Summary Basis for Regulatory Action

Date:	February 15, 2024
From:	Karin M. Knudson, PhD, Review Committee Chair, Office of Therapeutic Products (OTP), Office of Cellular Therapy and Human Tissue CMC, Division of Cell Therapy 1
BLA STN:	125773/0
Applicant:	Iovance Biotherapeutics, Inc.
Submission Receipt Date:	March 27, 2023
Action Due Date:	February 24, 2024
Proper Name:	Lifileucel
Proprietary Name:	AMTAGVI
Indication:	Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

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

Acting Director, Office of Therapeutic Products, Office of Clinical Evaluation

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer/Consultant - Center/Office/Division
CMC • CMC Product (OTP/OCTHT) OCBQ/DBSQC)	Karin Knudson, PhD, CBER/OTP/OCTHT Heba Degheidy, MD, PhD, CBER/OTP/OCTHT Iain Farrance, PhD, CBER/OTP/OCTHT Sukhanya Jayachandra, PhD, CBER/OTP/OCTHT Saravanan Karumbayaram, M Pharm, PhD, CBER/OTP/OCTHT Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT Brian Niland, PhD, CBER/OTP/OCTHT
• Facilities Review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and OTP/OCTHT)	Hector Carrero, CBER/OCBQ/DMPQ Grace Forsythia Cortesini, CBER/OCBQ/DMPQ Haitham Elnour, CBER/OCBQ/DMPQ
• QC, Test Methods, Product Quality (OCBQ/DBSQC)	Marie Anderson, MS, PhD, CBER/OCBQ/DBSQC Seth Schulte, CBER/OCBQ/DBSQC
Pre-License Inspection	Hector Carrero, CBER/OCBQ/DMPQ Grace Forsythia Cortesini, CBER/OCBQ/DMPQ Haitham Elnour, CBER/OCBQ/DMPQ Karin Knudson, PhD, CBER/OTP/OCTHT Brian Niland, PhD, CBER/OTP/OCTHT
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• Postmarketing Safety Pharmacovigilance Review (OBPV/DPV)	Douglas Rouse, MD, MPH, CBER/OBPV/DPV
• BIMO (OCBQ)	Char-Dell Edwards, BS, MT, CBER/OCBQ/DIS Peter Lenahan, DC, PhD, MPH, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB)	Qianmiao Gao, PhD, CBER/OBPV/DB
• Nonclinical data (OBPV/DB)	Tianjiao Dai, PhD, CBER/OBPV/DB
Nonclinical/Pharmacology/Toxicology (OTP/OPT)	Yongjie Zhou, PhD, MD, CBER/OTP/OPT
Clinical Pharmacology (OTP/OCE)	Million Tegenge, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM Teresa Vu, CBER/OCBQ/DCM
• Container/Package (OTP/OCTHT, OTP/ORMRR)	Karin Knudson, PhD, CBER/OTP/OCTHT Catherine Tran, MS CBER/OTP/ORMRR

Discipline Reviews	Reviewer/Consultant - Center/Office/Division
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI • PREA	Elin Cho, MS, CBER/OBPV/DB Carolina Panico, MD, PhD, CBER/OTP/OCTHT Andrey Sarafanov, PhD, CBER/OTP/OPPT Cinque Soto, PhD, CBER/OTP/OCTHT Wojtek Tutak, PhD, CBER/OTP/OCTHT Adrienne Hornatko-Munoz, CBER/ORO/RPB

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1. Introduction

Iovance Biotherapeutics, Inc. submitted a Biologics License Application (BLA), STN 125773, for licensure of lifileucel, with the proprietary name of AMTAGVI. AMTAGVI is an autologous tumor-derived T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

AMTAGVI is comprised of primarily (b) (4) T cells obtained from resected tumor material and expanded *ex vivo* in the presence of the cytokine interleukin-2 (IL-2), anti-CD3 (OKT3) antibody, and (b) (4) feeder cells (b) (4) . AMTAGVI is manufactured at (b) (4) Iovance Biotherapeutics Manufacturing LLC (previously Iovance Cell Therapy Center (iCTC)), (b) (4) located in Philadelphia, PA, USA. The drug product (DP) contains 7.5 x 10^9 to 72 x 10^9 viable cells suspended in (b) (4) cryopreservation solution containing 5% DMSO, 0.5% human serum albumin (HSA), and 300 IU/mL IL-2 (aldesleukin). The DP is provided to the treatment center in (b) (4) to four 100 – 125 mL infusion bags and is administered intravenously.

This document summarizes the basis for accelerated approval of AMTAGVI. A single clinical trial, Study C-144-01, provides the primary evidence of safety and effectiveness to support the BLA submission. Study C-144-01 is a single-arm, Phase 2, multicenter, multiregional (U.S. and Europe), multi-cohort clinical study of efficacy and safety of AMTAGVI in subjects with unresectable or metastatic melanoma previously treated with at least one line of anti-PD1-based immunotherapy, and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

The recommendation for accelerated approval is based on the objective response rate (ORR) supported by duration of response (DOR) demonstrated in Study C-144-01. The major risks of AMTAGVI include prolonged cytopenia, severe infection, internal organ hemorrhage, and cardiopulmonary and renal impairment. Based on efficacy and safety results from this single adequate and well controlled clinical trial, FDA concludes that the Applicant has demonstrated substantial evidence of effectiveness of AMTAGVI; and the overall benefit of AMTAGVI outweighs the risks to the intended patient population.

The review team recommends accelerated approval of this BLA. Continuing approval is contingent upon an Accelerated Approval Postmarketing Requirement (AA PMR) to provide verification of the clinical benefit of AMTAGVI via a randomized, well-controlled confirmatory clinical trial (IOV-MEL-301). Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMC) are recommended for lot release assay control, cumulative leachables testing over product manufacture, storage, and in-use period, and final product container closure integrity testing. The review team also recommends a CMC Advisory Comment be provided in the Approval Letter concerning establishment of analytical comparability following a major manufacturing change.

2. Background

Disease Background

Data from the US Surveillance, Epidemiology, and End Results (SEER) registry estimated approximately 97,610 new cases of melanoma and 7,990 melanoma-related deaths in 2023. Melanoma represents approximately 5% of all new cancer cases and 1.3% of all cancer-related deaths in the U.S. in 2023. The 1-year and 5-year relative survival for patients with metastatic melanoma is approximately 50% and 35%, respectively.

First-Line Systemic Therapies
Currently, FDA-approved first-line therapies for unresectable or metastatic melanoma include a PD-1 blocking antibody, as monotherapies or combination therapies, including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and nivolumab plus relatlimab, an anti-LAG3 agent. The approvals of these PD-1 blocking antibodies, with or without another immune checkpoint inhibitor (ICI), were based on improvement in progression-free survival (PFS) and/or overall survival (OS) via randomized controlled trials (RCTs).

Besides ICIs as first line therapies, BRAF inhibitor with or without a MEK inhibitor, including dabrafenib plus trametinib, vemurafenib plus cobimetinib, encorafenib plus binimetinib, or atezolizumab plus cobimetinib plus vemurafenib, are approved for unresectable or metastatic melanoma patients with positive BRAF V600 mutations.

However, at least 50% of melanoma patients do not respond to first line anti-PD1-based therapies, and at least 50% experience disease progression within a year.

Second or Subsequent Line of Systemic Therapy
There is no FDA-approved second or subsequent line of therapy for patients with unresectable or metastatic melanoma which has progressed following anti-PD1-based immunotherapies, and, if positive for BRAF V600 mutations, BRAF inhibitors with or without MEK inhibitors.

As standard of care, these patients may receive rechallenge with a different a PD-1 blocking antibody or a PD-1 blocking antibody in combination with anti-CTLA4 (ipilimumab) or anti-LAG3 (relatlimab), if previously not treated with these regimens. However, there is no high-level evidence regarding the clinical outcomes of these therapies. Therefore, this group of patients have a high unmet medical need.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND Submission Receipt Date	December 31, 2014
2. Fast Track Designation Granted	August 29, 2017
3. Orphan Drug Designation Granted	June 9, 2015
4. Regenerative Medicine Advanced Therapy (RMAT) Designation Granted	August 24, 2018
5. Pre-BLA Meeting	July 29, 2022
6. Rolling BLA Request Accepted	August 12, 2022
7. BLA 125773/0 Submission – Final Module of Rolling BLA Received	March 27, 2023
8. BLA Filed	May 26, 2023
9. Mid-Cycle Meeting	July 27, 2023
10. Pre-License Inspection Iovance Biotherapeutics Manufacturing LLC	August 21 – 25, 2023
11. Pre-License Inspection (WuXi Advanced Therapies, Inc.)	August 28 – September 1, 2023
12. Major Amendment	September 8, 2023
13. Late-Cycle Meeting	November 20, 2023
14. Action Due Date (ADD)	February 24, 2024

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

This BLA includes an adequate description of the manufacturing process of AMTAGVI. The CMC review team concludes that the manufacturing process, along with the associated test methods and control measures, can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description
AMTAGVI is an autologous product composed primarily of T cells collected from resected tumor material and expanded *in vitro*.

Manufacturing Summary
The manufacturing of AMTAGVI is continuous but occurs in two stages. In the first stage, also called the Pre-Rapid Expansion Phase (Pre-REP), resected tumors are shipped to (b) (4) manufacturing sites and undergo fragmentation and culture (b) (4) (b) (4) with IL-2 (b) (4) (b) (4) In the second stage, called the Rapid Expansion Phase (REP), (b) (4) cultured with IL-2, anti-CD3 antibody, (b) (4) (b) (4) the cultured cells are harvested, washed, and formulated with 48% Plasma-Lyte A, 2% of 25% HSA (final concentration 0.5% HSA), 50% CryoStor CS10 (final concentration 5% DMSO) and 300 IU/mL IL-2 (aldesleukin). The final formulated product containing 7.5 x 10^9 to 72 x 10^9 viable cells is filled into (b) (4) to four cryopreservation bags (100 mL to 125 mL each

bag), cryopreserved, and stored at ≤ 150°C. The product is administered without additional manipulation.

Manufacturing Controls

(b) (4) Lot release testing is performed on material collected at the appropriate stages of the manufacturing process to evaluate product safety and function. All release testing is completed prior to shipping of AMTAGVI to the treatment center and initiation of patient lymphodepletion. Product release testing on the formulated DP includes tests for sterility, mycoplasma, endotoxin, dose, purity, and potency-related attributes. While all assays have been validated, (b) (4) will be evaluated as a PMC.

Process Validation

The Applicant validated the manufacturing process at the (b) (4) commercial manufacturing sites, (b) (4) Iovance Biotherapeutics Manufacturing LLC, using (b) (4) batches manufactured from vendor-sourced (b) (4) tumor tissue. The process validation was assessed against established process parameters and predefined release criteria. Shipping and stability of the final product was established using (b) (4) batches.

Manufacturing Risks, Potential Safety Concerns, and Management

Transmission of infectious diseases is controlled by reagents and control of the manufacturing process. The (b) (4) is controlled by donor screening and testing and qualification of the public blood collection site.

AMTAGVI is an autologous product. As such, product mix-up of autologous lots would result in potential risks, including infection, graft versus host disease, and lack of anti-tumor effect. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of tumor resection/collection, checkpoints are indicated throughout the manufacturing process, and patient identifiers are confirmed prior to administration with identifiers printed on the product label. The COI/COC is maintained through integrated computer-based programs with human-readable identifiers also present on all labels.

The risk mitigation measures include segregation of activities during the manufacturing process, use of (b) (4) manufacturing processes (when possible), performing all aseptic operations in a (b) (4) in a Class (b) (4) clean room, operator

training and use of personal protective equipment, use of sterile single use materials, validated cleaning procedures, and environmental monitoring.

AMTAGVI may contain residual antibiotics (i.e., gentamicin, streptomycin, and amphotericin B) (b) (4) Through process validation, the level of each residual antibiotic has been determined to be at (b) (4) lower than the maximum therapeutic dose.

AMTAGVI may contain residual viable melanoma tumor cells derived from the starting material. The manufacturing process is not intended to expand melanoma tumor cells, and the frequency of residual melanoma tumor cells in the product is controlled with release testing. The risk of residual tumor cells in the product is unknown, as tumorigenicity was not evaluated in preclinical studies and was unable to be assessed in the intended patient population due to metastatic disease or natural disease progression.

Drug Product Stability and Shelf Life

The real-time stability studies using full-scale batches determine the product is stable at ≤ -150°C for up to six months. The thawed product is stable up to three hours at room temperature. The product is stored in 510(k) cleared cryopreservation bags for freezing cells. The bags are evaluated and tested, including for extractables and leachables with simulated product. However, the Applicant has not performed a (b) (4) assessment of all organic and elemental leachables for the product over its manufacturing, storage, and in-use period (i.e., cumulative leachables), which will be resolved as a PMC.

Comparability

Analytical comparability between the clinical manufacturing processes at (b) (4) (b) (4) has not been established. Thus, the primary efficacy analysis and product release specifications are based on batches manufactured at (b) (4) alone.

The Applicant has established comparability between (b) (4) Iovance Biotherapeutics Manufacturing LLC, so (b) (4) sites can be used to manufacture AMTAGVI. However, the protocol used to establish analytical comparability between (b) (4) Iovance Biotherapeutics Manufacturing LLC is not adequate to assess the impact of major manufacturing changes. The Mechanism of Action (MOA) of AMTAGVI is not well-characterized, and the Applicant has not identified product quality attributes with established relevance to the product's clinical efficacy. Thus, it will be very challenging for the Applicant to complete a convincing comparability exercise to support a major manufacturing change, and additional clinical studies may be necessary. This concern is reiterated as an Advisory Comment to the Applicant in the Approval Letter.

Additional Assays Used in Clinical Study

The Applicant uses the (b) (4) (b) (4) next-generation sequencing (NGS) to determine the (b) (4) from the TCR-beta chain of T cells to identify clonotypes, for assessing the *in vivo* persistence of AMTAGVI in patient blood. The (b) (4) is not used for product release nor determining information essential for the safe and effective use of AMTAGVI (i.e., not a companion diagnostic device). The

(b) (4) has been validated and shown to be able to provide AMTAGVI clonotype sequence information and qualitatively track clonotypes.

CMC PMCs

The CMC team recommends three PMCs. The rationale for the PMCs is described below, and the PMC agreements are detailed in section 11c of this document:

1. (b) (4) for determining T cell expression of (b) (4) (b) (4) (b) (4) do not include analysis of (b) (4) controls. The validation studies showed sufficient control of these assays, and the commercial release acceptance criteria are based on samples analyzed with the current control strategy. However, the accuracy of the release test results may be negatively affected by the absence of (b) (4) controls. Therefore, the Applicant agreed to conduct a PMC study to evaluate an (b) (4) control strategy for these assays and compare it to the original control strategy in a statistically significant number of batches, manufactured at (b) (4) Iovance Biotherapeutics Manufacturing LLC. In addition, the Applicant agreed to re-evaluate their (b) (4) (b) (4) acceptance criteria after completion of the study to ensure appropriate control of AMTAGVI.

2. The risk assessment of organic and elemental leachables in the final product is not acceptable as it only evaluated the organic and elemental leachables from the final container closure and did not include organic and elemental leachables from the manufacturing process and storage of AMTAGVI (i.e., cumulative organic and elemental leachables). Therefore, the Applicant should conduct a (b) (4) PMC study at (b) (4) (b) (4) Iovance Biotherapeutics Manufacturing LLC to assess the organic and elemental leachables during manufacturing, storage conditions, and in-use conditions.

3. The container closure integrity testing of the final product container did not include an adequate positive control to demonstrate the sensitivity of the method. Therefore, the Applicant should conduct container closure integrity testing that includes a positive control with an established sensitivity (i.e., (b) (4) See Section 3e Container/Closure System.

CMC Advisory Comment

The following CMC comment is provided as an Advisory Comment in the Approval Letter:

1. As previously communicated, the protocol and product quality attributes used to establish comparability between (b) (4) and Iovance Biotherapeutics Manufacturing LLC manufactured drug product will not be sufficient to establish analytical comparability after implementation of a major manufacturing change. We recommend you perform additional (b) (4) (b) (4) and elucidate the specific mechanism of action of your drug product (b) (4) (b) (4) We recommend you request a

formal meeting with us prior to incorporating new product quality attributes, implementing a major manufacturing change, and/or executing a comparability exercise. Your executed comparability study report(s) should be submitted as a Prior Approval Supplement. If product comparability cannot be established based on analytical comparability studies alone, additional clinical study(ies) with your drug product, AMTAGVI, may be required.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the AMTAGVI drug product were found to be adequate for their intended use.

The final product commercial release specifications are shown in Table 2.

Table 2. Final Product Commercial Release Specifications

Attribute	Test	Acceptance Criteria
Appearance	Visual Inspection – Drug Product	No sign of clumps
	Visual Inspection – Drug Product	Colorless to dark yellow
	Visual Inspection – Container	Intact bag[1]
Identity	(b) (4)	(b) (4)
Potency-Related	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	Dose (total viable cells)	7.5×10^9 – (b) (4) $\times 10^9$
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
Purity	Cell viability (%)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
Safety	Endotoxin (EU/mL)	(b) (4)
	Mycoplasma	Not detected
	Sterility	No growth

[1] Each bag is without visible defects or leaks

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that AMTAGVI is an autologous product as such each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of lifileucel are listed in the table below. The activities performed and inspectional histories are noted in Table 3 below.

Table 3. Facilities Involved in the Manufacture and Testing of AMTAGVI

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
Iovance Biotherapeutics Manufacturing LLC 300 Rouse Blvd., Philadelphia, PA 19112 (b) (4) *Drug Product Manufacturing, Release testing, Packaging, Labeling*	3020882632	118423955	Pre-License Inspection	CBER/DMPQ August 21-25, 2023 NAI
(b) (4) (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) Surveillance NAI

Abbreviations:
CBER: Center for Biologics Evaluation and Research, FEI: Facility Establishment Number, DMPQ: Division of Manufacturing and Product Quality, DUNS: Data Universal Numbering System, NAI: No Action Indicated, ORA: Office of Regulatory Affairs, VAI: Voluntary Action Indicated

CBER conducted a pre-license inspection (PLI) at Iovance Biotherapeutics Manufacturing LLC (previously Iovance Cell Therapy Center) from August 21 to August 25, 2023. No Form FDA 483 was issued, and the inspection was classified as no action indicated (NAI).

CBER conducted a PLI at (b) (4) from (b) (4) through (b) (4) and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

ORA performed a surveillance inspection of the (b) (4) facility in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

The container closure system for the drug product consists of the (b) (4) (b) (4) bags manufactured by (b) (4) The primary packaging component used for AMTAGVI is described in the table below. The primary components are (b) (4) at a qualified contract facility. Incoming packaging components are inspected for visual appearance, and verification of the certificate of conformance. The Applicant conducted the container closure integrity testing (CCIT) employing the (b) (4) method. The (b) (4) used in the CCIT were not adequate, resulting in a PMC.

Table 4. Container/Closure System

Attribute	Description
Dimensions	(b) (4)
Freeze volume	(b) (4)
Materials	Bag: (b) (4) (b) (4)

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were conducted with AMTAGVI. Instead, the Applicant cited published nonclinical data evaluating similar murine and human tumor-derived T lymphocytes to provide support for AMTAGVI. These studies demonstrate: 1) a positive correlation between the level of lymphocyte infiltration in primary MM of the skin and disease prognosis; 2) the ability of IL-2 to enhance ex vivo expansion of murine and human tumor-derived lymphocytes; 3) anti-tumor activity of tumor-derived lymphocytes, in combination with Cy and IL-2, in murine models of colon adenocarcinoma and sarcoma with lung and liver metastases.

5. Clinical Pharmacology

The data supporting clinical pharmacology of AMTAGVI is based on one clinical Study C-144-01 that included pharmacokinetics (i.e., expansion and persistence), pharmacodynamics, and dose-response assessments. Prior to AMTAGVI infusion, tumor-derived clonotypes can be detected in peripheral blood at a mean proportion of 16%, which was increased to 83% at Day 4 post-infusion of AMTAGVI. The clonotypes declined to 51% at Day 14 and persisted in the range of 37% to 41% up to Month 12 post-infusion of AMTAGVI.

Pharmacodynamic activity was evaluated by measuring longitudinal changes of cytokines and chemokines (IL-15, IL-6, IL-7, IL-9, IL-10, IL-12(p40), CCL2, CXCL10, interferon (IFN)-gamma, and tumor necrosis factor (TNF)-alpha) using plasma samples collected at baseline and post-infusion of AMTAGVI up to Month 3. The mean level of IL-15 and CXCL10 peaked following lymphodepletion and administration of AMTAGVI at Day 1-4, decreased over time, and returned to baseline levels within 1-3 months. The mean IFN-gamma level was below baseline post-lymphodepletion and AMTAGVI infusion at Day 1-4 and returned to baseline by Day 14. Other cytokines and chemokines listed above did not show any noticeable changes. No difference was observed in the cytokines and chemokines level between responding and non-responding patients.

Analysis of the dose-efficacy relationship based on DOR (categorized as ≥12 months or <12 months) showed no association between DOR and total infused dose. The dose-efficacy analysis showed a weak positive trend with best overall response (BOR). No significant correlation was found between exposure (i.e., persistence) and efficacy. Exploratory dose-exposure analysis showed a weak positive trend for increased persistence with higher dose.

Overall, the clinical pharmacology analysis supports the accelerated approval of AMTAGVI for treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

6. Clinical/Statistical

Considering the poor prognosis and a lack of FDA-approved systemic therapies available for patients with unresectable or metastatic melanoma previously treated with anti-PD1-based therapies, the clinical review team concludes that the benefit-risk profile of AMTAGVI observed in Study C-144-01 is acceptable and provides a meaningful therapeutic advantage as assessed by ORR and DOR. The clinical review team

recommends accelerated approval of AMTAGVI for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

a. Clinical Program

Study C-144-01, conducted under IND 16317, was a single-arm, Phase 2, multicenter, multiregional (U.S. and Europe) multi-cohort clinical study of efficacy and safety of AMTAGVI in subjects with unresectable or metastatic melanoma previously treated with at least one line of anti-PD1-based immunotherapy, and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. The primary endpoint was ORR, including complete response (CR) and partial response (PR), as assessed by a central Independent Response Committee (IRC) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) guidelines. DOR, as assessed by the IRC per RECIST v1.1, was the key secondary endpoint to support the primary efficacy evidence of AMTAGVI. The data cutoff for Study C-144-01 to support this BLA was September 15, 2021.

In Study C-144-01 Cohort 2 and Cohort 4,156 subjects received AMTAGVI (range: 1.2 x 10^9 to 99.5 x 10^9 viable cells); 67 subjects enrolled in Cohort 2, and 89 subjects enrolled in Cohort 4. These 156 subjects constitute the primary safety population to support this BLA.

Of the 156 subjects, the primary efficacy population was 82 subjects from Cohort 4 treated with AMTAGVI (1.34 x 10^9 to 72 x 10^9 viable cells) lots manufactured at (b) (4) that met the protocol-specified product release criteria. The primary efficacy to support this BLA was based on ORR and DOR results from these 82 subjects. FDA recommended dose range (7.5 x 10^9 to 72 x 10^9 viable cells) for the initial accelerated approval was based on a subset (n=73) of the primary analysis set that excluded 9 subjects who received less than 7.5 x 10^9 viable cells and did not achieve an objective tumor response.

The AMTAGVI treatment regimen included a non-myeloablative lymphodepletion (NMA-LD) preparative regimen with cyclophosphamide and fludarabine followed by a single infusion of AMTAGVI and post-infusion administration of IL-2 (aldesleukin). Bridging therapy was not allowed in Study C-144-01 during AMTAGVI manufacturing.

Efficacy Results

ORR among subjects in the primary efficacy set (n=82) was 28.0% [95% Confidence Interval (CI): 18.7% -39.1%] with a CR rate of 3.7% (n=3) and PR rate of 24.4% (n=20), as assessed by the IRC per RECIST v1.1

ORR among subjects with FDA-recommended dose for commercial release (n=73) was 31.5% (95% CI: 21.1%-43.4%) with a CR rate of 4.1% (n=3) and PR rate of 27.4% (n=20), as assessed by the IRC per RECIST v1.1. The median time to initial objective response was 1.5 months (min, max: 1.3, 4.2).

Among the responders (n=23), 56.5%, 47.8% and 43.5% remained with a durable response at 6, 9 and 12 months, respectively, following the initial response. Median DOR was not reached (NR, 95% CI: 4.1, NR).

Similar efficacy results were observed in the pooled Cohort 2 and 4 full efficacy set (n=153). The ORR, as assessed by IRC, was 31.4% (95% CI: 24.1%-39.4%) with a CR rate of 5.2% (n=8) and PR rate of 26.1% (n=40). The median DOR was not reached (range: 1.4+, 45.0+). Among the 48 responders, 62.5%, 56.3% and 54.2% remained durable responses at 6, 9 and 12 months, respectively, following the confirmed initial response.

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

Bioresearch Monitoring (BIMO) inspection assignments were issued for the Applicant and three clinical investigators (CI) who participated in the conduct of study protocol C-144-01. The inspections did not reveal substantiative issues that impact the data submitted in this original BLA.

c. Pediatrics

The Applicant has an Agreed initial pediatric study plan (iPSP) with FDA, dated April 7, 2022, to study the safety and efficacy of AMTAGVI in children with recurrent or refractory soft tissue sarcoma (rhabdomyosarcoma and Ewing sarcoma) or primary central nervous system malignancies.

However, upon further review, and in discussion with FDA's Oncology Subcommittee of the Pediatric Review Committee (OCE PeRC), it has been determined that AMTAGVI is not considered a molecularly targeted oncology product; therefore, Section 505B (a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (i.e., Pediatric Research Integrity Act or PREA), as amended by the FDA Reauthorization Act of 2017 (FDARA), does not apply to AMTAGVI.

In addition, AMTAGVI had been granted Orphan Drug Designation (ODD #15-4772) for the treatment of Stage IIB-Stage IV melanoma, which includes the indication to be approved. Therefore, according to PREA and 21 Code of Federal Regulations (CFR) 601.27(d), AMTAGVI is exempt from requirements for pediatric assessments under PREA.

FDA notified the Applicant on January 30, 2024 that all pediatric studies (IOV-PED-101 and IOV-PED-201) currently underway, including study timelines proposed by the Applicant, are considered voluntary.

d. Other Special Populations

AMTAGVI was not studied in other special populations.

7. Safety and Pharmacovigilance

Safety Results

Among the 156 subjects included in the primary safety analysis set, 92.3% (144/156) of subjects experienced at least one Grade 3 Treatment Emergent Adverse Event (TEAE) within 30 days after AMTAGVI infusion, defined as TEAE by the Applicant; 87.8% (137/156) of subjects experienced at least one Grade 4 TEAE.

The most common Grade 3 or 4 TEAEs included thrombocytopenia (79.5%), neutropenia (70.5%), anemia (66.7%), febrile neutropenia (47.4%), leukopenia (47.4%), lymphopenia (43.6%), hypophosphatemia (31.4%), infection (20.5%), hypoxia (13.5%), hypotension (12.2%), and pyrexia (12.2%).

Based on FDA's assessment, SAEs were related to twelve (7.5%) deaths in Study C-144-01, including two deaths during the lymphodepleting preparative chemotherapy, six deaths within 30 days post AMTAGVI infusion, and four deaths 38-150 days post-AMTAGVI infusion. These SAEs included severe infection (n=4), internal organ hemorrhage (n=2), cardiac arrhythmia (n=1), acute respiratory failure (n=1), acute renal failure (n=2), ascites and livery injury (n=1), and bone marrow failure (n=1).

The overall safety profile from Study C-144-01 was consistent with results from four other AMTAGVI trials (173 subjects received AMTAGVI) among subjects with advanced head and neck squamous cell carcinoma (HNSCC), cervical cancer, or non-small cell lung cancer (NSCLC), except for high pulmonary toxicity-related mortality in subjects with NSCLC (approximately 12% 30-day mortality rate).

Pharmacovigilance
The Applicant will conduct routine pharmacovigilance with adverse event reporting, in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for the following:

- Expedited (15-day) reporting (regardless of seriousness or expectedness) to the FDA Adverse Event Reporting System for three years post-licensure for uveitis, Cytokine Release Syndrome (CRS), Immune effector cell-associated neurotoxicity syndrome (ICANS), and Hemophagocytic Lymphohistiocytosis (HLH).

- Provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) in periodic safety reports for the above adverse events in individuals who receive AMTAGVI.

Completion of the ongoing clinical studies, (1) a Phase 3 adult study (IOV-MEL-301), (2) a voluntary Phase 1 interventional study in pediatric, adolescent, and young adult participants with solid tumors, and (3) a voluntary non-interventional postmarketing safety surveillance study (IOV-MEL-401), will provide additional safety and effectiveness follow-up for AMTAGVI.

The Applicant plans to conduct a voluntary non-interventional observational postmarketing safety surveillance study (IOV-MEL-401) for long term follow-up of patients with metastatic melanoma who receive treatment with commercial AMTAGVI in routine clinical practice in the United States (US). Study IOV-MEL-401 will enroll approximately 300 adult subjects, and each subject will be followed up for 5 years. Proposed study milestones are as follows:

- Final Protocol Submission: April 30, 2024
- Study Completion Date: November 30, 2031
- Final Study Report Completion: November 30, 2032

The Applicant is planning to distribute the product at Applicant-designated "authorized treatment centers" and voluntarily provide training materials to these centers for product manufacturing/handling and delivery to patients.

The proposed pharmacovigilance plan for AMTAGVI is adequate for the labeled indication. The available data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS) or a postmarketing requirement (PMR) study that is specifically designed to evaluate a particular safety issue as a primary endpoint.

8. Labeling

The proposed proprietary name, AMTAGVI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 18, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on July 27, 2023.

The Advertising and Promotional Labeling Branch (APLB) completed the review of the proposed prescribing information on February 14, 2024, and container and package labels on January 29, 2024, and found them acceptable from a promotional and comprehension perspective.

FDA-Recommended Dose Range and Uncertainties
Due to a lack of understanding of the MOA of AMTAGVI, relatively high risks associated with the AMTAGVI regimen, and an apparent trend that responders received higher AMTAGVI doses than non-responders overall, the FDA multidisciplinary review team recommends approving AMTAGVI at the dose range of 7.5×10^9 to 72×10^9 viable cells under the initial accelerated approval. The basis of this recommended dose is that the lowest and highest dose that showed an objective tumor response was 7.5×10^9 and 72×10^9 viable cells, respectively, among study subjects treated in the primary efficacy Cohort 4 of Study C-144-01.

For the following reasons, FDA recognizes uncertainties of the recommended AMTAGVI dose range:

a. Different AMTAGVI dosing ranges did not yield meaningful ORR differences.
b. AMTAGVI dose had no correlation with DOR.
c. AMTAGVI dose had a weak correlation with AMTAGVI persistence ($p = 0.0118$, $R^2 = 0.0525$).
d. AMTAGVI dose did not appear to be related to the seriousness of adverse events.
e. There were a limited number of study subjects across different dose ranges.

In addition, FDA recommends caution to compare AMTAGVI doses across patients given the patient-specific, autologous, and non-molecularly targeted nature of AMTAGVI.

Boxed Warning, Warnings and Precautions
Considering relatively high study treatment-related mortality rate (7.5%), high post-infusion intensive care unit (ICU) stay rate (23.6%), and high rate of Grade 4 TEAEs within 30 days post AMTAGVI infusion (87.8%), FDA recommends Boxed Warning and Warnings and Precautions be included in the USPI for treatment-related mortality which was mainly associated with prolonged severe cytopenia, severe infection, internal organ hemorrhage, cardiopulmonary, and renal impairment (refer to full prescribing information for AMTAGVI).

Patient Information
Per FDA request, Patient Information was submitted by the Applicant on December 18, 2023. The purpose of the Patient Information is to provide patients with general information about AMTAGVI, treatment setting, and potential risks.

9. Advisory Committee Meeting

No advisory committee meeting was held because the review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

This application received Fast Track, RMAT, and Orphan Drug designations. The application was granted Priority Review with ADD of November 24, 2023. FDA declared a Major Amendment on September 8, 2023 due to substantial new and re-evaluation of CMC information, and the ADD was revised to February 24, 2024.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Review Committee recommends accelerated approval of AMTAGVI for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. The recommendation for accelerated approval is based on ORR supported by DOR which serves as an intermediate clinical endpoint that is reasonably likely to predict clinical benefit.

b. Benefit/Risk Assessment

AMTAGVI has demonstrated an ORR of 28.0% (95% CI: 18.7% to 39.1%, n=82) and DOR at 6, 9, and 12 months of 56.5%, 47.8%, and 43.5%, respectively, in study subjects with unresectable or metastatic melanoma previously treated with a median of two lines of anti-PD1-based therapies and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Safety results from Study C-144-01 suggest relatively high occurrence rates of Grade 4 TEAE within 30 days post-AMTAGVI infusion (87.8%), post-infusion intensive care unit (ICU) stay (23.6%), and study treatment-related deaths (7.5%). However, the types of

adverse events were generally expected. The frequency and severity of most adverse events were expected based on the components of the regimen. Considering that patients with previously anti-PD1-treated unresectable or metastatic melanoma have no FDA-approved therapy available, FDA considers the benefit-risk profile of the AMTAGVI regimen acceptable at this time as a treatment for these patients with a high unmet medical need for new therapies.

The review team determined that AMTAGVI does not require a REMS. FDA recommends risk mitigation measures be instituted via Boxed Warning and Warnings and Precautions sections of the USPI as well as via Patient Information for patients to be treated with AMTAGVI.

c. Recommendation for Postmarketing Activities

Under the accelerated approval agreement, Iovance Biotherapeutics, Inc. is required to conduct a Phase 3 confirmatory trial (IOC-MEL-301) as a PMR. Trial IOV-MEL-301 is an ongoing multicenter, randomized, controlled, open-label global trial to compare AMTAGVI plus pembrolizumab versus pembrolizumab alone for the treatment of subjects with untreated, unresectable, or metastatic melanoma to verify the clinical benefit of AMTAGVI in improving progression free survival (PFS) without a detriment to overall survival (OS). PFS outcome is expected in Year 2028 and OS outcome is expected in Year 2030.

The Applicant's pharmacovigilance plan is adequate, and routine and enhanced pharmacovigilance activities will be conducted for postmarketing safety monitoring of AMTAGVI, with adverse event reporting as required under 21 CFR 600.80. A voluntary, non-interventional postmarketing safety surveillance study (IOV-MEL-401) will provide additional follow-up data regarding safety.

The Review Committee has determined that AMTAGVI does not require a PMR safety study or a Risk Evaluation and Mitigation Strategy. There is no agreed-upon PMC safety study for AMTAGVI.

Accelerated approval regulations require that the Applicant conduct adequate and well-controlled clinical trials to verify and describe clinical benefit attributable to this product. The Applicant agreed to conduct the following study as an Accelerated Approval Postmarketing Requirement (AA PMR):

AA PMR

1. Complete the Phase 3, multiregional, multicenter, randomized, open-label controlled trial (IOV-MEL-301) in patients with previously untreated unresectable or metastatic melanoma. Patients will be randomized to lifileucel (LN-144) regimen in combination with pembrolizumab or to pembrolizumab monotherapy. The dual primary endpoints will be objective response rate (ORR) and progression-free survival (PFS), with overall survival (OS) as the key secondary endpoint.

   Iovance Biotherapeutics, Inc. is required to follow the following timelines:

Final Protocol Submission: April, 30, 2024

Study Completion Date (based on final analysis of overall survival): March 31, 2030

Final Study Report Date: March 31, 2031

The Applicant agreed to the following CMC PMCs:

2. Iovance Biotherapeutics, Inc. commits to perform a study to develop and evaluate the suitability of (b) (4) controls for (b) (4) (b) (4) of (b) (4) on the drug product. This study is designed to include a comparative analysis of performance characteristics of the original control strategy (using (b) (4)) to the (b) (4) control strategy for (b) (4) in a statistically meaningful number of clinical batches manufactured at (b) (4) and Iovance Biotherapeutics Manufacturing LLC facilities. Iovance Biotherapeutics, Inc. also commits to re-evaluation of the (b) (4) commercial release acceptance criteria after completion of a statistically powered study. Iovance Biotherapeutics, Inc. will submit the study protocol, including justification for the number of batches to be used in the comparative analysis and re-evaluation of the commercial release acceptance criteria, for review and feedback as a product correspondence supplement by April 30, 2024. Iovance Biotherapeutics, Inc. will submit the final study report, which includes the validation report and justification for change to the commercial release acceptance criteria (if changes are necessary), as a Prior Approval Supplement by April 30, 2025.

   Study Protocol Submission: April 30, 2024

   Final Report Submission: April 30, 2025

3. Iovance Biotherapeutics, Inc. commits to execute a (b) (4) organic and elemental leachables study for lifileucel over the manufacturing, storage, and in-use period (i.e., for cumulative leachables in the drug product). Given the complexity of the biological product, this can be a simulated study [i.e., (b) (4) performed at (b) (4) and Iovance Biotherapeutics Manufacturing LLC manufacturing facilities. This study is designed to start at the manufacturing process step with high-risk for leachables (i.e., (b) (4) and evaluate respective maximal hold times for the drug product during manufacturing, long-term storage including freezing up to 6 months and thawing of the bag for use, and in-use conditions. The analytical data will be assessed for safety using at least a (b) (4) safety margin, considering analytical uncertainty of the methods. Iovance Biotherapeutics, Inc. will submit the final study report as a Postmarketing Commitment – Final Study Report by February 28, 2025.

Final Study Report Submission: February 28, 2025

4. Iovance Biotherapeutics, Inc. commits to performing the container closure integrity testing with a positive control with an established sensitivity, (i.e., a (b) (4) (b) (4)
   Iovance Biotherapeutics, Inc. will submit the final report as a Postmarketing Commitment – Final Report by February 28, 2025.

   Final Report Submission: February 28, 2025.