Summary Basis for Regulatory Action

Date:	August 1, 2024
From:	Elvira Argus, PhD, CBER/OTP/OGT
BLA STN:	BLA 125789
Applicant:	Adaptimmune LLC
Submission Receipt Date:	December 5, 2023
Action Due Date:	August 4, 2024
Proper Name:	afamitresgene autoleucel
Proprietary Name:	TECELRA
Indication:	Treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

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

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
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)	Elvira Argus, PhD Alan Baer, PhD Laura DeMaster, PhD Y Nguyen, PhD Marie Anderson, PhD Viviana Ramirez Maureen DeMar Simleen Kaur, MSc Salil Ghosh, MS, PhD Most Nahid Parvin
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Katherine Barnett, MD Abigail Johnson, RN, BSN, MPH Brendan Day, MD LCDR Malcolm Nasirah, PharmD, MS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Elin Cho, MS Cong Wang, PhD
Nonclinical/Pharmacology/Toxicology Toxicology (Product Office)	Yves (Maurice) Morillon, PhD
Clinical Pharmacology	Xiaofei Wang, PhD
Labeling • Promotional (OCBQ/APLB)	CAPT Teresa Vu, PharmD, BCSCP, MBA, RAC
Other Review(s) not captured above categories, for example: • Consults	OBRR – Meihong Liu, PhD OBRR-Zhugong Liu, PhD CDRH – Rupali Sharma, PhD CDRH – Fengmin Li, PhD E/L Consult – Andrey Sarafanov, PhD

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1. Introduction

Adaptimmune LLC submitted a Biologics License Application (BLA), STN 125789, for licensure of afamitresgene autoleucel (afami-cel, ADP-A2M4), with the proprietary name of TECELRA. TECELRA is a melanoma-associated antigen 4 (MAGE-A4)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

Synovial sarcoma (SS) is a rare type of soft tissue sarcoma (STS) representing approximately 5% to 10% of all histological types. The human MAGE-A4, which is a cancer-testis antigen with restricted expression in normal tissues, is overexpressed in SS.

TECELRA consists of autologous T cells that are genetically modified with the lentiviral vector (LVV) MAGE-A4-c1032 to constitutively express an affinity-enhanced T cell receptor (TCR) specific for human MAGE-A4. The TCR has been genetically engineered to recognize the HLA-A*02-restricted MAGE-A4 peptide GVYDGREHTV. The MAGE-A4 TCR coding sequence is comprised of TCRα and TCRβ chains separated by a (b) (4) In T cells transduced with MAGE-A4-c1032 LVV, the MAGE-A4 TCRα and β chains complex with the endogenous CD3 chains to form a functional TCR. Binding of TECELRA to MAGE-A4-expressing target cells leads to antigen-specific activation via the TCR-peptide-HLA-A*02 complex resulting in T cell proliferation, cytokine secretion, and lysis of MAGE-A4/HLA-A*02-expressing cells.

This document summarizes the basis for accelerated approval of TECELRA. A Phase 2, single-arm, open-label study (ADP-0044-002 Cohort 1) provides the primary evidence of safety and effectiveness for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices. The recommendation for accelerated approval is based on overall response rate (ORR) supported by duration of response (DOR). The major risks of TECELRA include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged severe cytopenia, infections, secondary malignancies, and hypersensitivity reactions.

The Applicant has provided substantial evidence of effectiveness based on a single, adequate and well controlled clinical trial. 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 TECELRA. As specified in section 506(g)(7) of the FD&C Act, products that have been granted Regenerative Medicine Advanced Therapy (RMAT) Designation and which receive accelerated approval may be able to fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials, such as collection of larger confirmatory data sets as agreed upon during product

development. The Applicant is conducting a confirmatory study of additional cohorts in ADP-0044-002 to provide verification of ORR supported by DOR.

The Chemistry, Manufacturing, and Control (CMC) review team recommends a PMR study to assess the cumulative effect of leachables in the drug product (DP), as well as postmarketing commitments (PMCs) related to quality assessments and container closure integrity testing for the (b) (4) the product, validation of the product shipping process, and validation of the (b) (4) method.

2. Background

Disease Background

Synovial sarcoma (SS) is a rare type of soft tissue sarcoma (STS) representing approximately 5% to 10% of all histological types. The oncogenic driver of SS is a translocation between chromosomes X and 18 that leads to the formation of the SS18:SSX fusion oncogenes. The human melanoma-associated antigen A4 (MAGE-A4), which is a cancer-testis antigen with restricted expression in normal tissues, is overexpressed in SS.

The estimated US annual incidence of SS is 800 to 1,000 cases per year. SS primarily affects adolescents and young adults with a mean age at diagnosis of 39 years. Approximately 50% of SS patients will develop recurrent or metastatic disease, which has a poor prognosis with a reported median OS of approximately 16 to 24 months.

Available Therapies

Standard first line treatment of advanced unresectable or metastatic SS includes combination anthracycline-based chemotherapy regimens. There is no consensus on optimal second line therapy. Pazopanib is the only FDA-approved therapy for patients with advanced STS who have received prior systemic therapy. Approval of pazopanib was based on improvement in median progression-free survival (PFS) of 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm (HR 0.35, 95% CI: 0.26, 0.48). In the subgroup of SS patients (n=25), median PFS was 4.1 months in the pazopanib arm versus 0.9 months in the placebo arm (HR 0.45, 95% CI: 0.19, 0.98). For STS overall, ORR for pazopanib was 4% (95% CI: 2.3, 7.9) with a median DOR of 9 months (95% CI: 3.9, 9.2). ORR was not reported for the subgroup of SS. Pazopanib was not associated with an overall survival benefit.

There are currently no FDA-approved therapies specifically for SS in any treatment setting, including after receiving standard systemic chemotherapy such as doxorubicin with or without ifosfamide. Published literature on real-world treatment outcomes indicate that ORR for metastatic synovial sarcoma in the first-line setting is approximately 39%, whereas ORR in the second line setting and later ranges from 13% to 22%.

Table 1: Regulatory History

Regulatory Events/Milestones	Date
Pre-IND meeting	October 25, 2016
IND submission	November 29, 2016
Orphan Drug designation granted	August 26, 2019
RMAT designation granted	November 27, 2019
Pre-BLA meeting	October 13, 2022
BLA 125789/0 submission	December 5, 2023
BLA filed	January 31, 2024
Mid-Cycle communication	April 8, 2024
Late-Cycle meeting	May 20, 2024
Action Due Date	August 4, 2024

Abbreviations: BLA, biologics license application; IND, investigational new drug application; RMAT, Regenerative Medicine Advanced Therapy

3. Chemistry Manufacturing and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and characterization of TECELRA. The FDA CMC review team concludes that the TECELRA manufacturing process and controls are capable of yielding autologous products with consistent quality attributes determined acceptable for commercial manufacturing under this BLA.

a. Product Quality

Manufacturing Summary

TECELRA is manufactured using patient apheresis material collected at qualified apheresis centers. The apheresis material is shipped to Adaptimmune's Navy Yard facility (Philadelphia, PA), where it is (b) (4) . The TECELRA manufacturing process starts with apheresis (b) (4) The enriched T cells are transduced with MAGE-A4-c1032 LVV and (b) (4) washed, and (b) (4) formulated (b) (4) . The final formulation calculation is performed based on (b) (4) Filled bags are visually inspected, then placed in individual metal cassettes, cryopreserved in a (b) (4) , and stored at ≤-130°C in vapor phase liquid nitrogen until lot release testing is complete. The number of DP bags required for administration are packaged into a vapor phase liquid nitrogen shipper and shipped to the administration site once the patient is scheduled for administration.

The MAGE-A4-c1032 LVV is manufactured at (b) (4)

Manufacturing Control Strategy

The chain of identity (COI) and chain of custody (COC) procedures are formally established at the time of patient leukapheresis collection and maintained throughout the manufacturing process to administration to ensure that the patient receives the correct autologous TECELRA batch.

The TECELRA control strategy begins with a material qualification program that includes raw material risk assessment, qualification and monitoring of suppliers, and material testing. Raw materials and reagents are accepted based on specified quality attributes. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents.

Manufacturing process parameters are established based on risk assessments and process characterization studies. In-process controls and monitoring are appropriately implemented to support process consistency. Lot release test methods are suitably validated or verified, except for the (b) (4) method (b) (4) studies and

(b) (4) assay controls, which will be resolved through PMCs. The product release specifications are adequate to ensure product quality and consistency. The ability of the TECELRA manufacturing process to consistently manufacture product that meets predetermined product specifications is demonstrated by process validation studies.

Process Validation

The suitability of the commercial TECELRA manufacturing process was assessed at Adaptimmune's Navy Yard manufacturing facility using healthy donor leukapheresis material. The process validation was assessed against established critical and non-critical parameters and predefined DP release criteria. Process validation studies demonstrated control of the manufacturing process. The (b) (4) manufacturing process at (b) (4) . is validated. However, additional validation data for the (b) (4) used in the (b) (4) manufacturing process was requested in a PMC. Shipment processes for the (b) (4) were also validated. Additional DP shipment validation data were requested through a PMC.

Comparability Assessments

Comparability assessments of manufacturing process versions P1.5.1, P1.6.0, and P1.6.1 demonstrated that DP manufactured with each process were comparable. Comparability assessment of the leukapheresis processing sites used during clinical trials was also performed and demonstrated that DP manufactured from the leukapheresis material processed at each site were comparable. Additionally, MAGE-A4-c1032 LVV comparability studies of LVV manufacturing process changes were performed. These studies demonstrated comparability between the pre-change and post-change LVV.

Manufacturing Risks, Potential Safety Concerns, and Management

Product Mix-Up

TECELRA is an autologous product and mix-ups with autologous TECELRA lots or other genetically modified T cell products manufactured at the same facility would result in potential risks, including infection, graft versus host disease, and lack of anti-tumor effect. The risks are mitigated by the validated COI/COC procedures that ensure each patient receives the correct autologous TECELRA batch.

TECELRA is manufactured in a multiproduct manufacturing facility. Product segregation is maintained via physical separation within the manufacturing suite, dedication of personnel to a (b) (4) , and relevant standard operating procedures. The MAGE-A4-c1032 LVV is supplied in distinct containers, identity is confirmed upon receipt and the correct LVV label is confirmed prior to transduction.

Replication Competent Lentivirus

Replication competent lentivirus (RCL) is a theoretical concern for the TECELRA manufacturing process. The likelihood of RCL generation is reduced by the MAGE-A4-c1032 LVV design: (1) (b) (4)

(b) (4) in accordance with current FDA guidance prior to release and use in the TECELRA manufacturing process.

Insertional Oncogenesis

Vector integration poses a risk for insertional mutagenesis. Activation of proto-oncogenes or disruption of tumor suppressor genes has the potential to cause secondary malignancies. To mitigate the risk of insertional mutagenesis, the vector used for TECELRA manufacturing was designed to (b) (4) Insertion site analysis did not identify areas of preferred integration near genes of concern. The insertional mutagenesis risk of TECELRA is managed by DP release specifications that limit (b) (4) to that within the clinical trial experience.

CMC PMR/PMCs

The following issues were identified but could not be resolved during the review cycle. These issues will be resolved through PMRs/PMCs by December 31, 2025.

Two unresolved issues were present for the assessment of process-related impurities in the DP: 1) evaluation of leachables in the DP did not include the contribution of major process components utilized in the TECELRA manufacturing process, and 2) no empirical data were provided to demonstrate the reduction of (b) (4) impurities in the DP manufacturing process. To resolve these issues, Adaptimmune will perform additional testing to evaluate the cumulative effect of leachables in the DP and will update the toxicological risk assessment as a PMR. Adaptimmune will also conduct a study to assess (b) (4) process-related impurities as a PMC.

There were unresolved issues with validation of DP lot release test methods, including the (b) (4) method (b) (4) data and the lack of proper (b) (4) assay controls. To address these issues, Adaptimmune will provide additional data to complete the (b) (4) method (b) (4) test and will investigate additional (b) (4) assay controls as PMCs.

An issue with lack of container closure integrity testing (CCIT) for the DP shipping validation could not be resolved. Adaptimmune will provide additional shipping validation data as a PMC. There were also unresolved issues with CCIT for the final product and the (b) (4). Adaptimmune will provide additional data to resolve these issues as a PMC.

There were unresolved issues with the (b) (4) manufacturing process and testing, including validation of the (b) (4) used in the manufacturing process, qualification of the sterility test method, and handling of the sterility test samples. To resolve these issues, Adaptimmune will perform a supplemental validation study for the (b) (4), a requalification of the (b) (4) sterility test, and a (b) (4) study for the sterility test samples as PMCs.

b. Testing Specifications

The final TECELRA lot release specifications are shown in Table 2. TECELRA lot release analytical methods and their validations and/or qualifications were found to be adequate for the intended use, except for the outstanding (b) (4) method (b) (4) studies and investigation of (b) (4) assay controls. The Applicant has provided written commitments to resolve these issues as PMCs.

Table 2: Commercial TECELRA Release Specifications

Attribute Type Test	**Method**	**Acceptance Criteria**
Appearance	-	-
Visual inspection	Visual inspection for absence of leaks	(b) (4)
Visual inspection	Visual inspection for physical state: (b) (4)	(b) (4)
Particulates	(b) (4)	Absence of visible foreign particulates
Color	(b) (4)	(b) (4)
Clarity	(b) (4)	(b) (4)
Identity	-	-
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Quantity	-	-
Number of MAGE-A4 TCR positive T cells	Calculated	≥2680.0 × 10^6 cells2
Potency	-	-
Cytotoxic activity	Cytotoxicity assay with flow cytometry	(b) (4)
Purity	-	-
Cell viability	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Safety	-	-
Sterility	(b) (4)	No growth
(b) (4)	(b) (4)	(b) (4)

Attribute Type Test	Method	Acceptance Criteria
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

[1] (b) (4) .
[2] The number of DP bags released for patient administration is controlled by the Quality Assurance for the DP manufacturing site to ensure that the quantity of the DP provided for patient administration does not exceed the upper limit for the recommended dose range.
Abbreviations: EU, endotoxin units; (b) (4) ; MAGE-A4, melanoma-associated antigen 4; TCR, T cell receptor; USP, United States Pharmacopeia

Impurity Profile: TECELRA is a MAGE-A4 TCR-positive T cell product. Impurities can be classified into product-related and process-related and were evaluated during process characterization and process validation studies. Product-related impurities include non-viable cells, non-genetically modified (b) (4) T cells, and cellular components derived from the apheresis that are not (b) (4) T cells. These product-related impurities, along with process-related (b) (4) impurities, are controlled as part of DP lot release specifications. The TECELRA manufacturing process consistently removed other process-related impurities, including (b) (4) components. Additional studies to assess the cumulative effect of leachables in the DP and to evaluate the reduction of (b) (4) process-related impurities were requested through a PMR and a PMC, respectively.

Stability

Long term stability studies support 6 months of storage for TECELRA when stored at ≤-130°C in vapor phase of liquid nitrogen. In-use stability testing supports a post-thaw expiry of (b) (4) hours, although a decreasing trend in cell viability was observed following a hold of the thawed DP at room temperature. Long term stability studies for MAGE-A4-c1032 LVV support (b) (4) of storage at (b) (4)

c. CBER Lot Release

CBER Lot Release, including the submission of product samples to CBER, is not required. The basis for this decision is that TECELRA 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 TECELRA are listed in Table 3. The activities performed and inspectional histories are noted in the table.

Table 3: Manufacturing Facilities Table for TECELRA

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification /Results
Adaptimmune LLC 351 Rouse Boulevard Philadelphia, PA 19112 Manufacture of drug substance and drug product, drug product release testing	3013525969	78438854	PLI	CBER/DMPQ April 2024 VAI
(b) (4) MAGE-A4-c1032 lentiviral vector manufacture and quality control testing (b) (4)	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) VAI

Abbreviations: CBER, Center for Biologics Evaluation and Research; DMPQ, Division of Manufacturing and Product Quality; DUNS, Data Universal Numbering System; FEI, FDA Establishment Identifier; LV, Lentiviral Vector; PLI, Pre-License Inspection; VAI, Voluntary Action Indicated

Adaptimmune LLC

The pre-license inspection (PLI) was conducted from April 1-5, 2024. At the end of the inspection a Form FDA 483, Inspectional Observations, was issued. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (4)

The pre-license inspection (PLI) was conducted from (b) (4). At the end of the inspection a Form FDA 483, Inspectional Observations, was issued. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The container closure system consists of (b) (4) Cryogenic Storage Container, (b) (4), manufactured by (b) (4). The container consists of polyethylene and ethylene-vinyl acetate, and includes ports, fill tube, luer lock caps and leads.

(b) (4) methods for container closure integrity (CCI) testing were performed by (b) (4) All acceptance criteria were met, however, the sensitivity of the method was not

appropriately established. Adaptimmune committed to performing additional studies with an established sensitivity and provide this information as a post-marketing commitment.

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

The applicant conducted comprehensive in silico and in vitro characterization of MAGE-A4 expression in healthy human tissues which demonstrated that the target antigen was primarily restricted to the testes and placenta, suggesting a low potential for off-tumor toxicities. A comprehensive analysis of cross-reactivity was performed using a peptide library screen with single amino-acid substitutions at each position of the antigenic peptide sequence (X-scan) and peptides from MAGE family member proteins. Cross-reactivity studies using cells presenting these defined peptides identified activity against two MAGE family members. These antigens were shown to have similar tissue expression profiles as MAGE-A4. An alloreactivity screen against a panel of cells expressing a range of HLA alleles indicated in vitro alloreactivity against HLA-A*02:05.

Co-culture studies of MAGE-A4 TCR-T cells with MAGE-A4 positive or MAGE-A4 negative tumor lines, normal primary cells, iPSC-derived cells, organotypic models, and primary cancer cells demonstrated that product activity was dependent on the presence of both MAGE-A4 and HLA-A*02 in target cells. Murine in vivo xenograft studies demonstrated dose-dependent TECELRA-mediated tumor control. Consistent with in vitro data, murine studies suggest in vivo anti-tumor activity with high tumor expression of HLA-A*02 and MAGE-A4.

Traditional in vitro and in vivo genotoxicity and carcinogenicity assessments were not conducted using TECELRA. However, vector integration site analysis demonstrated that the insertion site profile for the product was similar to other lentiviral vector products and was not expected to represent a greater risk for the development of insertional oncogenesis.

No animal reproductive and developmental toxicity studies were conducted with TECELRA which is acceptable based on the product characteristics and safety profile.

5. Clinical Pharmacology

The clinical pharmacology section in the current BLA includes two clinical studies: a Phase 2, single-arm, open-label study (ADP-0044-002) of TECELRA in HLA-A*02 subjects with MAGE-A4-expressing metastatic or inoperable (advanced) SS or myxoid/round cell liposarcoma (MRCLS), and a Phase 1, first-in-human, cell dose escalation and expansion study (ADP-0044-001) in HLA-A*02 patients with MAGE-A4-positive unresectable locally advanced or metastatic tumors. The clinical pharmacology review focused on the Phase 2 study (ADP-0044-002) which provided the primary evidence supporting efficacy and safety of TECELRA. The Phase 1 study data was reviewed for supportive evidence.

Following a single intravenous infusion (dose range: 2.68 x 10^9 to 9.99 x 10^9 MAGE-A4 TCR positive T-cells, median dose: 8.00 x 10^9 MAGE-A4 TCR positive T-cells), TECELRA exhibited an initial apparent expansion phase followed by a contraction and persistence phases. The median time to achieve the peak levels of TECELRA in blood was 7 days (range: Day 1 to Day 89) post dosing. High inter-subject variability was observed for TECELRA transgene exposure. Persistence was observed in the majority of patients: TECELRA blood levels were above 1000 copies/µg DNA in 40 out of 44 patients before 50 days post-infusion. The expansion of TECELRA increased with increasing dose. The impact of various intrinsic and extrinsic factors on TECELRA PK was evaluated. No intrinsic and extrinsic factors except dose was found to have a statistically significant impact on the exposure (Cmax and AUC) of TECELRA. No dose adjustment is needed.

After administration of TELCERA, a transient increase was evident for most cytokine markers. The median concentrations of some key cytokines, IFN gamma, IL-6, IL-8, IL-15 and IL-2Ralpha increased from baseline to post-infusion, generally peaking between Days 3 to 8. Serum levels were significantly greater in subjects with cytokine release syndrome (CRS) than in patients without CRS for IFN gamma, IL-10, IL-15, IL-2Ralpha, and IL-6.

Dose-efficacy response analysis of TECELRA was conducted for the dose range of 2.68 x 10^9 to 10.0 x 10^9 MAGE-A4 TCR positive T-cells. The overall response rate (ORR) in patients who received less than 8.0 x 10^9 MAGE-A4 TCR positive T cells was higher than that in the highest dose subgroup (8.13 – 10.0 x 10^9 MAGE-A4 TCR positive T cells), while patients who received more than 8.13 x 10^9 MAGE-A4 TCR positive T cells had higher probability of longer duration of response (DOR). Give the observation that the ORR in the highest dose subgroup (8.13 – 10.0 x 10^9 MAGE-A4 TCR positive T cells) was 27.3%, the dose range of 2.68 x 10^9 to 10.0 x 10^9 MAGE-A4 TCR positive T-cells is acceptable from an efficacy perspective.

TECELRA's PK parameter, $AUC_{0\text{-}6M}$ appeared to be positively associated with ORR. Subjects with the highest quantile of exposure (Cmax and AUCs) tended to have higher probability of longer DOR.

There were very limited numbers of Grade ≥3 CRS and ICANS (<Grade 2) observed within the dose range of 2.68 x 10^9 to 9.99 x 10^9 MAGE-A4 TCR positive T-cells. The administered doses of TECELRA in patients who had Grade ≥3 CRS or ICANS were less than 8.0 x 10^9 MAGE-A4 TCR-positive T cells. Due to the limited number of adverse events of ICANS and severe CRS, there was no clear relationship established between the dose/exposure of TECELRA and the risks of ICANS and severe CRS.

In summary, the dose/exposure-response relationship analysis results support the Applicant's proposed dose range of 2.68 x 10^9 to 10.0 x 10^9 MAGE-A4 TCR positive T-cells.

No subjects were positive for replication-competent lentivirus (RCL) testing at the time of data cutoff date (March 29, 2023).

6. Clinical/Statistical

The clinical review team recommends granting accelerated approval for TECELRA for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive, and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

a. Clinical Program

Primary evidence of effectiveness of TECELRA in the indicated population comes from patients with SS dosed in Cohort 1 of ADP-0044-002, which is a Phase 2 single-arm, open label, multi-cohort, multicenter, multiregional (United States, Europe, and Canada) study. The primary endpoint was ORR and a key secondary endpoint was DOR, as assessed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

At enrollment, patients underwent leukapheresis. received lymphodepletion with fludarabine and cyclophosphamide, followed by one dose of TECELRA (Day 1) containing 2.68 $x10^9$ to 10 $x10^9$ MAGE-A4, TCR-positive T-cells. During product manufacturing, patients could receive bridging therapy at the discretion of the investigator.

Fifty-two patients with synovial sarcoma were enrolled in ADP-0044-002 Cohort 1 and underwent leukapheresis, 45 patients (86.5%) received lymphodepletion, and 44 patients (84.6%) received TECELRA. The median time from leukapheresis to start of lymphodepletion for the primary efficacy population (n=44) was 1.7 months. Four patients did not receive product after initial (first) manufacture. The manufacturing failure rate in Cohort 1 was 7.7% (4 of 52 patients).

Among the 44 patients included in the primary efficacy analysis, the median age was 41 years (range: 19 to 73 years), 50% were female, and 89% were White, and 96% were HLA-A*02:01P. The median number of prior lines of systemic therapies was three (range: 1 to 12 lines). Prior therapies included ifosfamide (100%), doxorubicin (95%), pazopanib (48%), trabectedin (25%), dacarbazine (11%), and gemcitabine (11%). Between leukapheresis and initiation of lymphodepletion, 16 (36%) of the 44 patients received bridging therapy. The most commonly used bridging therapy was pazopanib (69%). The median dose of TECELRA was 8$x10^9$ MAGE-A4 TCR positive T cells (range: 2.68 x 10^9 to 9.99 $x10^9$).

During the review of the BLA, several data quality and study conduct issues were identified that raised concerns regarding the reliability of study results to establish effectiveness. These issues included inaccurate target lesion measurements, inconsistencies in adherence to RECIST v1.1, inconsistencies in the implementation of response adjudication, and use of several efficacy data cut-off dates for efficacy analyses. Consequently, FDA requested, and the Applicant agreed to an independent, third-party blinded re-review of imaging for the efficacy evaluable population in Cohort 1. The results of this re-review are the basis for FDA's determination of the efficacy results of the study.

Efficacy Results

The primary efficacy analysis was performed in 44 patients with SS treated with TECELRA in ADP-0044-002 Cohort 1. The ORR was 43.2% (95% CI: 28.4, 59.0) with complete response (CR) in 2 (4.5%) patients and partial response (PR) in 17 (38.6%) patients. The Kaplan-Meier (KM) estimated median duration of response was 6.0 months (95% CI: 4.6, NR) with a median follow up of 21.9 months by reverse KM estimate. Among the 19 responders, durable response at 6, 12, and 24 months was 45.6%, 39%, and 39%, respectively based on KM estimate.

The ORR supported by durability of response constitutes substantial evidence of TECELRA's effectiveness. The effects on ORR and DoR are considered clinically meaningful in this pre-treated population with limited available effective therapies.

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

Bioresearch Monitoring (BIMO) inspections were issued for four clinical study sites that participated in the conduct of study Protocol No. ADP-0044-002 and one for the study Applicant. The inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (BLA).

c. Pediatrics

The Applicant has an agreed initial pediatric study plan with FDA, dated March 4, 2021. The Applicant requested a partial waiver of the pediatric assessment for the pediatric population under 2 years of age, and requested a deferral of submission of the pediatric assessment for the pediatric population aged 2 to17 years at the time of BLA submission. The partial waiver request was based on the grounds that the necessary studies in these pediatric subsets are impossible or highly impracticable (section 505B(a)(4)(B)(i) of the Act). The deferral was requested on the grounds that the biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

TECELRA had been granted Orphan Drug Designation (DRU-2018-6660) for the treatment of soft tissue sarcoma on August 26, 2019.

However, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), as amended by the FDA Reauthorization Act of 2017 (FDARA), because the molecular target "MAGE-A4" is relevant to the growth or progression of a pediatric cancer, the Applicant is required to conduct a molecularly targeted pediatric cancer investigation in patients with solid tumors that are expressing MAGE-A4 to evaluate dosing, pharmacokinetics, safety, and antitumor activity of TECELRA following lymphodepletion with fludarabine and cyclophosphamide. The study should enroll patients aged ≥2 years <17 years with synovial sarcoma, malignant peripheral nerve sheath tumor, neuroblastoma, or osteosarcoma, who have received prior systemic therapy for advanced disease, and are positive for HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P and whose tumor expresses the MAGE-A4 antigen.

ADP-0044-004: pediatric patients 2-<17 years old with MAGE-A4 positive tumors:

a. Final Protocol Submission Date: Completed
b. Study Completion Date: April 2027

c. Final Report Submission Date: September 2027

d. Other Special Populations

TECELRA was not studied in other special populations.

7. Safety and Pharmacovigilance

The safety analysis included assessments starting at the time patients began the entire treatment regimen, which included lymphodepletion followed by TECELRA. Risks related to the entire treatment regimen were evaluated during this assessment. The Applicant collected all adverse events (AEs) and serious adverse events (SAEs) from the start of lymphodepletion until completion of the interventional phase of the study. During the LTFU phase, monitoring and collection of AEs continued.

The primary safety analysis was performed in 44 patients with SS treated in ADP-0044-002 Cohorts 1.

A total of 24 patients died and all deaths were due to disease under study and occurred greater than 30 days after TECELRA administration.

The most common adverse reactions (occurring in ≥20%) were cytokine release syndrome (75.0%), nausea (65.9%), vomiting (36.4%), fatigue (34.1%), infections (32%) pyrexia (31.8%), constipation (31.8%), dyspnea (27.3%), abdominal pain (25.0%), non-cardiac chest pain (22.7%), decreased appetite (22.7%), tachycardia/sinus tachycardia (20.5%), back pain (20.5%), hypotension (20.5%), diarrhea (20.5%), and edema (20.5%).

Grade 3 or higher adverse reactions included pyrexia (4.5%), abdominal pain (4.5%), back pain (4.5%), dyspnea (4.5%), cytokine release syndrome (2.3%), headache (2.3%), hypertension (2.3%), weight decreased (2.3%), nausea (2.3%), asthenia (2.3%), non-cardiac chest pain (2.3%), and decreased appetite (2.3%). Other adverse events of special interest (AESI) included ICANS of Grade 1 in one patient.

Viral reactivation occurred in one patient following treatment with TECELRA who developed Epstein-Barr-positive lymphoproliferative disease.

Pharmacovigilance Plan

The Pharmacovigilance Plan (PVP) for TECELRA (BLA 125789/0.54, received June 20, 2024) includes the Applicant's assessment of important identified risks, important potential risks, and missing information. Important identified risks include cytokine release syndrome and prolonged cytopenia. Important potential risks include infections, neurologic toxicity (including ICANS), and secondary malignancy (including vector insertion site). Missing information includes long-term safety, safety in pediatric populations, safety in elderly patients above 75 years, safety during pregnancy following T-cell therapy, generation of replication competent lentivirus, and new occurrence or exacerbation of autoimmune disorders.

The Applicant will conduct routine pharmacovigilance, which includes adverse event reporting, in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for secondary malignancies of T-cell origin. Enhanced pharmacovigilance will include

expedited (15-day) reporting of secondary malignancies of T-cell origin regardless of seriousness or label status. In addition, the Applicant agrees to provide aggregate safety assessments in their periodic safety reports, based on interval and cumulative safety data, for the risk of all secondary malignancies, and specifically T-cell malignancies.

In addition to routine and enhanced pharmacovigilance, the Applicant will also conduct a registry-based, observational postmarketing safety study as a postmarketing requirement (PMR) under 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess the risk of secondary malignancy following administration of TECELRA. This study will enroll patients with synovial sarcoma with long term follow-up (LTFU) for up to 15 years after infusion. The plan for 15 years LTFU in this study, as well as the clinical studies submitted in support of this BLA (ADP-0044-002 and ADP-0044-001), is consistent with FDA Guidance "Long Term Follow-up After Administration of Human Gene Therapy Products" (January 2020), which recommends 15 years LTFU for gene therapies with integrating vectors (such as lentiviral vectors) available at https://www.fda.gov/media/113768/download.

The proposed pharmacovigilance plan for TECELRA is adequate for the labeled indication. The available data do not indicate a safety signal which would require a Risk Evaluation and Mitigation Strategy (REMS). There is no safety-related study as an agreed upon postmarketing commitment (PMC) at this time.

8. Labeling

The proposed proprietary name, TECELRA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 20, 2024 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on February 28, 2024.

Through July 29, 2024, APLB iteratively reviewed the draft PI, PPI, and package and container labels with the TECELRA Review Team and provided comments on the revised labeling from a comprehension, readability, and promotional perspective.

Boxed Warning, Warnings and Precautions

Risk mitigation strategies will be instituted in the United States Prescribing Information (USPI) through a Boxed Warning for cytokine release syndrome (CRS) and Warnings and Precautions section for CRS, ICANS, prolonged severe cytopenia, infections, secondary malignancies and hypersensitivity reactions.

9. Advisory Committee Meeting

The Division did not refer the application to an Advisory Committee or seek input from Special Government Employees for this BLA as no significant review issues necessitating input from external experts were identified during the review of this application.

10. Other Relevant Regulatory Issues

This application received RMAT, Priority Review, and Orphan Drug designations.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends granting accelerated approval for TECELRA for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive, and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices. The basis for the recommendation is ORR supported by median duration of response and an acceptable risk profile.

b. Benefit/Risk Assessment

The magnitude and durability of ORR demonstrated in Study ADP-0044-002 Cohort 1 establishes the effectiveness of TECELRA in the indicated population. The safety profile is acceptable for this population. Given these effects, the poor prognosis of the disease, and the lack of effective therapies, treatment with TECELRA represents an improvement over available therapy in the intended patient population. Additional advantages of treatment with TECELRA include a shorter treatment course than that of available therapies in the context of an acceptable risk profile.

The overall benefit-risk profile of TECELRA supports accelerated approval for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive, and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

Risk mitigation strategies will be instituted in the United States Prescribing Information (USPI) through a Boxed Warning for cytokine release syndrome and Warnings and Precautions section for CRS, ICANS, prolonged severe cytopenia, infections, secondary malignancies and hypersensitivity reactions, as well as via the Medication Guide for patients to be treated with TECELRA.

Continued approval is contingent upon fulfilment of a Postmarketing Requirement (PMR) to provide verification of the clinical benefit of TECELRA. As specified in section 506(g)(7) of the FD&C Act, products that have been granted Regenerative Medicine Advanced Therapy (RMAT) Designation and which receive accelerated approval may be able to fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials, such as collection of larger confirmatory data sets as agreed upon during product development. The Applicant is conducting a confirmatory study of additional cohorts in ADP-0044-002 to provide verification of ORR supported by DOR.

c. Recommendation for Postmarketing Activities

1. Accelerated Approval - Required Study: The Applicant should submit the Final Report, including datasets from ADP-0044-002 Cohorts 2 and 3 to verify and describe the clinical benefit of afamitresgene autoleucel, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -

A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

Overall response rate and duration of response will be assessed by independent review and all patients will be followed for at least 15 months to assess duration of response.
Final Protocol Submission: October 31, 2024
Study/Trial Completion: July 31, 2025
Final Report Submission: December 31, 2025

2. Conduct a molecularly targeted pediatric cancer investigation in a sufficient number of patients with solid tumors expressing MAGE-A4 to evaluate dosing, pharmacokinetics, safety, and antitumor activity of afamitresgene autoleucel following lymphodepletion with fludarabine and cyclophosphamide. The study should enroll patients aged ≥2 years <17 years with synovial sarcoma, malignant peripheral nerve sheath tumor, neuroblastoma, or osteosarcoma, who have received prior systemic therapy for advanced disease, and are positive for HLA-A*02:01, -A*02:02, -A*02:03, or -A*02:06 allele.

   Final Protocol Submission Date: Completed
   Study Completion Date: April 2027
   Final Report Submission Date: September 2027

   The Applicant will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, and the following safety study as a PMR under section 505(o) of the FDCA, to assess the unexpected serious risk of secondary malignancies:

3. A postmarketing, prospective, multi-center, observational study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with afamitresgene autoleucel (Study CM21-177). The study will include patients with synovial sarcoma who received afamitresgene autoleucel, and each enrolled patient will be followed for 15 years after product administration.

   The Applicant's proposed study milestone dates are as follows:

   Final Protocol Submission: October 31, 2024
   Study Completion Date: December 31, 2044
   Final Report Submission: October 31, 2045

4. An adequate assessment of leachables in the DP including the contribution of (b) (4) major process components utilized in Step (b) (4) of the afamitresgene autoleucel manufacturing process, and an updated toxicological risk assessment once the study is completed.

   The Applicant's proposed study milestone dates are as follows:

   Initial Protocol Submission for FDA Review: August 9, 2024
   Final Protocol Submission: September 30, 2024
   Study Completion: October 1, 2025
   Final Study Report Submission: December 31, 2025

The Applicant has agreed to the following PMCs:

5. Adaptimmune LLC commits to conduct a requalification of the (b) (4) sterility test using the (b) (4) method. The final qualification study report will be submitted as a Postmarketing Commitment - Final Study Report by October 31, 2024.

   Final Study Report Submission: October 31, 2024.

6. Adaptimmune LLC commits to implement storage and shipping of (b) (4) sterility samples at (b) (4) and conduct a (b) (4) study. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by October 31, 2024.

   Final Study Report Submission: October 31, 2024.

7. Adaptimmune LLC commits to conduct a study measuring (b) (4) process-related impurities in the afamitresgene autoleucel manufacturing process. The final study report will be submitted as a Postmarketing Commitment- Final Study Report by April 30, 2025.

   Final Study Report Submission: April 30, 2025.

8. Adaptimmune LLC commits to conduct a feasibility study to investigate potential negative controls for the (b) (4) assay. The final study report will be submitted as a Postmarketing Commitment- Final Study Report by April 30, 2025.

   Final Study Report Submission: April 30, 2025.

9. Adaptimmune LLC commits to providing the outstanding results of the additional shipping validation performed for the drug product (b) (4) that includes performing container closure integrity testing (CCIT) to demonstrate integrity of the drug product container after shipping. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by September 30, 2024.

   Final Study Report Submission: September 30, 2024.

10. Adaptimmune commits to providing the results of the hypothesis testing to understand the root cause of the damage to the drug product bags observed in the initial shipping study. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by September 30, 2024.

    Final Study Report Submission: September 30, 2024.

11. Adaptimmune LLC commits to providing the study results of the additional container closure integrity testing using a positive control with an established sensitivity (i.e., (b) (4) for the afamitresgene autoleucel drug product (b) (4) The final study report will be submitted as a Postmarketing Commitment – Final Study Report by September 30, 2024.

    Final Study Report Submission: September 30, 2024

12. Adaptimmune LLC commits to providing a supplemental (b) (4) efficacy validation study for the (b) (4) , that evaluates the (b) (4) . The final study report will be submitted as a Postmarketing Commitment - Final Study Report by December 31, 2025.

    Final Study Report Submission: December 31, 2025

13. Adaptimmune LLC commits to performing an (b) (4) test using the (b) (4) assay on samples of drug substance taken at (b) (4) data reported in document number VAL 02609, Comparability of the (b) (4) assay to (b) (4) using (b) (4) Controls. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by December 31, 2024.

    Final Study Report Submission: December 31, 2024