



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Pharmacovigilance (DPV)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**To:** Elvira Argus, PhD  
Chair of the Review Committee  
Office of Therapeutic Products

**Through:** Christopher Jason, MD  
Branch Chief, PB2

Narayan Nair, MD  
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OBPV, CBER, FDA

**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Adaptimmune LLC

**Product:** TECELRA (afamitresgene autoleucel)<sup>1</sup>

**Application Type / Number** BLA 125789/0

**Proposed Indication** Adults with unresectable or metastatic synovial sarcoma who have received prior systemic therapy

**Submission Date:** December 5, 2023

**Action Due Date:** August 2, 2024

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<sup>1</sup> Also referred to as ADP-A2M4<sup>C1032</sup>T-cells, MAGE-A4<sup>C1032</sup>T-cells, or ADP-A2M4 in the clinical development program

## **1 OBJECTIVE**

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125789 based on the safety profile of TECELRA (afamitresgene autoleucel). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for TECELRA (afamitresgene autoleucel), should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

## **2 BACKGROUND**

Synovial sarcoma (SS) is a rare malignancy that originates from primitive mesenchymal cells and comprises 5-10% of all soft tissue sarcomas (STS). Approximately 1000 patients are diagnosed with SS each year in the US, with an age-adjusted incidence of 0.81/1,000,000 in children and 1.42/1,000,000 in adults. According to recent estimates, patients with SS have a median 5-year survival between 59-75% [1]. SS can originate anywhere in the body (including from bone), but typically arises near joints in the extremities. Adolescents and young adults are most often affected, presenting with a slow-growing, painful soft tissue mass.

Diagnosis involves imaging (e.g., magnetic resonance imaging [MRI] with contrast), biopsy, and pathology. Staging involves cross-sectional chest imaging (since the lung is the most common site of metastasis) as well as molecular staging via fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR). More than 95% of cases demonstrate the pathognomonic translocation t(X;18).

Treatment of SS is individualized for each patient, but generally involves surgical resection with possible addition of radiation therapy and/or chemotherapy depending on patient and tumor characteristics [1]. Novel therapies are also in development for SS, and a tyrosine kinase inhibitor (pazopanib) is currently approved for patients with advanced soft tissue sarcoma who have received prior chemotherapy [2]. Finally, according to the Sponsor's assessment (p.15, Module 2.5 Clinical Overview), there is no clear "gold standard of care" for metastatic SS after first-line therapies are given. Within this context, afamitresgene autoleucel was developed as a form of adoptive T-cell therapy, to use the patient's own T-cells to target tumor cells.

## **3 PRODUCT INFORMATION**

### **3.1 Product Description**

TECELRA (afamitresgene autoleucel) is a genetically modified autologous T-cell immunotherapy product consisting of CD4 and CD8 positive T-cells transduced with a self-inactivating lentiviral vector (LV) expressing an affinity-enhanced T-cell receptor (TCR) specific for the human melanoma-associated antigen A4 (MAGE-A4).

Autologous T-cells transduced with MAGE-A4-c1032 LV express the affinity-enhanced TCR on the cell surface. The TCR recognizes an HLA-A\*02 restricted MAGE-A4

peptide. MAGE-A4 is an intracellular cancer-testis antigen that has restricted expression in normal tissues and is expressed across a range of solid tumors at varying frequencies.

TECELRA is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard leukapheresis procedure. The PBMCs are enriched for T-cells and are then transduced with a replication-incompetent LV containing the MAGE-A4 TCR transgene. The transduced T-cells are expanded, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release and shipping as a frozen suspension in one or more infusion bag(s). The product is thawed prior to infusion back into the patient.

The drug product formulation contains 5% dimethyl sulfoxide (DMSO).

### **3.2 Proposed Indication**

The sponsor's proposed indication statement as submitted to the original BLA 125789/0.8 is:

"TECELRA is a genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic synovial sarcoma who have received prior systemic therapy, are positive for HLA-A\*02:01P, -A\*02:02P, -A\*02:03P, or -A\*02:06P, and negative for HLA-A\*02:05P, and whose tumor expresses the MAGE-A4 antigen as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial."

*Reviewer comment: Of note, TECELRA is administered after pre-treatment with a lymphodepleting chemotherapy regimen of fludarabine and cyclophosphamide. OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.*

## **4 PERTINENT REGULATORY HISTORY**

On December 5, 2023, the Sponsor submitted roll 3 of 3 for this rolling BLA submission. On January 31, 2024, FDA sent the Sponsor a filing notification and classified this application as Priority Review, with a goal review date of August 4, 2024. TECELRA has not yet been approved for marketing in any country.

## **5 DESCRIPTION OF TECELRA CLINICAL TRIAL SAFETY DATABASE**

### **5.1 Clinical studies**

The clinical study safety data reviewed are from the Clinical Study Reports, Clinical Overview, and Safety Update Report submitted to BLA 125789/0 (amendments 0.1 and 0.8). OBPV defers to the product office on final review of the clinical database, including

safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125789/0 be approved. Please refer to the package insert for the final clinical safety data.

The clinical development program for afamitresgene autoleucel consists of three studies described in Table 1. ADP-0044-002 serves as the primary evidence to support the indication for afamitresgene autoleucel in advanced synovial sarcoma. ADP-0044-001 and ADP-0044-001R provide additional supportive safety data. After submission of the Clinical Study Reports and Clinical Overview (BLA 125789/0.1), the Sponsor submitted a Safety Update Report (BLA 125789/0.8), which includes pooled safety data with a later data cut-off (DCO) date for Study ADP-0044-002 (29-Mar-2023) and the same DCO dates for the other studies as in the Clinical Overview (01-Sep-2020 for Study ADP-0044-001; 13-Jan-2022 for Study ADP-0044-001R).

**Table 1. Summary of clinical studies supporting the safety of afamitresgene autoleucel\***

Study	N	Description
ADP-0044-002	44 (Cohort 1)	Phase 2, single-arm, open-label, multi-center, clinical trial to evaluate the efficacy and safety of ADP-A2M4 SPEAR™ T cells in subjects aged 16 to ≤75 years with advanced synovial sarcoma or myxoid/round cell liposarcoma (MRCLS)
ADP-0044-001	38	Phase 1, single-arm, open-label, multi-center, dose escalation, multi-tumor study to assess the safety, tolerability, and anti-tumor activity of genetically engineered MAGE-A4 <sup>C1032T</sup> in HLA-A2+ adult subjects (aged 18 to ≤75 years) with inoperable locally advanced or metastatic MAGE-A4 positive tumors
ADP-0044-001R	5	Low dose radiation therapy substudy within Study ADP-0044-001 to evaluate the safety and tolerability of low dose radiation in combination with afamitresgene autoleucel

### 5.1.1 Study ADP-0044-002

*Note: Results in this section are from Safety Update Report (data cut-off date: 29-Mar-2023 for Study ADP-0044-002).*

#### Study Design

Study ADP-0044-002 is a phase 2, single-arm, open-label, multi-center, clinical trial to evaluate the efficacy and safety of ADP-A2M4 SPEAR™ T cells in subjects aged 16 to ≤75 years with advanced synovial sarcoma or myxoid/round cell liposarcoma (MRCLS).

#### Study Population

The study population was comprised of two cohorts (Cohorts 1 and 2). Cohort 1 included individuals with metastatic or inoperable (advanced) synovial sarcoma or MRCLS. Cohort 2 was created in a protocol amendment and designed to enroll only subjects with advanced synovial sarcoma. Approximately 45 subjects were planned for treatment in Cohort 1. As of 29-Mar-2023, 44 subjects with advanced synovial sarcoma received afamitresgene autoleucel infusion in Cohort 1. This group of subjects (n=44, referred to as “SS Cohort 1”) is the source of safety data presented in section 6 “Adverse Reactions” of the proposed US Package Insert (BLA 125789/0.8). Therefore, discussion of Study ADP-0044-002 in this memorandum focuses on this subgroup.<sup>2</sup>

Males and females were evenly represented in SS Cohort 1 (n=22 or 50% each). Most subjects were white (88.6%) and not Hispanic or Latino (86.4%). The median age was 40.5 years (range 19-73 years). Most subjects received significant pretreatment, with 31.8% having received 4 or more prior lines of systemic therapy and the median number of prior lines of systemic therapy being 3 (range 1-12 lines).

#### Most common AEs

Most subjects in SS Cohort 1 (90.9%) experienced TEAEs related to T-cell therapy and serious TEAEs related to T-cell therapy were common (25%). No subjects experienced TEAEs with a fatal outcome (Table 2).

**Table 2. Overall Summary of AEs in Study ADP-0044-002 (SS Cohort 1)\***

<b>Category (# subjects)</b>	<b>Overall (N=44) n (%)</b>
Any AEs	44 (100)
Any TEAEs	44 (100)
Any TEAEs related to T-cell therapy	40 (90.9)
Any TEAEs ≥Grade 3	44 (100)
Any TEAEs related to T-cell therapy ≥Grade 3	20 (45.5)
Any serious TEAEs	23 (52.3)
Any serious TEAEs related to T-cell therapy	11 (25)
Any SAEs with a fatal outcome	0 (0)

\*Source: Adapted from Table 8, Safety Update Report, Module 5.3.5.3, BLA 125789/0.8

Abbreviations: adverse event (AE), treatment-emergent adverse event (TEAE), serious adverse event (SAE)

For SS Cohort 1, the most common (non-laboratorial) TEAEs (reported by ≥20% subjects) included Cytokine Release Syndrome (CRS) (75.0%), nausea (65.9%), vomiting (36.4%), fatigue (34.1%), constipation and pyrexia (31.8% each), dyspnea (27.3%), abdominal pain (25.0%), decreased appetite and non-cardiac chest pain (22.7% each), and back pain, diarrhea, hypotension, edema, and tachycardia/sinus

<sup>2</sup> According to the Safety Update Report submitted to BLA 125789/0.8, 130 subjects overall were treated with afamitresgene autoleucel in studies ADP-0044-002 (Cohorts 1 & 2), ADP-0044-001, and ADP-0044-001R. This includes 96 subjects with SS and 34 subjects with other tumors (including MRCLS). Study ADP-0044-002 included 44 subjects in SS Cohort 1 and 80 subjects in SS Cohorts 1 & 2.

tachycardia (20.5% each). The most common TEAEs (>20% subjects) related to T-cell therapy were CRS (75.0%), WBC count decreased (20.5%), and pyrexia (22.7%). Although most TEAEs were Grade 1 or 2, 45.5% of TEAEs were ≥Grade 3.

Laboratorial TEAEs were common and included lymphopenia (97.7%), neutropenia (90.9%), leukopenia (86.4%), anemia (40.9%), and thrombocytopenia (34.1%). The most common TEAEs related to T-cell therapy were leukopenia (27.3%) and neutropenia (22.7%).

All subjects in SS Cohort 1 experienced at least 1 TEAE that was ≥Grade 3 and related to lymphodepleting (LD) chemotherapy. The most common (reported by ≥20% subjects) laboratorial TEAEs related to LD chemotherapy included lymphocyte count decreased (70.5%), WBC count decreased (68.2%), neutrophil count decreased (59.1%), anemia (38.6%), neutropenia (29.5%), lymphopenia (27.3%), platelet count decreased (22.7%), and leukopenia (20.5%). The most common (reported by ≥20% subjects) non-laboratorial TEAEs related to LD chemotherapy included nausea (50%) and vomiting and fatigue (20.5% each).

### SAEs

For SS Cohort 1, the most common serious TEAEs (≥3 subjects) were CRS (9.1%) and pleural effusion (6.8%). All serious TEAEs of CRS and one case of pleural effusion were considered treatment-related. Other serious TEAEs that were considered treatment-related included deep vein thrombosis, superior vena cava syndrome, empyema, pulmonary embolism, anemia, platelet count decreased, pyrexia, pancytopenia, acute kidney injury, and lymphoproliferative disorder (2.3% or 1 each).

### Deaths

No subjects experienced TEAEs with a fatal outcome. However, 24 (54.5%) subjects died in Cohort 1 during the study. All deaths occurred >30 days after T-cell infusion and were attributed to disease under study.

### AESIs

Adverse events of special interest (AESIs) in this study's protocol included CRS and neurotoxicity (including immune effector cell-associated neurotoxicity syndrome [ICANS]). Prolonged cytopenia is also described in the Safety Update Report as an AESI.

### *Cytokine Release Syndrome (CRS)*

Most (75%) subjects in SS Cohort 1 experienced CRS and all but one of these subjects experienced Grade 1 or Grade 2 CRS. One (2.3%) subject (b) (6) in Cohort 1 had Grade 3 CRS that was related to T-cell therapy and was serious. The median time to onset for all cases was 2 days (range 1-5 days). Tocilizumab was administered to 18 (54.5%) subjects. Median time to resolution was 3 days (1-14 days).

### *Neurotoxicity*

Most (61.4%) subjects in SS Cohort 1 experienced neurological AEs (MedDRA Preferred Terms under the System Organ Classes “Nervous System Disorders” and “Psychiatric Disorders”). Grade  $\geq 3$  neurological AEs included headache, spinal cord compression, and syncope (2.3%; 1 subject each). Neurological AEs related to T-cell infusion included insomnia, hypoaesthesia, presyncope, ICANS, anosmia, emotional distress, irritability, and lethargy (2.3%; 1 subject each). The subject (b) (6) in SS Cohort 1 with ICANS experienced Grade 1 ICANS concurrent with Grade 2 CRS on Day 2, which resolved the following day after treatment with tocilizumab and dexamethasone.

#### *Prolonged cytopenia*

Nine (20.5%) subjects in SS Cohort 1 experienced prolonged cytopenia ( $\geq$ Grade 3 neutropenia, anemia, or thrombocytopenia persisting for  $\geq 4$  weeks). This includes neutropenia (11.4%), anemia (9.1%), and thrombocytopenia (4.5%).

*Reviewer comment: In addition to the above described AEs, the Safety Update Report also describes cases of febrile neutropenia, granulocyte colony stimulating factor (G-CSF) use, infections, cardiac disorders (sinus tachycardia, tachycardia, atrial fibrillation), tumor pain, and skin rash reported in association with afamitresgene autoleucel.*

*Of note, after the data cutoff date for the Safety Update Report (29-Mar-2023 for Study ADP-0044-002), the Sponsor submitted an expedited IND safety report (IND 17235/0.171, received 29-Jun-2023) regarding a subject who experienced Grade 4 (life-threatening) CRS and subsequently died from septic shock related to a peripherally inserted central catheter (PICC) line infection. The subject was a 66-year-old male (SAE 2023-ADP-000016) with metastatic synovial sarcoma who was enrolled in Study ADP-0044-002. The subject began to experience CRS symptoms the same day as the T cell infusion, which by Day 3 had progressed to Grade 4 symptoms (ventilatory dependent respiratory failure and shock requiring vasopressors). Blood, urine, and tracheal aspirate cultures were negative, and he was treated with tocilizumab and dexamethasone with gradual improvement in symptoms. However, approximately one hour after extubation, he developed fever, chills, and hemodynamic deterioration, ultimately resulting in multiple organ system failure and death. Blood cultures at this time were positive for gram-negative bacteria, which was attributed to a PICC line infection. This case was notable for being a Grade 4 CRS case and fatality within 9 days of receiving TECELRA.*

#### **5.1.2 Study ADP-0044-001**

*Note: Results in this section are from Clinical Study Report for ADP-0044-001 (data cutoff date: 01-Sep-2020) and Study Synopsis for ADP-004-001R (data cutoff-date: 13-Jan-2022).*

#### Study Design

Study ADP-0044-001 is a phase 1, single-arm, open-label, multi-center, dose escalation, multi-tumor study to assess the safety, tolerability, and anti-tumor activity of genetically engineered MAGE-A4<sup>C1032T</sup> in HLA-A2+ adult subjects (aged 18 to  $\leq 75$

years) with inoperable locally advanced or metastatic MAGE-A4 positive tumors. The following tumor types were included in the study: urothelial, melanoma, head and neck, ovarian, non-small cell lung cancer (NSCLC), esophageal (squamous and adenocarcinoma), gastric, synovial sarcoma, or myxoid/round cell liposarcomas (MRCLS).

### Study Population

Among the 63 subjects who enrolled, 38 underwent leukapheresis, lymphodepleting (LD) chemotherapy (with cyclophosphamide and fludarabine), T-cell therapy (infusion of afamitresgene autoleucel) and were included in the modified intent-to-treat (mITT) population. Most subjects were male (57.9%), white (92.1%), and not Hispanic or Latino (94.7%). The median age was 58 years (range 31-78 years). Most subjects received significant pretreatment, with 39.5% having received 4 or more prior lines of systemic therapy and 97.4% of subjects having received prior cytotoxic chemotherapy.

The majority of subjects (n=16; 42.1%) had synovial sarcoma (SS) for their primary tumor type. The median age in this subgroup was 49 years (range 31-76). All patients in the SS subgroup were treated with the dose ultimately selected as the optimal dose. One subject in the SS subgroup received a second dose of T-cell therapy after meeting study protocol criteria for a second infusion.

### Most common AEs

Most subjects in the study (76.3%) experienced TEAEs related to T-cell therapy and serious TEAEs related to T-cell therapy were common (34.2%). Three subjects experienced TEAEs with a fatal outcome, 2 (5.3%) of which were considered related to study treatment (Table 3).

**Table 3. Overall Summary of AEs in Study ADP-0044-001\***

<b>Category (# subjects)</b>	<b>Overall (N=38) n (%)</b>
Any AEs	38 (100)
Any TEAEs	38 (100)
Any TEAEs related to T-cell therapy	29 (76.3)
Any TEAEs ≥Grade 3	38 (100)
Any TEAEs related to T-cell therapy ≥Grade 3	17 (44.7)
Any serious TEAEs	27 (71.1)
Any serious TEAEs related to T-cell therapy	13 (34.2)
Any SAEs with a fatal outcome	3 (7.9)

\*Source: Adapted from Table 13, Clinical Study Report for Study ADP-0044-0018, Module 5.3.5.2, BLA 125789/0.1

Abbreviations: adverse event (AE), treatment-emergent adverse event (TEAE), serious adverse event (SAE)

For the overall mITT population, the most common TEAEs (reported by ≥50% subjects) were lymphocyte count decreased (97.4%), white blood cell count decreased (89.5%), neutrophil count decreased (86.8%), anemia (71.1%), fatigue and nausea (63.2%)



each), pyrexia (57.9%), CRS and platelet count decreased (55.3% each), and vomiting (50%). The most common TEAEs (>20% subjects) related to T-cell therapy were pyrexia (39.5%) and fatigue (36.8%). The most common TEAEs ≥Grade 3 (reported by ≥50% subjects) were lymphocyte count decreased (97.4%), white blood cell count decreased (89.5%), neutrophil count decreased (86.8%), and anemia (63.2%).

For the SS subgroup, the most common TEAEs ≥Grade 3 (reported by ≥20% subjects) were lymphocyte count decreased (100%), WBC count decreased (87.5%), neutrophil count decreased (81.3%), platelet count decreased (43.8%), anemia (43.8%), hypophosphataemia (43.8%), and febrile neutropenia (37.5%).

*Reviewer comment: The most common AEs were notable for cytopenia and CRS, both of which have been reported after other adoptive T-cell therapies (e.g., chimeric antigen receptor T-cell [CAR T] therapy) [3, 4]. Of note, CRS was more common in the SS subgroup, affecting 87.5% of subjects with SS.*

### SAEs

For the overall mITT population, the most common SAEs (≥10% of subjects) were CRS (23.7%), pyrexia (13.2%), and pancytopenia (10.5%). The most common (>5%) related SAEs were CRS (23.7%) and pyrexia (5.3%).

For the SS subgroup, 12 (75%) subjects experienced at least 1 SAE and the most common SAEs (≥10% of subjects) were CRS (43.8%), pyrexia (18.8%), pancytopenia (12.5%), and platelet count decreased (12.5%). One of the two subjects (both with synovial sarcoma) who received a second T-cell infusion experienced a Grade 3 SAE of pulmonary embolism, which was considered not related to infusion.

### Deaths

For the overall mITT population, 18 (47.4%) deaths were reported. The most common cause of death was “diseases under study” (n=14; 36.8%). Three subjects had SAEs with fatal outcomes (Table 4), and 2 (5.3%) of these subjects died from treatment-related SAEs.

**Table 4. SAEs with fatal outcome**

Subject	Tumor type	Fatal SAE	Relatedness
(b) (6)	Synovial sarcoma	aplastic anemia	probably related to LD chemotherapy and T-cell infusion
(b) (6)	Ovarian	cerebrovascular accident	not related to LD chemotherapy but possibly related to T-cell therapy
(b) (6)	Esophageal	acute kidney injury	related to the disease under study

Two subjects with fatal SAEs (aplastic anemia, cerebrovascular accident) were elderly and had received the highest dose of LD chemotherapy regimen; these deaths

prompted protocol amendments to reduce the dose of LD chemotherapy and decrease the age limit to 75 years.

### AESIs

AESIs in this study included CRS, neurotoxicity, prolonged cytopenia, and graft versus host disease (GVHD). No subjects experienced GVHD in this study.

### *Cytokine Release Syndrome (CRS)*

Most (55.3%) subjects in the mITT population experienced CRS and most of these subjects (90.5%) experienced Grade 1 or Grade 2 CRS events. The median time to onset was 3 days (range 1-9 days). Tocilizumab was given to 13 (34.2%) subjects. Time to resolution ranged from 1-19 days.

Two (5.3%) subjects experienced  $\geq$ Grade 3 CRS; both subjects were in the SS subgroup. One subject experienced Grade 3 CRS for one day. Another subject experienced two episodes of CRS: an episode of Grade 3 CRS starting on Day 2 and lasting for 12 days and an episode of Grade 4 CRS starting on Day 39 and lasting for 14 days. All  $\geq$ Grade 3 CRS events were treated with anti-IL6 medications.

Nine (23.7%) subjects experienced CRS as an SAE. This included 7 of 16 (43.8%) subjects in the SS subgroup.

### *Neurotoxicity*

Eight (21%) subjects in the mITT population experienced neurotoxicity (according to the Society for Immunotherapy of Cancer guidelines and American Society for Transplantation and Cellular Therapy consensus), including encephalopathy/immune effector cell-associated neurotoxicity syndrome (ICANS). One subject with ovarian cancer experienced Grade 2 encephalopathy. One subject with NSCLC with brain metastases experienced Grade 1 ICANS. Finally, one subject (b) (6) died from an ischemic cerebrovascular accident that was considered not related to LD chemotherapy but possibly related to T-cell infusion. Two subjects in the SS subgroup experienced neurotoxicity events of headache and peripheral sensory neuropathy, respectively.

### *Prolonged cytopenia*

Seventeen (44.7%) subjects experienced prolonged cytopenia ( $\geq$ Grade 3 neutropenia, anemia, or thrombocytopenia persisting for  $\geq$ 4 weeks). This includes four subjects with SAEs of platelet count decrease, pancytopenia, aplastic anemia, neutrophil count decrease, and platelet count decrease. Five subjects with prolonged cytopenia had receive the highest LD chemotherapy regimen. Subjects in the SS subgroup experienced more neutropenia (43.8% vs. 23.7%) and thrombocytopenia (37.5% vs. 26.3%) compared to the overall population.

### Long-term follow-up

Among the 20 (52.6%) subjects who entered the LTFU phase, the following TEAEs were reported: decreased platelet count (related to LD chemotherapy), myelodysplastic syndrome (not related), and sepsis (fatal; not related).

### Radiation therapy substudy

Study ADP-0044-001R was a low dose radiation therapy substudy within Study ADP-0044-001 to evaluate the safety and tolerability of low dose radiation in combination with afamitresgene autoleucel. Among the eight initially enrolled subjects, four received radiation treatment following lymphodepleting chemotherapy and infusion with afamitresgene autoleucel and one subject received radiation 1.5 years after afamitresgene autoleucel infusion. One of the patients who received radiation treatment was in the SS subgroup. Of the five subjects who received radiation treatment, one subject experienced ICANS considered related to T-cell infusion and one subject experienced myocarditis as a sequelae of CRS. The Sponsor considered the safety profile comparable to those who did not receive radiation therapy.

*Reviewer comments: The studies submitted in support of this BLA are open-label, single-arm trials that lack a placebo control. This is a significant limitation, which introduces substantial uncertainty when assessing for causal relationships between reported AEs and the study treatment. Furthermore, the study population for each study (especially for those with SS) is relatively small, which further limits our ability to detect and determine the relationship to study treatment for specific AEs. Finally, the study population included subjects with advanced malignancies, most of whom had received substantial amounts of cytotoxic chemotherapy before the study – factors which increase these subjects’ risk for serious adverse events and death (irrespective of study treatment). Nonetheless, review of the submitted clinical safety data demonstrates that LD chemotherapy followed by afamitresgene autoleucel is associated with a high frequency of AEs, of which SAEs and ≥Grade 3 reactions are common and also which includes fatal, treatment-related AEs (aplastic anemia, cerebrovascular accident). Although a wide range of treatment-related SAEs were reported, CRS and prolonged cytopenia appeared to be the most common, clinically significant safety concerns across studies, and this is reflected in their inclusion as Important Identified Risks in the proposed Pharmacovigilance Plan (PVP) (BLA 125789/0.1).*

## **6 SUMMARY OF POSTMARKETING EXPERIENCE**

Not applicable. TECELRA has not yet been approved for marketing in any country.

## **7 SPONSOR’S PHARMACOVIGILANCE PLAN**

A summary of the Sponsor’s Pharmacovigilance Plan (PVP) is provided in Table 5 below. In addition to routine pharmacovigilance activities (adverse event reporting, signal detection, periodic safety reporting), the Sponsor also plans a Post-Authorization Safety Study (PASS) to further evaluate multiple safety concerns in the PVP, including the important potential risk of secondary malignancy.

**Table 5. Sponsor’s Pharmacovigilance Plan**

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	Cytokine release syndrome	Routine PV Follow-up of cases Individual and aggregate review of cases

		PASS
	Prolonged cytopenia	Routine PV Follow-up of cases Individual and aggregate review of cases PASS
Important Potential Risk	Infections	Routine PV Follow-up of cases Individual and aggregate review of cases PASS
	Neurologic toxicity (including ICANS)	Routine PV Follow-up of cases Individual and aggregate review of cases PASS
	Secondary malignancy (including vector insertion site)	Routine PV Expedited reporting of secondary malignancies of T-cell origin Follow-up of cases Individual and aggregate review of cases PASS
Missing Information	Long-term safety	Routine PV PASS
	Safety in pediatric population	Routine PV Follow-up of cases Individual and aggregate review of cases
	Safety in elderly patients above 75 years	Routine PV Follow-up of cases Individual and aggregate review of cases PASS
	Safety during pregnancy following T-cell therapy	Routine PV Follow-up of cases PASS
	Generation of replication competent lentivirus	Routine PV Follow-up of cases
	New occurrence or exacerbation of autoimmune disorders	Routine PV Follow-up of cases

Abbreviations: PV = pharmacovigilance, PASS = post-authorization safety study

\*Adapted from Tables 12, Pharmacovigilance Plan, STN 125789/0.1, Module 1.16.1 Risk Management (Non-REMS) and updated after review of the Pharmacovigilance Plan submitted to STN 125789/0.54 Module 1.16.1 Risk Management (Non-REMS)

### 7.1 Enhanced Pharmacovigilance

Aside from the PASS described in the next subsection, the Sponsor did not propose any additional pharmacovigilance activities beyond those required in 21 CFR 600.80. However, in an information request response received on June 20, 2024 (BLA 125789/0.54), the Sponsor agreed to the following enhanced pharmacovigilance for secondary malignancies:

- 1) Submit expedited (15-day) reports for all secondary malignancies of T-cell origin, regardless of seriousness of the event or label status.
- 2) In your periodic safety reports,
  - a) Provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies, and specifically for T-cell malignancies. In your assessments, specify the data sources for reports of secondary T-cell malignancy, i.e., clinical trial data, or data from postmarketing safety study(ies), or data from postmarketing spontaneous reports.
  - b) Please include a summary of any available interim reports, as applicable, for your ongoing long term follow up (LTFU) postmarketing safety study(ies) to assess a serious risk of secondary malignancies occurring after treatment with TECELRA.

## **7.2 Safety-related Post-marketing Study (CM21-177)**

*Note: Draft protocol versions 0.3 and 0.4 were reviewed for this original BLA submission.*

### Study title

A Cellular Therapy Prospective Multi-Annual Post-Authorization Safety Study for Afamitresgene Autoleucel (Protocol number CM21-177)

### Study design

This study is a prospective, noninterventional (observational) study that utilizes an established cellular therapy database managed by the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR cellular therapy database is currently being utilized for all commercially approved CAR T therapies in the US.

### Objectives

The primary objective is to evaluate the development of all secondary malignancies (SMs) after administration of afamitresgene autoleucel in the postmarketing setting. Secondary objectives include assessments of overall survival and causes of death, hematologic SMs (particularly T-cell neoplasms due to lentiviral integration into the host genome), additional safety outcomes of interest (CRS, hemophagocytic lymphohistiocytosis [HLH], ICANS, tumor lysis syndrome [TLS], prolonged cytopenias, and clinically significant infections), and pregnancy outcomes.

### Study population

Patients treated with afamitresgene autoleucel in the postmarketing setting in the US for unresectable/metastatic synovial sarcoma. The target sample size is 300 patients treated at approximately 18 infusion centers. The target sample size is expected to be large enough to detect at least one SM event with a 95% probability, assuming an SM rate of 1%. The accrual goal is estimated to take 5 years.

### Variables

The study will include a broad range of patient-related, disease-related, and treatment-related variables, as outlined in protocol section 9.4.

#### Follow-up and study duration

Participating infusion centers will submit data to CIBMTR at the time of T-cell therapy infusion and again during follow-up visits at 100 days, 6 months, 12 months, then yearly thereafter. Subjects will be followed until death, loss to follow-up, withdrawal of consent, or up to 15 years, whichever occurs first.

#### Data collection and biospecimen data

Participating infusion centers will submit data to CIBMTR electronically using a data collection infrastructure that is already in place. CIBMTR conducts regular data validation and management procedures throughout the study.

Infusion centers are encouraged to report SMs to Adaptimmune LLC within 72 hours of their awareness of an SM. When an infusion center reports to the CIBMTR that a patient has developed an SM, the CIBMTR will notify Adaptimmune LLC within 2 calendar days. Biospecimen collection is strongly recommended for all SMs (except for non-melanoma skin cancer) and Adaptimmune LLC will offer testing to detect the persistence of afamitresgene autoleucel for all SMs. If persistence is detected, integration site analysis will be performed. Biospecimen collection may be done using CIBMTR biorepository services.

#### Data analysis

Continuous variables will be described using N, mean, standard deviation, median, minimum, maximum, and range. Categorical variables will be described using frequency and percentage of participants in each category. Cumulative incidence will be calculated for development of SMs, competing risks outcomes, and hematologic recovery of neutrophils and platelets. The Kaplan-Meier method will be used to evaluate overall survival.

#### AE reporting

The CIBMTR Research Database does not capture safety data in the same way clinical trials do (i.e., sufficiently detailed information to generate individual case safety reports). Therefore, CIBMTR does not intend to submit safety data in the form of AE reports. However, individualized pseudonymized data will be shared with Adaptimmune LLC, which will allow for signal detection using CIBMTR collected safety data.

#### Limitations

Because this is a secondary database that relies on voluntary reporting, not all patients treated with TECELRA in the postmarketing setting will necessarily be included in the study. In addition, because this is a non-interventional/observational study, patient assessments will be at the discretion of the treating physician, so there may be variability in how patients are assessed for certain clinical outcomes when patients report symptoms to their treating physician. Lastly, loss to follow up is expected given the advanced condition of participants at enrollment and the long duration of follow up.

### Milestones

Milestone dates, including start of data collection, end of data collection, study progress report dates, interim report dates, and final study report dates, are described in the protocol as “to be determined.” Interim analyses are planned for 5, 10, and 15 years post-approval.

*Reviewer comment: This reviewer presented the aforementioned postmarketing safety study to the Safety Working Group (SWG) on May 23, 2024, and recommended that it be considered a Title IX Postmarketing Requirement (PMR). The rationale included 1) to be consistent with FDA guidance which recommends 15-year long term follow-up (LTFU) for gene therapies with integrating vectors (such as lentiviral vectors), 2) to identify an unexpected serious risk (secondary malignancies) when available data indicates the potential for a serious risk, and 3) to ensure consistency in regulatory requirements across products in a similar class (all CAR-T therapies have 15-year LTFU PMR studies to assess the risk of secondary malignancy). In addition, DPV performed an Active Postmarket Risk Identification and Analysis (ARIA) assessment and determined that the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA (the Sentinel program) is not sufficient to evaluate this serious risk. The evaluation of the serious risk of secondary malignancies associated with TECELRA requires a long follow up period (15 years) and collection of tumor tissue and analysis for persistence of the vector used in TECELRA, which is not feasible in claims-based data sources like the CBER Sentinel program. SWG concurred with the recommendation to classify this postmarketing safety study as a PMR and there was general consensus regarding the proposed sample size of 300 patients.*

*On June 7, 2024, DPV sent the Sponsor an Information Request providing feedback on the proposed study protocol and requesting enhance pharmacovigilance for all secondary malignancies of T-cell origin. On June 20, 2024, the Sponsor responded and provided an updated study protocol and an updated PVP. The Sponsor made clarifications and agreed to changes we recommended in the protocol. The Sponsor also provided additional details on the testing of secondary malignancies identified in the postmarketing setting, which this reviewer deferred to CMC for further review in an email on June 24, 2024. This reviewer reviewed the updated study protocol (Protocol version 0.4 [Draft], dated June 18, 2024) and did not have any immediate follow up questions or comments.*

*On July 8, 2024, in response to discussions with the clinical review team, DPV sent the Sponsor an information request asking for additional details regarding the proposed sample size of 300 patients. On July 11, 2024, the Sponsor responded (BLA 125789/0.73), providing their rationale in further detail. On July 16, 2024, after review of the Sponsor’s response, DPV agreed with the Sponsor’s proposed sample size of 300 and recommended to OTP that the sample size not be lowered, but would defer to OTP on final language for the approval letter. In addition, on July 16, 2024 (BLA 125789/0.79), the Sponsor also provided milestone dates for the study as follows:*

- Final protocol submission: October 31, 2024*

- Study completion date: December 31, 2044
- Final study report (FSR) submission: October 31, 2045

*On July 9, 2024, FDA sent the Sponsor a Postmarketing Requirement (PMR) Notification Letter, which included notice that FDA will require the following study: “A postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with afamitresgene autoleucel. This study will enroll patients with synovial sarcoma who received treatment with afamitresgene autoleucel. The enrolled patients will be followed for 15 years after product administration.” In addition, FDA requested that the Sponsor submit milestone dates and a protocol number for this study.*

### **7.3 Risk Evaluation and Mitigation Strategy (REMS)**

The Sponsor did not propose a REMS in this original BLA submission. Of note, each of the 6 currently FDA-approved chimeric antigen receptor T (CAR T) therapies<sup>3</sup> has a REMS with the following goal:

“The goals of the [CAR T product name] REMS are to mitigate the risks of cytokine release syndrome (CRS) and neurologic toxicities by:

1. Ensuring that hospitals and their associated clinics that dispense [CAR T product name] are specially certified and have on-site immediate access to tocilizumab.”

On several occasions, the review team discussed whether to require a REMS for TECELRA to mitigate the risks of CRS and neurologic toxicities. At the mid-cycle meeting on March 20, 2024, this reviewer noted this product is associated with serious risks of CRS and neurological toxicities (including immune effector cell-associated neurotoxicity syndrome [ICANS]) and that all six currently FDA-approved adoptive T-cell therapies (all CAR T products) have a REMS to mitigate the risks of CRS and neurological toxicities.

At a Safety Working Group meeting on April 25, 2024, given the similar safety profile of TECELRA compared to approved CAR T products, it was determined that a REMS is needed to mitigate the risks of CRS and neurologic toxicities. Specifically, the REMS would be aligned with those of CAR T products, to ensure that hospitals and their associated clinics that dispense TECELRA are specially certified and have on-site, immediate access to tocilizumab. OBPV/DPV agreed with and supported this decision. However, prior to the applicant late-cycle meeting on May 20, 2024, OTP advised the sponsor that “Currently, a Risk Evaluation Mitigation Strategy (REMS) is not anticipated.”

At a Safety Working Group meeting on May 23, 2024, OTP presented their rationale for not requiring a REMS. OTP stated that the risks of CRS and neurological toxicities

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<sup>3</sup> Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltacabtagene autoleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), Yescarta (axicabtagene ciloleucel)



could be managed through labeling alone, because the medical community is now familiar with managing these risks with tocilizumab. In addition, OTP noted that tocilizumab is currently only FDA approved for CAR-T therapy-induced CRS, and from a regulatory perspective it would be inconsistent to have a REMS that required off label use of a medication.

*Reviewer comment: OBPV/DPV defers to the product office for the final decision regarding a REMS for TECELRA.*

## **8 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN**

### **8.1 Important Identified Risks**

#### **8.1.1 Cytokine Release Syndrome**

CRS is characterized by a large, rapid release of cytokines into the bloodstream in response to T-cell activation and proliferation. Signs and symptoms of CRS include fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing [5]. CRS can lead to life-threatening complications such as cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation [6]. CRS is considered a class effect of adoptive cell therapies and has been observed following administration of chimeric antigen receptor T (CAR T) therapies [7].

In the clinical safety data reviewed for this BLA, CRS was a commonly reported AE following administration of afamitresgene autoleucel. According to the Safety Update Report, in the Pooled SS cohort (n=96), 76% of subjects experienced CRS, including 2 (2.1%) Grade 3 cases and one (1%) Grade 4 case. This is comparable to the CRS frequencies reported for CAR T products, according to this reviewer's assessment of currently approved United States Package Inserts (USPIs) for CAR T products.

To address this safety concern in the postmarketing setting, the Sponsor proposes routine pharmacovigilance, follow-up and thorough evaluation of cases, cumulative medical review of postmarketing reports as part of signal management, medical review of individual case reports, and medical review of serious cases from clinical studies. Lastly, the Sponsor plans to further assess this safety concern in the PASS.

The proposed Package Insert (BLA 125789/0.8) includes a Boxed Warning that describes the risk of CRS as potentially severe or life-threatening. The Boxed Warning directs the reader to section 2.4 Dosage and Administration, which outlines supportive care and treatment for CRS, and section 5.1 Warnings and Precautions, which characterizes the risk in more detail and provides further guidance (e.g., having at least two doses of tocilizumab available for each patient prior to infusion, monitoring patients daily for at least 7 days in a healthcare facility, advising patients to monitor for CRS for 4 weeks after infusion). The text in the proposed Package Insert describes this risk as life-threatening, conveys how common CRS is in subjects who received TECELRA, and provides guidance on management.

*Reviewer comment: As mentioned above, the OTP clinical review team determined that a REMS is not needed and that the risk of CRS can be adequately managed through labeling.*

### **8.1.2 Prolonged Cytopenia**

Prolonged cytopenia is an expected hematologic adverse event following LD and has been reported after use of CAR T therapies [3]. Cytopenia can be unilineage, bilineage, or multilineage, manifesting as anemia, thrombocytopenia, and/or leukopenia (or more specifically, neutropenia), which in turn can increase risk for infections, bleeding, and various anemia-related symptoms [8, 9]. Complications of cytopenia can be life-threatening or fatal.

In the clinical safety data reviewed for this BLA, prolonged cytopenia at Week 4 was a commonly reported AE following administration of afamitresgene autoleucel. According to the Safety Update Report, in the Pooled SS cohort (n=96), 21.9% of subjects experienced prolonged cytopenia, which were all by definition Grade 3 or higher and included anemia (10.4%), thrombocytopenia (11.5%), and neutropenia (14.6%).

To address this safety concern in the postmarketing setting, the Sponsor proposes routine pharmacovigilance, follow-up and thorough evaluation of cases, cumulative medical review of postmarketing reports as part of signal management, medical review of individual case reports, and medical review of serious cases from clinical studies. Lastly, the Sponsor plans to further assess this safety concern in the PASS.

The proposed Package Insert (BLA 125789/0.8) includes a Warnings and Precautions subsection (5.2 Prolonged Cytopenias) which describes the risk and provides monitoring and management recommendations.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for prolonged cytopenia are adequate.*

## **8.2 Important Potential Risks**

### **8.2.1 Infections**

People living with cancer can experience an increased risk for infection due to the cancer itself and/or the treatment associated with cancer [10]. Specifically, lymphodepleting therapy can cause leukopenia, which can increase the risk for severe viral, bacterial, and fungal infections [3].

In the clinical safety data reviewed for this BLA, infections were commonly reported following administration of afamitresgene autoleucel. According to the Safety Update Report, in the Pooled SS cohort (n=96), 33.3% of subjects experienced any infection (any grade), and 11.5% of subjects experienced ≥Grade 3 infections. The most commonly reported infections (any grade) were Nasopharyngitis (n=4), followed by Pneumonia, Upper respiratory tract infection, and Urinary tract infection (n=3 each). Most reports of infections caused by specific pathogens (e.g., Klebsiella infection) were

only reported once and there was no pattern or trend in AEs concerning for a specific type of infection.

To address this safety concern in the postmarketing setting, the Sponsor proposes routine pharmacovigilance, follow-up and thorough evaluation of cases, cumulative medical review of postmarketing reports as part of signal management, medical review of individual case reports, and medical review of serious cases from clinical studies. Lastly, the Sponsor plans to further assess this safety concern in the PASS.

The proposed Package Insert (BLA 125789/0.8) includes a Warnings and Precautions subsection (5.4 Infections) which describes the risk of infection following lymphodepleting chemotherapy and TECELRA infusion and provides guidance on monitoring for and preventing infection and viral reactivation.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for infections are adequate.*

### **8.2.2 Neurologic toxicity (including ICANS)**

Neurotoxicity, including ICANS, is a known and potentially life-threatening complication of CAR T cell therapy. ICANS is associated with increased cerebrospinal fluid (CSF) cytokine levels and disruption of the blood-brain barrier. ICANS can present with a broad range of neurologic symptoms, including “confusion, headache, attention deficits, word finding difficulties, focal neurological deficits, or encephalopathy to life threatening cerebral edema, transient coma, or seizures” [11].

In the clinical safety data reviewed for this BLA, neurologic toxicity was commonly reported following administration of afamitresgene autoleucel. Specifically, 61.4% of subjects in SS Cohort 1 and 65% of subjects in SS Cohorts 1 & 2 experienced any neurologic AE, with ≥Grade 3 neurologic AEs reported among 6.8% and 5% of subjects, respectively. Grade 1 ICANS was reported in 1 subject (2.3%) in SS Cohort 1 and in 2 subjects (2.5%) in SS Cohorts 1 & 2. The most common neurologic AEs in SS Cohorts 1 & 2 were headache (28.8%), dizziness (13.8%), insomnia (10%), and anxiety (7.5%).

To address this safety concern in the postmarketing setting, the Sponsor proposes routine pharmacovigilance, follow-up and thorough evaluation of cases, cumulative medical review of postmarketing reports as part of signal management, medical review of individual case reports, and medical review of serious cases from clinical studies. Lastly, the Sponsor plans to further assess this safety concern in the PASS.

The proposed Package Insert (BLA 125789/0.8) includes a Warnings and Precautions subsection (5.3 Immune Effector Cell-associated Neurotoxicity Syndrome [ICANS]) which describes the risk of ICANS following TECELRA infusion and provides guidance on monitoring for symptoms for 4 weeks following treatment.

*Reviewer comment: As mentioned above, the OTP clinical review team determined that a REMS is not needed and that the risk of neurologic toxicity (including ICANS) can be adequately managed through labeling.*

### **8.2.3 Secondary malignancy (including vector insertion site)**

Because lentiviral vectors integrate into the human genome, they have the potential to activate oncogenes or inactivate tumor suppressor genes, resulting in oncogenesis [12]. CAR T cell therapies, which also use integrating vectors, have recently been associated with the development of secondary T-cell malignancy, resulting in class safety labeling changes for all CAR T products [13]. To monitor for the risk of oncogenesis and other potential gene therapy-related delayed adverse events, FDA has provided guidance to industry that recommends 15 years of long term follow-up after administration of integrating vectors (such as gammaretroviral and lentiviral vectors) [14].

In the clinical safety data reviewed for this BLA, there were no reports of insertional oncogenesis, clonal predominance, or malignancy of T-cell origin observed in association with TECELRA for a maximum follow-up time of 39 months. Of note, there were secondary malignancies observed in the supportive clinical studies (specifically, myelodysplastic syndrome and Epstein-Barr-positive lymphoproliferative disease) but these were not considered related to T-cell therapy.

To address this safety concern in the postmarketing setting, the Sponsor proposes routine pharmacovigilance, follow-up and thorough evaluation of cases, cumulative medical review of postmarketing reports as part of signal management, medical review of individual case reports, and medical review of serious cases from clinical studies. According to the study protocols for Study ADP-0044-002 (BLA 125789/0.1) and Study ADP-0044-001 (BLA 125789/0.1), all subjects will be followed for 15 years from the time of T cell infusion for observation of delayed AEs in accordance with FDA requirements for gene therapy clinical trials. Lastly, the Sponsor plans to further assess this safety concern (as the primary objective) in the PASS.

The proposed Package Insert (BLA 125789/0.8) includes a Warnings and Precautions subsection (5.5 Secondary Malignancies) which describes the risk of secondary malignancy or recurrence of their cancer following TECELRA infusion and advises that Adaptimmune be contacted in the event of a secondary malignancy so that patient samples can be collected for testing.

As mentioned above, the Sponsor agreed to enhanced pharmacovigilance for secondary malignancy, including expedited (15-day) reporting for all secondary malignancies of T-cell origin, regardless of seriousness of the event or label status.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for secondary malignancies are adequate.*

## **8.3 Important Missing Information**

### **8.3.1 Long-term safety**

As mentioned above, lentiviral vectors carry a potential risk of secondary malignancy. This and other potential gene therapy-related delayed adverse events could be observed once TECELRA is used in a larger population for a longer period of time than in current clinical trials.

The sponsor plans to address this missing information through routine pharmacovigilance and the PASS.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for long-term safety are adequate.*

### **8.3.2 Safety in pediatric population**

Subjects < 16 years of age were excluded from Cohort 1 of Study ADP-004-002. Therefore, safety in pediatric population is considered missing information.

The sponsor plans to address this missing information through routine pharmacovigilance, follow-up of cases, and individual and aggregate review of cases.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for safety in pediatric population are adequate.*

### **8.3.3 Safety in elderly patients above 75 years**

Study ADP-0044-002 included subjects aged 16 to  $\leq 75$  years. In the clinical development program, there were 6 subjects with synovial sarcoma aged 65 years and older. The incidence of serious treatment-related AEs was higher in this group than those younger than 65 years of age (50% vs. 28%). However, the low number of subjects precludes drawing definitive conclusions about safety in older subjects. Therefore, safety in elderly patients above 75 years is considered missing information.

The sponsor plans to address this missing information through routine pharmacovigilance, follow-up of cases, individual and aggregate review of cases, and the PASS.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for safety in elderly patients above 75 years are adequate.*

### **8.3.4 Safety during pregnancy following T-cell therapy**

The target antigen of TECELRA is expressed in fetal germ line tissue and placenta. In addition, lymphodepleting chemotherapy may harm fetal development and the use of fludarabine and cyclophosphamide is contraindicated during breastfeeding. Subjects who were pregnant, or intending to become pregnant, or breastfeeding, were excluded from TECELRA studies. No pregnancies occurred in the clinical studies. Since the safety of TECELRA during pregnancy has not been established in humans, safety during pregnancy following T-cell therapy is considered missing information.

The sponsor plans to address this missing information through routine pharmacovigilance, follow-up of cases, and the PASS.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for safety during pregnancy following T-cell therapy are adequate.*

### **8.3.5 Generation of replication competent lentivirus**

Although TECELRA is prepared using a replication-incompetent lentivirus that is used for transduction of T-cells, the possibility of unintentional recombination leading to a replication-competent and pathogenic virus exists [12].

The sponsor plans to address this missing information through routine pharmacovigilance and follow-up of cases.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for generation of replication competent lentivirus are adequate.*

### **8.3.6 New occurrence or exacerbation of autoimmune disorders**

Subjects with a history of autoimmune or immune-mediated disease were excluded from Study ADP-0044-002. Similarly, subjects with a history of chronic or recurrent severe autoimmune or immune-mediated disease requiring steroids or other immunosuppressive treatments were excluded from Study ADP-0044-001. Therefore, new occurrence or exacerbation of autoimmune disorders is considered missing information.

The sponsor plans to address this missing information through routine pharmacovigilance and follow-up of cases.

*Reviewer comment: The Sponsor's proposed pharmacovigilance activities for new occurrence or exacerbation of autoimmune disorders are adequate.*

## **9 DPV ASSESSMENT**

Review of Sponsor-submitted safety data demonstrated that TECELRA is associated with a high frequency of treatment-emergent adverse events, including a broad range of serious adverse events and several fatal adverse events. However, due to limitations in the submitted clinical data (small, open-label, single-arm studies in populations with advanced comorbidity and prior chemotherapy), it is unknown whether many reported adverse events were attributable to TECELRA, the preceding lymphodepleting chemotherapy, the patient's underlying disease, or prior treatments. In addition, because of the small sample sizes in the clinical trials, serious risks that were not observed in the clinical trials could emerge in the postmarketing setting, once the product is used in a larger, more diverse patient population. Nonetheless, trends in adverse events observed suggest that the most consistently observed serious risks in the clinical trials were appropriately included as important risks in the proposed Pharmacovigilance Plan (PVP). Because TECELRA has not yet been approved for marketing in any country, there were no postmarketing safety data available for review. Notwithstanding these limitations, this reviewer concluded that the Sponsor's proposed PVP (submitted to BLA 125789/0.54 on June 20, 2024) is acceptable.

The Sponsor agreed to enhanced pharmacovigilance for reporting of secondary malignancies of T-cell origin regardless of seriousness or label status. In addition, the Sponsor was notified (on July 9, 2024) that the proposed PASS would be a Postmarketing Requirement (PMR). Lastly, as noted previously, the OTP clinical review

team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not needed for TECELRA.

## 10 DPV RECOMMENDATIONS

Should this original BLA be approved, OBPV/DPV has the following recommendations for postmarketing safety monitoring of TECELRA:

1. The Sponsor should perform routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
2. The Sponsor should submit expedited (15-day) reports for all secondary malignancies of T-cell origin, regardless of seriousness of the event or label status.
  - a. In their periodic safety reports,
    - i. Provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies, and specifically for T-cell malignancies. In their assessments, specify the data sources for reports of secondary T-cell malignancy, i.e., clinical trial data, or data from postmarketing safety study(ies), or data from postmarketing spontaneous reports.
    - ii. Include a summary of any available interim reports, as applicable, for your ongoing long term follow up (LTFU) postmarketing safety study(ies) to assess a serious risk of secondary malignancies occurring after treatment with TECELRA.
3. Require as a Postmarketing Requirement (PMR) a postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with afamitresgene autoleucel. (PMR Notification letter sent July 9, 2024).

As mentioned above, the OTP clinical review team determined that the available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS). There is no postmarketing commitment (PMC) for a safety study for this product.

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## APPENDIX

### Materials Reviewed

**Table A1: Materials reviewed in support of this assessment**

Date	Source	Document Type	Document(s) Reviewed
30-Mar-2023	Sponsor	BLA 125789/0.1	1.16.1 Risk Management (Non-REMS), Pharmacovigilance Plan
30-Mar-2023	Sponsor	BLA 125789/0.1	1.16.1 Risk Management (Non-REMS), Post-approval Safety Registry – Proposed Protocol
30-Mar-2023	Sponsor	BLA 125789/0.1	2.5 Clinical Overview
30-Mar-2023	Sponsor	BLA 125789/0.1	5.3.5.2 Study Reports of Uncontrolled Clinical Studies, ADP-0044-001, Main Study Report
30-Mar-2023	Sponsor	BLA 125789/0.1	5.3.5.2 Study Reports of Uncontrolled Clinical Studies, ADP-0044-002, Study Report Body
30-Mar-2023	Sponsor	BLA 125789/0.1	5.3.5.4 Other Study Reports, ADP-0044-001R, Synopsis
22-Feb-2024	Sponsor	BLA 125789/0.8	5.3.5.3 Reports of Analyses of Data from More than One Study, Safety Update Report (SUR)
22-Feb-2024	Sponsor	BLA 125789/0.8	1.14.1.3 Draft Labeling Text- USPI Version 0.2, Medication Guide Version 0.2
20-Jun-2024	Sponsor	BLA 125789/0.54	1.11.3 Clinical Information Amendment – Response to DPV IR 1 dated June 7, 2024
20-Jun-2024	Sponsor	BLA 125789/0.54	1.16.1 Risk Management Plan (Non-REMS) – Pharmacovigilance Plan (Clean and Tracked Changes)
20-Jun-2024	Sponsor	BLA 125789/0.54	1.16.1 Risk Management Plan (Non-REMS) – Post-approval Safety Registry – Proposed Protocol – (Clean Version and Redlined Version)
11-Jul-2024	Sponsor	BLA 125789/0.73	1.11.3 Clinical Information Amendment – Response to DPV IR 2 dated July 8, 2024
16-Jul-2024	Sponsor	BLA 125789/0.79	1.17.2 Correspondence Regarding Postmarketing Requirements

**Table A2: DPV Information Requests and Sponsor Responses**

IR #	IR sent	Description of IR	Sponsor response received	STN
DPV IR #1	07-Jun-2024	Feedback on post-authorization safety study; request for enhanced pharmacovigilance for secondary malignancies of T-cell origin	20-Jun-2024	BLA 125789/0.54
DPV IR #2	08-Jul-2024	Rationale for proposed sample size for post-authorization safety study	11-Jul-2024	BLA 125789/0.73

DPV IR #3	10-Jul-2024	Response to Sponsor's questions about submitting milestone dates and PMR final protocol	16-Jul-2024	BLA 125789/0.79
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Abbreviations: Division of Pharmacovigilance (DPV), Information Request (IR), submission tracking number (STN)