumab) or other therapies. Anti-PD-1 therapy must have been the last line of prior therapy. Patients must have also had measurable disease per RECIST v1.1 and at least one measurable tumor of 1 cm or greater in longest diameter, or 1.5 cm or greater in shortest diameter for lymph nodes and injectable lesions. Treatment was administered as follows:

- TUDRIQEV was injected at a first dose of 1×10^6 plaque-forming units (PFU)/mL, followed by subsequent doses of 1×10^7 PFU/mL every 2 weeks for up to 8 total cycles (~4 months), starting at Day 1.
- Nivolumab 240 mg was administered every 2 weeks for Cycles 2 to 9 (~4 months), followed by 480 mg every 4 weeks for Cycles 10 to 30 (~20 months), or 240 mg every 2 weeks at the discretion of the investigator, until confirmed progression or intolerable toxicity occurred or for a total of 29 cycles (~2 years).

At the investigators' discretion, treatment with TUDRIQEV could be continued beyond progression. Both superficial and deep/visceral intratumoral (IT) injections of TUDRIQEV were allowed. Multiple tumors could be injected until all injectable tumors had been treated or 10 mL of TUDRIQEV had been used. New tumors were eligible for injection. There was no minimum size for injectable lesions.

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.

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. The results are presented in Table 4.

Table 4. Efficacy Results for the IGNYTE Study

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)	14.1 (10.7, NR)

**91 patients with at least one noninjected lesion.*

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.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspection assignments were issued for three clinical study sites that participated in the conduct of study Protocol: RPL-001-16; An Open-Label, Multicenter, Phase 1/2 Study of RP1 as a Single Agent and in Combination with PD1 Blockade in Patients with Solid Tumors. The inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (BLA).

c. Pediatrics

TUDRIQEV is granted partial waiver for pediatric assessments in patients <12 years of age with advanced melanoma because melanoma is rare in this age group and a pediatric study of TUDRIQEV within this age group is highly impossible or impractical.

TUDRIQEV is granted deferred submission of results of a pediatric assessment in pediatric patients aged 12 to <17 years because the pediatric assessment is incomplete, while TUDRIQEV is ready for approval for use in adult patients. Pediatric patients of this age group will be enrolled in the confirmatory trial IGNYTE-3 (RP1-104, NCT06264180) to support the identification of the safe and effective dose of TUDRIQEV in this patient population.

d. Other Special Populations

In the IGNYTE Study, 57 out of 140 patients (41%) were 65 years of age or older, and 20 (14%) were 75 years of age and older. No overall difference in safety or effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger adult patients. TUDRIQEV was not studied in other special populations.

7. Safety and Pharmacovigilance

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.

Pharmacovigilance Plan

- The applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80. A voluntary postmarketing sponsor study (RPL-123-01) will provide 5-year long term safety follow up on patients who receive treatment with TUDRIQEV. RPL-123-01 is an observational, prospective study which will follow and evaluate effectiveness and safety in patients treated with TUDRIQEV. Enrolled patients will be followed for up to 5 years from the first dose of TUDRIQEV.

- The available safety data do not indicate a need for a Risk Evaluation and Mitigation Strategy that is specifically designed to evaluate a particular safety issue as a primary endpoint. There is no agreed-upon postmarketing commitment safety study for this product.

- Additional safety data will be collected under the accelerated approval postmarketing requirement study (Study RPL-104 (IGNYTE-3)).

8. Labeling

The proposed proprietary name, TUDRIQEV, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on May 15, 2025, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on June 10, 2025. Proposed name suffixes were submitted on June 28, 2024 and the proposed suffix –*wtpg* was found acceptable on May 30, 2025.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, package and container labels, and found them acceptable from a comprehension and promotional perspective.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information and Medication Guide to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

9. Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) convened on July 30, 2026 to evaluate two discussion questions: (1) whether the single-arm IGNYTE 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 IGNYTE is indicative of systemic antitumor activity attributable to TUDRIQEV.

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

10. Other Relevant Regulatory Issues

This application received Breakthrough Therapy and Priority Review designations.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

OTP/OCE recommends accelerated approval for TUDRIQEV 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-based regimen. The basis for the recommendation is ORR supported by median duration of response and a manageable risk profile.

b. Benefit/Risk Assessment

The magnitude and durability of ORR shown in the anti-PD-1 failed melanoma cohort of the Phase 2 portion of the IGNYTE trial establishes the effectiveness of TUDRIQEV in the target patient population, with a favorable benefit-risk profile.

Given the established effectiveness of TUDRIQEV, poor prognosis of the disease, limited treatment options and a lack of meaningful clinical benefit with continued treatment with single agent anti-PD-1, treatment with TUDRIQEV in combination with nivolumab represents an improvement over available therapies in the intended patient population.

The overall benefit-risk profile of TUDRIQEV supports accelerated approval of TUDRIQEV, indicated in combination with nivolumab for the treatment of adult patients

with unresectable advanced cutaneous melanoma who experienced disease progression with an anti-PD-1 based regimen.

Risk mitigation strategies will be instituted in the United States Prescribing Information (USPI) through Warnings and Precautions for accidental exposure, herpetic infection or reactivation and visceral injury.

Continued approval is contingent upon fulfillment of the Postmarketing Requirement (PMR) to verify the clinical benefit of TUDRIQEV through the IGNYTE-3 (RP1-104) trial. The IGNYTE-3 is an ongoing Phase 3 multiregional, randomized, controlled, open-label trial to evaluate the safety and efficacy of TUDRIQEV in combination with nivolumab compared with treatment of physician's choice. The trial enrolls patients aged 12 years and older with unresectable advanced cutaneous melanoma who experienced disease progression on an anti-PD-1 and anti-CTLA-4 therapy, administered in combination or in sequence. The primary endpoint is overall survival.

c. Recommendation for Postmarketing Activities

Accelerated approval regulations require that the Applicant conduct adequate and well-controlled trial(s) to verify and describe the clinical benefit of TUDRIQEV. The Applicant agreed to the following PMR:

PMR #1 Accelerated Approval Required Study:
Replimune, Inc. is required to complete the IGNYTE-3 (RP1-104) trial (NCT06264180), an ongoing Phase 3 multicenter, multiregional, randomized, controlled, open-label confirmatory trial to evaluate the safety and efficacy of TUDRIQEV 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 either in combination or in sequence. Overall survival is the primary endpoint. Approximately 400 patients will be randomized at 1:1 ratio to the two treatment arms.

Replimune, Inc. is required to follow the following timelines:

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

Pediatric Research Equity Act (Public Law 108-155) (PREA), as amended in the Federal Food, Drug, and Cosmetic Act (the Act) section 505B (21 U.S.C. 355B), requires the conduct of pediatric studies for certain drug and biological products. The Applicant agreed to the following PMR:

PMR #2 Required Pediatric Assessment:
Replimune, Inc is required to conduct an assessment of TUDRIQEV 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-4 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).

Refer to PMR #1 above for the required timelines.

The applicant agreed to the following CMC PMCs:

3:
Replimune commits to re-evaluate the (b) (4) acceptance criterion for lot release testing of the TUDRIQEV (b) (4) based on manufacturing experience when data from (b) (4) total PPQ and post-PPQ batches are available and revise the acceptance criterion if appropriate. The final re-evaluation report will be submitted as a "Postmarketing Study Commitment – (b) (4) Acceptance Criterion Final Study Report" within 60 days after release of the (b) (4) batch.

Final study report submission date: July 31, 2028.

4:
Replimune commits to re-assess the (b) (4) based on data from (b) (4) according to study protocol 1131-0157 Rev.01. Replimune will submit the final study report as a "Postmarketing Study Commitment – (b) (4) Final Study Report" by December 31, 2026.

Final study report submission date: December 31, 2026

5:
Replimune commits to conduct an in-use stability study to support a maximum hold duration in the syringe for 2 hours after storage of thawed TUDRIQEV drug product under the worst-case conditions according to Section 16.2 Table 4 of the approved USPI. Replimune will submit the final study report as a "Postmarketing Study Commitment – In-use Stability Final Study Report" and revise the hold duration in the syringe in the USPI as supported by the in-use stability data.

Final study report submission date: December 31, 2026.

6:
Replimune commits to provide the leachables analytical data and associated toxicological assessment (for (b) (4) compounds) from ongoing leachable assessment study with drug product stability lot(s) at 24-, 36-, 48- and (b) (4) month timepoints.

Final report of 36-month data submission date: October 31, 2026

Final report of 48-month data submission date: October 31, 2027

12. 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. Pavlick AC et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0, J Immunother Cancer, 11(10).
5. Wolchok JD, et al. Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med. 2025;392(1):11-22.