

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original Biologic License Application
Application Number(s)	125789/0
Priority or Standard	Priority
Submit Date(s)	December 5, 2023
Received Date(s)	December 5, 2023
PDUFA Goal Date	August 2, 2024
Division/Office	Division of Clinical Evaluation Oncology/ Office of Therapeutic Products
Review Completion Date	July 31, 2024
Established Name	Afamitresgene autoleucel
(Proposed) Trade Name	TECELRA
Pharmacologic Class	Melanoma-associated antigen A4 (MAGE-A4) directed, genetically modified autologous T cell immunotherapy
Code name	ADP-A2M4
Applicant	Adaptimmune LLC
Formulation(s)	Intravenous infusion
FDA Recommended Dosing Regimen	A single dose containing 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells provided in one or more infusion bag(s)
Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	Priority Review
Recommended Indication(s)/Population(s) (if applicable)	TECELRA is a melanoma-associated antigen A4 (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.

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NDA/BLA Multi-disciplinary Review and Evaluation BLA 125789
TECELRA (afamitresgene autoleucel)

Abbreviations: BIMO, bioresearch monitoring; CMC, Chemistry, Manufacturing, and Controls; DBSQC, Division of Biological Standards and Product Quality; DCEO, Division of Clinical Evaluation Oncology; DMPQ, Division of Manufacturing and Product Quality; DPV, Division of Pharmacovigilance; MORE, Medical Oncology Review and Evaluation; OBPV, Office of Biostatistics and Pharmacovigilance; OPPT, Office of Plasma Protein Therapeutics; RPM, Regulatory Project Manager; TEB, Therapeutics Evaluation Branch

Glossary

ACA	anterior cerebral artery
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the concentration-time curve
AUC _{D0-D7}	Area under the concentration-time curve from Day 0 to Day 7
AUC _{D0-D28}	Area under the concentration-time curve from Day 0 to Day 28
AUC _{D0-D3M}	Area under the concentration-time curve from Day 0 to Month 3
AUC _{D0-D6M}	Area under the concentration-time curve from Day 0 to Month 6
BLA	Biologics license application
BOR	Best overall response
BW	Body weight
CAR T	Chimeric antigen receptor T cell
CARTOX	chimeric antigen receptor T cell therapy associated toxicity
CBER	Center for Biologics Evaluation and Research
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CI	Confidence interval
C _{max}	Maximum concentration in circulation
CMC	Chemistry, manufacturing, and controls
CMV	cytomegalovirus
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
E-R	Exposure-response
EBV	Epstein-Barr virus

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ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-3L	European Quality of Life-5 Dimensions 3 Response Levels
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GCP	Good clinical practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
HLA	Human leukocyte antigen
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN γ	Interferon γ
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	Interleukin
IND	Investigational New Drug
iPS	Induced pluripotent stem
IRC	Independent Review Committee
ISS	Integrated summary of safety
ITT	Intent-to-treat
IV	Intravenous
LD	lymphodepleting
LTFU	Long-term follow-up
LV	Lentiviral vector
MAGE-A4	Melanoma-associated antigen 4
max	Maximum
MCA	middle cerebral artery
MDACC/RM	MD Anderson Cancer Center and The Royal Marsden National Health Service Foundation Trust
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
min	Minimum
mITT	Modified intent-to-treat
MRCLS	Myxoid/round cell liposarcoma
mSS	metastatic synovial sarcoma
NCA	Noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

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TECELRA (afamitresgene autoleucel)

NDA	New drug application
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PARP	poly ADP-ribose polymerase
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PFS	Progression-free survival
PICA	posterior inferior cerebellar artery
PICC	peripherally inserted central catheter
PK	Pharmacokinetics
PR	Partial response
PRO	patient reported outcome
PT	Preferred term
RBC	Red blood cell
RCL	Replication competent lentivirus
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk evaluation and mitigation strategy
RT-PCR	Reverse Transcription - Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SCA	superior cerebellar artery
SCS	Summary of Clinical Safety
SLD	Sum of longest diameter
SOC	System organ class
SS	Synovial sarcoma
STS	Soft-tissue sarcomas
SUR	Safety Update Report
TCR	T cell receptor
TCR-T	T cell receptor (engineered) T cells
TEAE	Treatment emergent adverse event
TESAE	Treatment-emergent serious adverse event
TTR	Time to response
USPI	United States Prescribing Information
VCN	Vector copy number
WBC	White blood cell

1. Executive Summary

1.1 Product Introduction

The FDA's Assessment:

[On December 5, 2023, Adaptimmune (the Applicant) submitted a Biologic License Application (BLA), seeking an indication for TECELRA (afamitresgene autoleucel) for 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.]

Afamitresgene autoleucel is a genetically modified autologous T cell immunotherapy consisting of cluster of differentiation (CD) 4 and CD8 positive T cells transduced with a self-inactivating lentiviral vector (LV) expressing an enhanced-affinity T cell receptor (TCR) specific for the human melanoma-associated antigen A4 (MAGE-A4). Autologous T cells transduced with the LV express the enhanced-affinity TCR on the cell surface. The TCR recognizes a human leukocyte antigen (HLA)-A*02 restricted MAGE-A4 peptide.]

1.2 Conclusions on the Substantial Evidence of Effectiveness

[Substantial evidence of effectiveness was demonstrated in Study ADP-0044-002 Cohort 1, a Phase 2 single-arm, open label, multi-cohort, multicenter, multiregional (United States, Europe, and Canada) study in adults with unresectable or metastatic synovial sarcoma (mSS) who have received prior chemotherapy. The study included patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1 , prior anthracycline or ifosfamide containing regimen, positive for HLA-A*02:01, HLA-A*02:03 or HLA-A*02:06 allele, with tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of $\geq 2+$ staining in $\geq 30\%$ of the cells by immunohistochemistry and measurable disease according to RECIST v1.1. The study excluded patients who were positive for HLA-A*02:05, on systemic corticosteroids for at least 14 days prior to leukapheresis and lymphodepletion, and had received or planned to receive allogeneic hematopoietic stem cell transplant or gene therapy using an integrating vector prior to leukapheresis or lymphodepleting chemotherapy. The treatment consisted of a single intravenous (IV) infusion of 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells following lymphodepletion with fludarabine and cyclophosphamide. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. Afamitresgene autoleucel was administered 4 days following completion of lymphodepleting chemotherapy.]

Efficacy:

The primary efficacy outcome measure in Study ADP-0044-002 Cohort 1 was overall response rate (ORR) as assessed by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). The study also evaluated durability of response as a key outcome measure. The efficacy evaluable population consisted of patients with SS who received afamitresgene autoleucel in Cohort 1 of ADP-0044-002.

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 (see additional details in [Section 8.1.2](#) of this review). 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.

The primary efficacy analysis was performed in 44 patients with SS treated with afamitresgene autoleucel 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 afamitresgene autoleucel's effectiveness. The effects on ORR and DoR are considered clinically meaningful in this pre-treated population with limited available effective therapies.

Safety:

The primary safety analysis was performed in 44 patients with SS treated with afamitresgene autoleucel in Study ADP-0044-002 Cohort 1, and supportive safety analysis included 80 patients with SS in Study ADP-0044-002 Cohorts 1 and 2, as well as 130 patients with synovial sarcoma, MRCLS, and solid tumors from ADP-0044-002 (Cohorts 1 and 2); ADP-0044-001, which is a Phase 1 study to evaluate safety of afamitresgene autoleucel in HLA-A*02 positive patients with MAGE-A4 positive, inoperable, locally advanced or metastatic tumors; and ADP-0044-001R, a sub-study of ADP-0044-001 of low dose radiation in combination with afamitresgene autoleucel.

In the primary safety analysis of 44 patients, all deaths were due to disease under study and occurred greater than 30 days after afamitresgene autoleucel administration.

The most common adverse reactions (occurring in $\geq 20\%$) were cytokine release syndrome (CRS; 75%), nausea (70%), vomiting (36%), fatigue (34%), infections (32%) pyrexia (32%), constipation (32%), dyspnea (27%), abdominal pain (25%), non-cardiac chest pain (23%), decreased appetite (23%), tachycardia/sinus tachycardia (21%), back pain (21%), hypotension (21%), diarrhea (21%), and edema (21%). Grade 3 or higher adverse reactions included pyrexia (5%), abdominal pain (5%), back pain (5%), dyspnea (5%), CRS (2%), headache (2%), hypertension (2%), weight decreased (2%), nausea (2%), asthenia (2%), non-cardiac chest pain (2%), and decreased appetite (2%). Other adverse events of special interest (AESI) included immune effector cell-associated neurotoxicity syndrome (ICANS) of Grade 1 in one patient.

Conclusions:

The magnitude and durability of ORR demonstrated in Study ADP-0044-002 Cohort 1 establishes the effectiveness of afamitresgene autoleucel 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 afamitresgene autoleucel represents an improvement over available therapy in the intended patient population. Additional advantages of treatment with afamitresgene autoleucel include a shorter treatment course than that of available therapies in the context of an acceptable risk profile.

The overall benefit-risk profile of afamitresgene autoleucel 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) via the Boxed Warning for cytokine release syndrome and Warnings and Precautions section for ICANS, infections, prolonged severe cytopenia, secondary malignancies and hypersensitivity reactions, as well as via the Medication Guide for patients to be treated with afamitresgene autoleucel.

Continued approval is contingent upon fulfillment 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.]

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

[The benefit-risk assessment for afamitresgene autoleucel for the indicated population is based on the results of Study ADP-0044-002 Cohort 1 an open-label, multicenter, single-arm trial of afamitresgene autoleucel 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. Of note, for study population in Cohort 1, prior chemotherapy regimen included anthracycline- and/or ifosfamide-based chemotherapy. A total of 44 patients with unresectable or metastatic synovial sarcoma constituted the efficacy analysis population. The primary efficacy endpoint is overall response rate (ORR) as determined by independent response committee (IRC) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), with duration of response as a key secondary outcome measure.

The totality of the data from Study ADP-0044-002 Cohort 1 demonstrates a favorable benefit-risk for afamitresgene autoleucel as treatment for adult patients 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.

Efficacy: Study ADP-0044-002 Cohort 1 demonstrates clinically meaningful efficacy of afamitresgene autoleucel based on ORR of 43.2% (95% CI: 28.4, 59.0) supported by median duration of response of 6.0 months (95% CI: 4.6, NR) in a patient population with limited treatment options.

Additionally, afamitresgene autoleucel represents a new treatment modality with a shorter treatment course, as well as a different safety profile, than that of other therapies available for the intended patient population.

Safety: The safety profile includes cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which can be life-threatening or fatal. Some patients may develop prolonged severe cytopenia, which could result in a fatal outcome; therefore, monitoring and intervention or growth factor support may be required. Infections may occur, which could result in a fatal outcome. Patients should be evaluated for infection and managed with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. These risks may

be managed with appropriate monitoring and treatment strategies. These adverse events represent toxicities that are acceptable from a benefit-risk perspective in the intended population.

Overall benefit-risk assessment:

Afamitresgene autoleucel has an overall favorable benefit-risk profile in patients 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. Based on ORR supported by duration of response, afamitresgene autoleucel has demonstrated clinically meaningful improvement over available therapies and supports accelerated approval for the intended population.]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Synovial sarcoma (SS) is a type of soft tissue sarcoma (STS) representing approximately 5% to 10% of all histological types. SS is a rare disease, with an estimated US annual incidence of 800 to 1,000 cases a year. Advanced unresectable and metastatic synovial sarcoma has a poor prognosis, with a reported median OS of approximately 16 to 24 months. 	<ul style="list-style-type: none"> Synovial sarcoma is a serious and fatal disease.
Current Treatment Options	<ul style="list-style-type: none"> 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 mSS in the first-line setting is approximately 39%, whereas ORR in the second line setting and later ranges from 10% to 22%. 	<ul style="list-style-type: none"> The available treatment options for patients with SS remains extremely limited. There is need for more innovative therapies with high and durable response rates. Patients may benefit from short, single course treatments options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> Study ADP-0044-002 is a single-arm, open label, multi-cohort, multicenter, multiregional Phase 2 study that enrolled patients with HLA-A*02 positive, MAGE-A4 expressing, advanced synovial sarcoma who previously received either an anthracycline- or ifosfamide-containing regimen. Patients underwent leukapheresis, received lymphodepletion with fludarabine and cyclophosphamide, followed by one dose of afamitresgene autoleucel. The primary endpoint was ORR. The primary efficacy analysis was performed in 44 adult patients treated in ADP-0044-002 Cohort 1. According to the IRC re-review by the second imaging vendor, 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 KM median DOR 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 by KM estimate. 	<ul style="list-style-type: none"> ORR supported by DOR represents an improvement over available therapy in the intended patient population..
Risk and Risk Management	<ul style="list-style-type: none"> Cytokine release syndrome (CRS) is a serious adverse event which is included in the USPI Boxed Warning. At the first sign of CRS, patients should be immediately evaluated for hospitalization and treatment with supportive care should be instituted. Healthcare providers administering afamitresgene autoleucel should have immediate access to medications and resuscitative equipment to manage CRS. Additional serious adverse events include and immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged severe cytopenia, infections, secondary malignancies, and hypersensitivity reactions. Healthcare providers administering afamitresgene autoleucel should have 	<ul style="list-style-type: none"> The evidence suggests that the risk of afamitresgene autoleucel do not outweigh the benefits in adult patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>immediate access to medications and resuscitative equipment to manage ICANS.</p> <ul style="list-style-type: none">• There is theoretical risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. However, no such cases occurred by the data cut-off date in this study.	

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	Section 8.1.2
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	Section 8.1.2
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other:	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

2. Therapeutic Context

2.1 Analysis of Condition

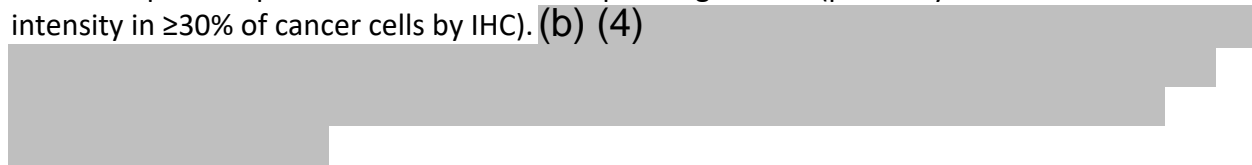
The Applicant's Position:

Synovial sarcoma (SS) is a type of soft tissue sarcoma (STS) representing approximately 5% to 10% of all histological types [Joseph 2019, Wang 2017, Stacchiotti 2018]. SS is a rare disease, with an estimated US annual incidence of 800 to 1,000 cases a year [Stacchiotti 2018], and 5-year prevalence of 0.65 per 100,000 [Joseph 2019] and affects young individuals with a median age of first clinical presentation in the third decade [Aytekin 2020]. The etiological driver of


sarcomagenesis is the t(X;18) reciprocal translocation leading to formation of the SYT-SSX fusion oncogene [Nielsen 2015]. Pathological diagnosis of SS can only be made with molecular confirmation of the respective chromosomal translocation, as per National Comprehensive Cancer Network (NCCN) guidelines, using fluorescence in situ hybridization, or fusion gene testing using RT-PCR or next-generation sequencing.

SS is a serious, life-threatening disease, with a 5-year overall and cancer-specific survival of approximately 52% and 66% respectively [Corey 2014; Sultan 2009]. Outcomes are particularly poor in the metastatic setting, with a 5-year overall survival (OS) rate after the date of diagnosis of the metastasis of 15% [Moreau-Bachelard 2022; Riedel 2018]. The lungs (including pleura) are the most common sites of metastasis, and metastasis to the lungs is the main cause of disease-specific mortality; however, intra-abdominal, bone, brain, and lymph node metastasis can also arise with lower frequency [Riedel 2018; Kreig 2011].


The human melanoma-associated antigen A4 (MAGE-A4), is a cancer-testis antigen with restricted expression in normal tissues and is overexpressed across a range of solid tumors, including SS. By immunohistochemistry (IHC), approximately 60-82% of SS tumors express MAGE-A4 [Kakimoto 2019, Iura 2017]. Based on Adaptimmune screening data in SS, 67% of HLA-A*02 positive patients have MAGE-A4 expressing tumors (positivity defined as $\geq 2+$ intensity in $\geq 30\%$ of cancer cells by IHC). (b) (4)



Three independent, retrospective studies evaluated the prognostic impact of HLA-A*02, MAGE-A4, or HLA-A*02 and MAGE-A4 in combination in SS:

- (b) (4)
- 

(b) (4)



(b) (4)

The FDA's Assessment:

[Synovial sarcoma (SS) is a rare type of soft tissue sarcoma (STS) that primarily affects adolescents and young adults with a mean age at diagnosis of 39 years ([Aytekin et al. 2020](#)). Approximately 50% of patients with SS will develop recurrent or metastatic disease ([Blay et al. 2023](#)). Advanced unresectable and metastatic SS has a poor prognosis, with a reported median OS of approximately 16 to 24 months ([Blay et al. 2023](#), [Pollack et al. 2020](#)). Favorable prognostic factors reported for metastatic SS include younger age, lung as primary metastatic site, fewer metastases, and metachronous metastases ([Blay et al. 2023](#)).

To better understand the prognostic relevance of MAGE-A4 and HLA-A*02, the Applicant provided results from two independent retrospective clinicopathological studies: (b) (4)

However, based on current information, (b) (4)

In summary, the prognostic impact of the biomarkers (MAGE-A4 and HLA-A*02) on advanced/metastatic SS is not known.]

2.2 Analysis of Current Treatment Options The Applicant's Position:

The standard of care treatment for synovial sarcoma in the localized setting is neoadjuvant radiation followed by surgical resection [[NCCN 2022](#)]. Despite this ~ 50% of synovial sarcoma

patients will develop recurrent or metastatic disease [Blay et al 2023]. Neoadjuvant or adjuvant chemotherapy can be considered in high-risk patients [NCCN 2022]. Size, grade, and location are prognostic factors for synovial sarcoma survival as well as for locally advanced disease [Blay et al 2023]. For patient's that have locally advanced disease which may be unresectable or borderline resectable disease, aggressive therapy including neoadjuvant chemotherapy (anthracycline/ifosfamide) and radiation is required to maximize the patient's chance of obtaining a surgical resection [NCCN 2022]. If a surgical resection is possible, these patients may obtain a disease-free survival benefit, but are still high risk of developing recurrence/metastatic disease and needing subsequent treatment. If a surgical resection is not possible with neoadjuvant chemotherapy and radiation, then these patients will proceed to a succession of palliative systemic chemotherapies. Because of the dose-limiting cardiotoxic effects of anthracyclines, doxorubicin may not necessarily be repeated in the first-line metastatic setting if given for neoadjuvant treatment. Additionally, the benefit obtained neoadjuvant dox/ifos chemotherapy is not expected to be different to the benefit obtained in the first-line metastatic setting. There are no curative treatment options for patients with SS in the unresectable or metastatic setting. For many types of STS, including SS, standard first-line chemotherapy for metastatic disease involves administration of single-agent doxorubicin, or in combination with ifosfamide [Casali 2018, NCCN 2022]. Despite the high response rates reported for ifosfamide-containing regimens in the first-line metastatic setting (ORR ~40%, [Moreau-Bachelard 2022]), there is no reported improvement in OS. In the second-line and beyond setting (Table 1), therapeutic options are limited and time-to-next-treatment and OS progressively worsen per subsequent line of treatment [Savina 2017]. No systemic treatment has been shown to improve OS in the second line and beyond setting. NCCN guidelines recommend systemic therapies as palliative therapies for patients with unresectable recurrent or metastatic disease and clinical trials as the preferred treatment option for patients with metastatic disease [NCCN 2022].

Pazopanib, is the only approved agent in the US for patients with STS previously treated with chemotherapy [Votrient™ USPI] (Table 1). However, in the registration-directed trial, SS represented a sub-population (N=25) of a larger STS patient pool (N= 246). Pazopanib was also not associated with an improvement in OS compared with placebo [van der Graaf 2012]. Despite being the only licensed second-line therapy in the US, real-world evidence suggests only about 12% of second-line metastatic patients are treated with pazopanib [Pollack 2020]. Trabectedin is approved in the US for patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline containing regimen [Yondelis USPI] but is used for the treatment of SS off-label [Sanfilippo 2015, Endo 2020]. Although not specifically authorized, combination gemcitabine/docetaxel chemotherapy is used for the treatment of second-line advanced STS [Casali 2018], but the therapeutic utility of this regimen in second-line and above metastatic SS is very low [Pender 2018]. Real-world evidence from large volume SS centers in the US indicate there is no standard of care in the second-line metastatic setting

with a number of different systemic therapies being utilized [[Pollack 2020](#)]. There are no approved therapies that target MAGE-A4 expression in SS.

Both clinical trial and real-world evidence has shown that ORRs for pazopanib or trabectedin are low ([Table 1](#)). Overall, there is a high unmet medical need for a novel therapy which is highly efficacious, and which could potentially improve the prognosis of patients with metastatic SS who relapse/ are refractory to first-line therapy.

Table 1: Applicant – Therapies Used for 2nd Line and Beyond Treatment of Advanced SS

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval1	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for STS					
VOTRIENT (pazopanib)	Patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy	2012 (full approval)	800 mg orally once daily	<p>Phase 3 study (Vontrient USPI, van der Graaf 2012): ORR= 4% (95% CI: 2.3, 7.9; n=246 overall STS) mPFS= 4.1 months in SS (n= 25) mOS=8.7 months in SS (Votrient SmPC)</p> <p>Meta-analysis in mSS [Carroll 2022]: ORR (N=4; n=96) =18.9% (95% CI: 8.5, 41.8); ORR in studies with n≥10 (N=3; n=78) = 15.9% (95% CI: 4.7,53.8) mPFS (N=4; n=88) = 5.3 months (95% CI: 4.2, 6.7); mPFS in studies with n≥10 (N=3; n=84) = 5.0 months (95% CI: 4.0, 6.4) mOS (N=4; n=96) = 10.3 months (95% CI: 8.4, 12.6); mOS in studies with n≥10 (N=3; n=92) = 10.5 months (95% CI: 8.2, 13.4)</p>	Phase 3 study (Vontrient USPI): Transaminase elevation, fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, skin hypopigmentation.
Other Treatments					
YONDELIS (Trabectedin)	Patients with unresectable or metastatic	2015 (off-label use in	1.5 mg/m ² body surface area as a 24h IV, every	Phase 2 study [Garcia-Carbonero	Leukopenia, neutropenia, AST and ALT

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Product (s) Name	Relevant Indication	Year of Approval And Type of Approval1	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
	liposarcoma or leiomyosarcoma who received prior anthracycline-containing regimen. *In the EU indicated for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.	STS) *In the EU approval for STS in 2007 under exceptional circumstances; full approval in 2015	3 weeks	2004): ORR= 8% (STS overall; n= 36). No responses in SS (n=6). <u>Phase 3 study</u> [Le Cesne 2021] : ORR= 13.7% (STS overall, n= 103); No responses in SS (n=2) <u>Meta-analysis in metastatic SS</u> [Carroll 2022] : ORR (N=7; n=162) = 12.3% (8.0, 18.9); ORR in studies with n≥10 (N=4; n=155) = 12.9% [8.4, 19.8] mPFS (N= 5; n=226) = 3.4 (2.7, 4.4); mPFS in studies with n≥10 (N=4; n= 223) = 3.5 months (95% CI: 2.9, 4.1) mOS (N=4; n=165) = 10.4 months (95% CI: 7.3, 14.8); mOS in studies with n≥10 (N=3; n=162) = 10.8 months (95% CI: 8.4, 13.9)	elevation, severe thrombocytopenia.
IFEX (Ifosfamide) 2 nd line	In combination with certain other approved antineoplastic agents for third-line chemotherapy of germ cell testicular cancer.	1988 (Off-label use in STS)	3g/m ² x 3days [van Oosterom 2002]	<u>Phase 2 study</u> [van Oosterom 2002] : ORR = 8% (95% CI: 2, 20), mOS = 8.3 months (STS overall)	Leukopenia, neutropenia, thrombocytopenia, anemia, fatigue, nausea, vomiting, alopecia, neurotoxicity (encephalopathy), acute kidney injury, infection.
GEMZAR (Gemcitabine)	Ovarian cancer in combination with	1996 (Off-label use in STS)	1200 mg/m ² IV at day 1 and 8, every 21 days	<u>Phase 2 study</u> [Maki 2007] : ORR= 8%, mPFS= 3	Thrombocytopenia, (requiring platelet

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Product (s) Name	Relevant Indication	Year of Approval And Type of Approval ¹	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
	carboplatin. Breast cancer in combination with paclitaxel. Non-small cell lung cancer in combination with cisplatin. Pancreatic cancer as a single-agent.		[Maki 2007] .	months, mOS= 11.5 months (STS overall)	transfusion), febrile neutropenia, pulmonary fatigue, myalgia or muscle weakness
Combo Gemcitabine + Docetaxel	-	- Off-label use in STS	Gemcitabine: 900 mg/m ² IV days 1 and 8 + Docetaxel: 100 mg/m ² IV day 8, every 21 days [Maki 2007] .	Phase 2 study [Maki 2007] : ORR=17%, mPFS: 6.2 months, mOS 17.9 months (STS overall)	Thrombocytopen ia; anemia (requiring blood transfusions)
Combo Gemcitabine + Dacarbazine	-	- Off-label use in STS	Gemcitabine 1,800 mg/m ² + Dacarbazine 500 mg/m ² IV every 2 weeks, total of 12 cycles [Garcia del Muro 2011] .	Phase 2 study [Garcia del Muro 2011] : ORR= 12% (95% CI: 5, 24); no responses in SS. mPFS 4.2 months, mOS= 16.8 months (STS overall)	Granulocytopeni a, febrile neutropenia, anemia, thrombocytopeni a, fatigue, nausea, vomiting, stomatitis, alopecia

1. Accelerated approval or full approval.

Abbreviations: CI= confidence interval; mOS= median overall survival; mPFS= median progression free survival; N = number of studies; n= number of subjects; ORR= overall response rate; SS= synovial sarcoma; STS = soft tissue sarcoma

The FDA's Assessment:

[FDA agrees with the Applicant's assessment of available treatment options for SS following first-line therapy.

Pazopanib is the only FDA-approved therapy for patients with advanced STS who have received prior systemic therapy ([Votrient 2012](#)). The safety and effectiveness of pazopanib was evaluated in a randomized Phase 3 study of patients with metastatic STS (n=369) who had received prior chemotherapy and were randomized to receive treatment with either pazopanib or placebo. The study showed an 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 patients with SS (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). Pazopanib was not associated with an OS 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 SS in the first-line setting is approximately 39%, whereas ORR in the second line setting and later ranges from 10% to 22% ([Carroll et al. 2022](#), [Moreau-Bachelard et al. 2022](#)).]

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

No prior marketing applications have been submitted to the US Food and Drug Administration (FDA), or any other Health Authority, for afamitresgene autoleucel for any indication, including SS. No marketing application has been rejected or deemed not approvable by FDA or any other Health Authority globally.

The FDA's Assessment:

[FDA concurs that afamitresgene autoleucel is not currently registered or approved in the United States or any other country in the world.]

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Key regulatory interactions with FDA that occurred during afamitresgene autoleucel clinical development program for SS and that are relevant to this BLA, are summarized in [Table 2](#).

Table 2: Applicant – Summary of Key Regulatory Interactions

Date	Regulatory Interaction	Topics
October 25, 2016	Pre-IND Meeting (Teleconference)	Preclinical safety package and Adaptimmune's mitigation strategies enabling the investigation of the product in the proposed first-in-human study. Design aspects of the clinical study.
November 29, 2016	Initial IND 17235	Adaptimmune submitted Initial IND for afamitresgene autoleucel.
December 28, 2016		FDA issued Study May Proceed correspondence.

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Date	Regulatory Interaction	Topics
October 3, 2018	Type C Meeting- CMC (Written Responses)	New (b) (4) potency assay to be used for (b) (4) lot release and stability studies.
August 26, 2019	Orphan Drug Designation (DRU-2018-6660)	FDA granted Orphan Drug Designation to afamitresgene autoleucel for the treatment of soft tissue sarcoma.
November 27, 2019	RMAT Designation	FDA granted RMAT Designation to afamitresgene autoleucel for the treatment of synovial sarcoma.
April 14, 2020	RMAT Kick-off Meeting (Teleconference)	Initial multidisciplinary meeting covering a range of topics including proposed (b) (4) potency assay, non-clinical and clinical studies intended to support a BLA submission, in vitro diagnostic HLA assay.
August 31, 2020	Type B Meeting – CMC (Written Responses)	Approach for LV and drug product stability studies and reporting and presentation of the analytical data.
March 04, 2021	Initial Pediatric Study Plan	FDA issued agreed pediatric study plan letter.
June 28, 2021	Type B Meeting – CMC (Written Responses)	(b) (4) potency assay; approach used to determine the quantity of (b) (4) to use for drug product manufacture; planned comparability exercise between sites of leukapheresis processing; drug product appearance testing strategy for lot release; process validation plan.
October 04, 2021	Proposed Proprietary Name	FDA determined the proposed proprietary name TECELRA “acceptable at this time”.
January 21, 2022	Type B Meeting – Clinical/ Companion Diagnostics (Teleconference)	Plan to evaluate the prognostic relevance of MAGE-A4 expression in patients with synovial sarcoma; plan for assessment of adverse events of special interest, plan for supporting eligible HLA-A*02 inclusion alleles in indication statement and plans for confirmatory evidence post-approval.
March 16, 2022	Type B Meeting- CMC (Written Responses)	Characterization data for LV proposed for inclusion in the BLA; comparability exercise to assess the potential impact of changes related to LV production intended for implementation prior to commercial supply
June 24, 2022	Post-meeting feedback	FDA review of LV comparability study protocol
October 13, 2022	Pre-BLA Meeting (Teleconference)	Proposed content, format and timing for submission of CMC, Nonclinical and Clinical sections to support afamitresgene autoleucel BLA filing and review.
April 21, 2023	Type B Meeting – Clinical (Written Responses)	Proposed confirmatory evidence package
July 03, 2023	Type B Meeting – CMC (Written Responses)	Proposed potency data set for inclusion in the BLA and management of reference standards for the potency assay for future commercial manufacture
January 26, 2024	BLA Application Orientation Meeting & Data Walkthrough Meeting	Overview of BLA application and supporting clinical datasets

The FDA’s Assessment:

[FDA concurs with the Applicant regarding the regulatory history.]

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FDA noted the following during the Type B, Pre-BLA teleconference on October 13, 2022:

- a) Afamitresgene autoleucel is eligible for consideration of a rolling review by virtue of its regenerative medicine advanced therapy designation.
- b) FDA will notify Adaptimmune if a risk evaluation and mitigation strategy (REMS) is needed during review.
- c) The Applicant should work with the HLA companion diagnostic device manufacturer to ensure that the device is approved or cleared contemporaneously with afamitresgene autoleucel. With this approach, the device will be available for use when the therapeutic product is approved. FDA recommends that Adaptimmune use the same assay as the clinical study, which is One Lambda's SeCore HLA assay.
- d) FDA recommends submitting a 510K for the companion HLA diagnostic testing at the same time as the BLA for afamitresgene autoleucel. The companion HLA diagnostic should be cleared during the review cycle for the BLA. A delay in the clearance of the HLA assay may impact or delay action on the BLA.
- e) FDA clarified that patient narratives should include patients who died within 30 days of receiving the investigational products regardless of causality, and patients with deaths that are considered at least possibly related to the investigational products during the study. FDA also requested submission of all case report forms in the BLA.]

Table 3: FDA – Relevant Regulatory History

Date	Submission
December 28, 2016	IND 17235: ADP-0044-001 Phase 1 Trial of ADP- A2M4 in adult patients with advanced solid tumors. Safe to proceed
March 2019	Initiated ADP-004-002 (SPEARHEAD-1) Phase 2 study in patients with advanced SS or MRCLS
August 26, 2019	Granted Orphan Drug Designation for the treatment of soft tissue sarcoma.
November 27, 2019	Granted Regenerative Medicine Advanced Therapy designation for the treatment of HLA-A*02 allele positive patients with synovial sarcoma and whose tumor expresses the ADP A2M4 tumor antigen
March 4, 2021	Agreed iPSP
October 13, 2022	Pre-BLA meeting
December 5, 2023	Final module of rolling BLA received
January 31, 2024	BLA filed. The filing met priority review criteria.
January 27, 2024	Application orientation meeting and data walk through
April 3, 2024	Mid-cycle meeting with Applicant with discussion of CMC and clinical review issues.

May 20, 2024 *	<p>Late-Cycle meeting with Applicant with discussion of clinical review concerns related to response assessment and reliability of results. FDA raised concerns regarding study conduct irregularities and data quality issues, specifically pertaining to response assessment, which may affect the reliability of the data to support the efficacy claims, especially in the context of the small study size. The Applicant agreed to a re-review of the response assessment in the Efficacy population with a different blinded independent central review imaging vendor.</p> <p>Additionally, FDA raised concerns that the same issues may be present in Cohort 2 and requested that the Applicant provide a plan to address these issues.</p>
August 2, 2024	PDUFA Action Date

Abbreviations: BLA = biologics license application, CMC = chemistry, manufacturing and controls, IND = investigational new drug application, iPSP = initial pediatric study plan, MRCLS = myxoid/round cell liposarcoma, PDUFA = Prescription Drug User Fee Act, SS = synovial sarcoma

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Bioresearch Monitoring (BIMO)

[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 sponsor Adaptimmune LLC. The inspections did not reveal substantive issues that impact the data submitted in this BLA.]

Refer to Bioresearch Monitoring Final Discipline review memo.]

4.2 Product Quality

[There were no chemistry, manufacturing, and control (CMC) concerns regarding the product quality or manufacturing issues.]

4.3 Clinical Microbiology

[There were no CMC concerns regarding clinical microbiology.]

4.4 Devices and Companion Diagnostic Issues

The FDA's Assessment:

[Afamitresgene autoleucel is 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. These additional FDA-approved or cleared companion diagnostic devices are needed to support the benefit risk assessment of afamitresgene autoleucel. Refer to SSED for the premarket application (P230016) regarding the MAGE-A4 antigen companion diagnostic assay from CDRH/OHT7/DMGP/MGB and to the review memo for the premarket notification submission (BK241074) regarding the HLA companion diagnostic assay from CBER/OBRR/DBCD/DRB.]

5. Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

[Based on review of the nonclinical data in this BLA submission, there were no nonclinical deficiencies identified in the pharmacology/toxicology studies. The nonclinical data provided in this BLA submission support the approval of this licensure application. Refer to FDA Pharmacology/Toxicology review memo for this BLA.]

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable. There are no referenced BLAs or Master Files related to nonclinical pharmacology or toxicology.

5.3 Pharmacology

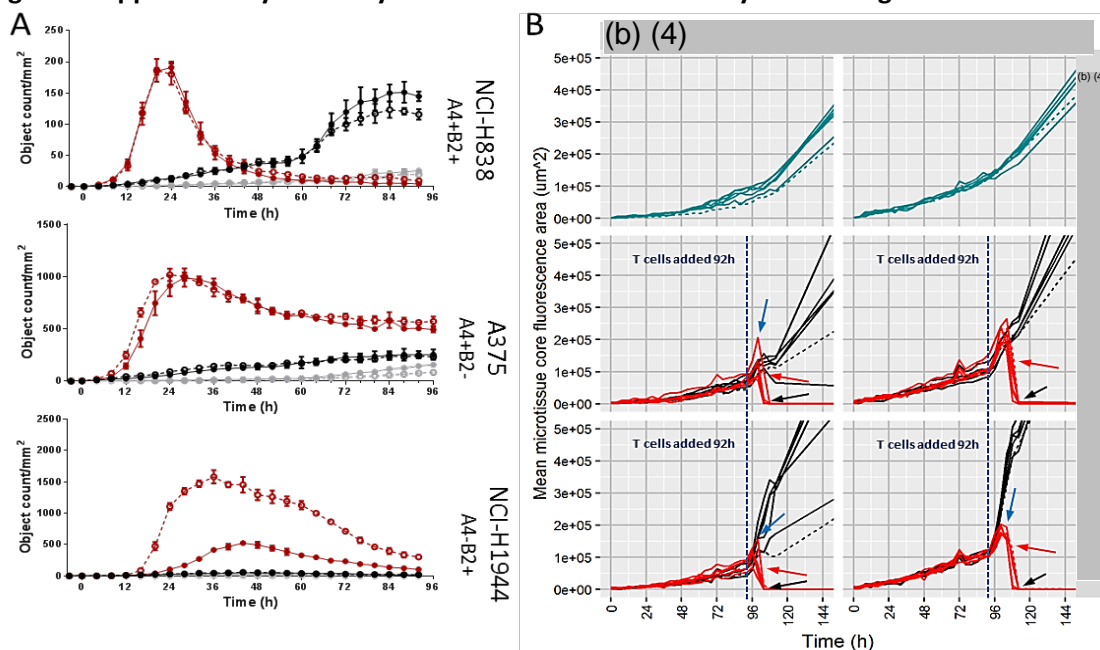
Primary pharmacology

The Applicant's Position:

In vitro studies

Afamitresgene autoleucel demonstrated the ability to proliferate and to release IFN γ in response to MAGE-A4-positive, HLA-A*02:01-positive tumor cell lines and primary tumor material. In both 2D and 3D culture systems ([Figure 1](#)), afamitresgene autoleucel showed strong cell killing activity against MAGE-A4 positive tumor cell lines. Analysis of other common HLA-A*02 alleles found that afamitresgene autoleucel had comparable potency against MAGE-A4 peptides when displayed by other HLA-A*02 subtypes, including the non -A*02:01 alleles expressed by patients enrolled in afamitresgene autoleucel trials, i.e. HLA-A*02:02, -A*02:03, -A*02:06 ([Figure 2](#)), indicating that these alleles are likely to support similar clinical efficacy to A*02:01 or other A*02:01P alleles such as A*02:09, which share an identical T-cell receptor (TCR)/peptide binding region.

Figure 1: Applicant – Cytotoxicity of MAGE-A4+ Tumor Lines by Afamitresgene Autoleucel

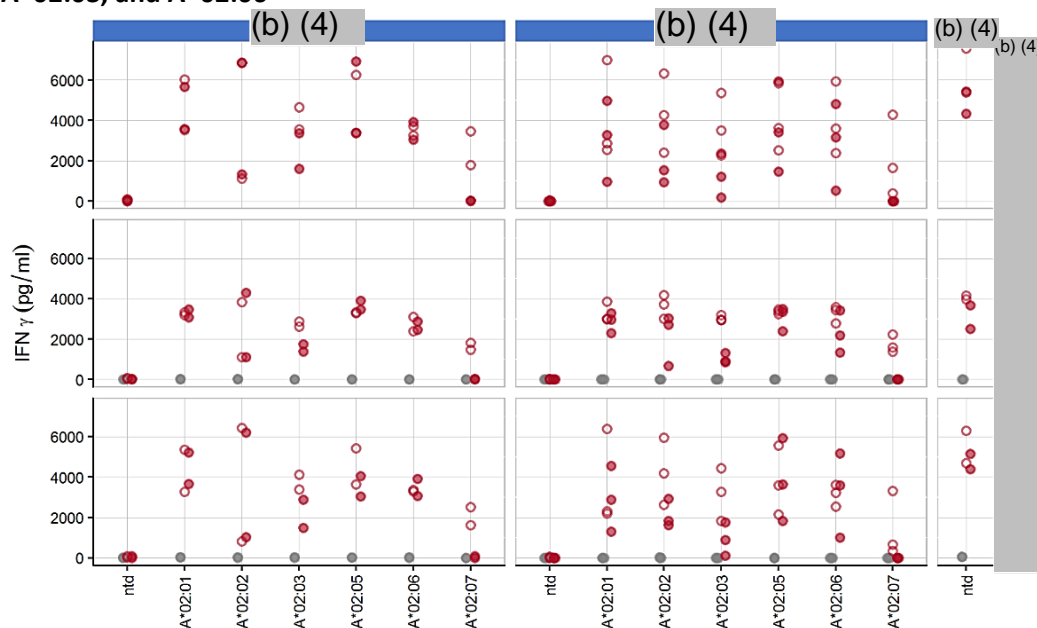


Source: 2.6.2 Pharmacology Written Summary, Figure 8.

(A) Cytotoxicity of antigen-positive tumor lines by afamitresgene autoleucel, as determined by time-lapse microscopy using a caspase-3/7 cleavable substrate. Plots represent the time course of cytotoxicity over 96 h after addition of afamitresgene autoleucel (red points) or non-transduced T-cells (black points), quantified as the mean \pm SEM of apoptotic target cells/mm². Certain wells additionally included 10⁻⁵ M MAGE-A4 peptide (unfilled points/dashed lines). Wells without T-cells are shown in gray. Data shown are from a single T-cell product, representative of 3. (B) Cytotoxicity of 3D microtissues derived from the MAGE-A4+ melanoma cell line A375, as determined by time-lapse imaging of GFP-labeled cells. Plots represent the mean microtissue area over a 144-hour period, with addition of afamitresgene autoleucel (red lines) or non-transduced controls (black lines). Each line shows the individual time course of a single microtissue from a single well. Target cells were seeded at 2 densities to produce microtissues of (b) (4) at the point of T-cell addition. Wells with MAGE-A4 peptide (10⁻⁵ M) added at the point of T-cell addition are shown in dashed lines.

Abbreviations: 3D = three dimensional; GFP = green fluorescent protein; MAGE-A4 = melanoma-associated antigen-A4; SEM = standard error of the mean.

Figure 2: Applicant – Recognition of Endogenous Antigen in Targets Transduced With HLA-A*02:02, A*02:03, and A*02:06



Source: Report 2.6.2 Pharmacology Written Summary, Figure 9

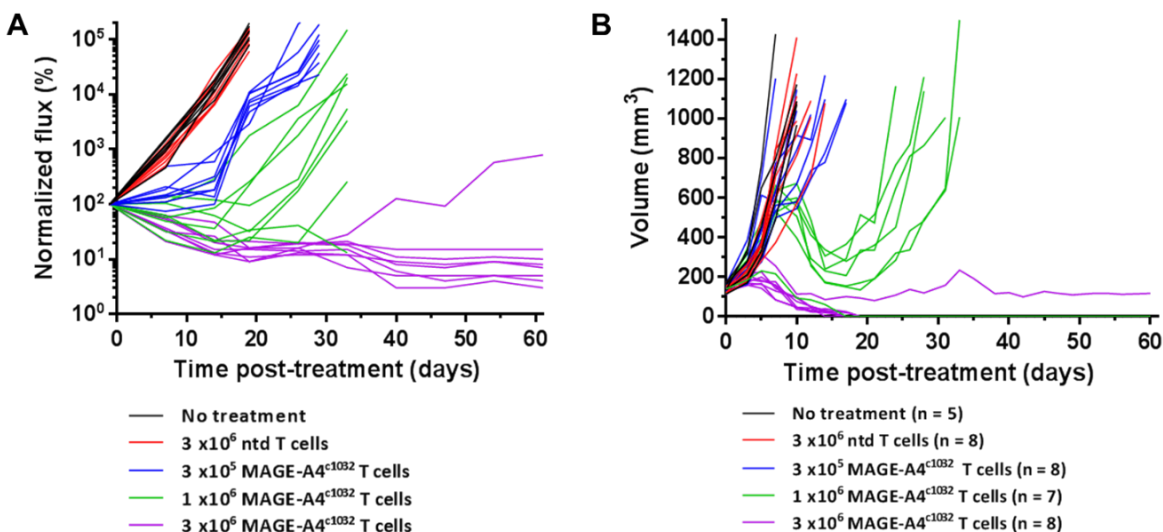
Response of afamitresgene autoleucel toward endogenous antigen and synthetic exogenous MAGE-A4₂₃₀₋₂₃₉ index peptide in (b) (4) cells transduced to express the HLA-A*02 subtypes, A*02:01, A*02:02, A*02:03, A*02:05, A*02:06, and A*02:07. Additional control lines, (b) (4) and non-transduced (b) (4) and (b) (4) are included for comparison. T-cell responses were assessed by means of IFN γ cell-based ELISA. Data are faceted according to T-cell donor and target line. Each point represents the data obtained from a single well. Gray and red points represent non-transduced T-cells and afamitresgene autoleucel, respectively. Closed circles represent no peptide present, and open circles represent the inclusion of 10⁻⁵ M index peptide.

Abbreviations: EC₅₀ = half-maximal effective concentration; ELISA = enzyme-linked immunosorbent assay; HLA = human leukocyte antigen; IFN γ = interferon-gamma; MAGE-A4 = melanoma-associated antigen-A4

In vivo studies

In a mouse melanoma model, intravenous (IV) administration of afamitresgene autoleucel resulted in a dose-dependent reduction of melanoma tumor burden, with variable responses in the middle dose group (1x10⁶ viable transduced T-cells) and pronounced tumor regression in all mice treated with the highest dose (3x10⁶ viable transduced T-cells). At the end of the study, following treatment with the highest afamitresgene autoleucel dose, 7 out of 8 sub-cutaneous tumors had disappeared, and macroscopic tumor could only be detected in 1 out of 8 mice intravenously inoculated with melanoma cells ([Figure 3](#)). Histological analysis demonstrated that in mice that did not respond to afamitresgene autoleucel with reduced tumor burden, there was a loss of HLA expression in tumor tissue that was accompanied by a decrease of afamitresgene autoleucel infiltration, even though the tumors retained high MAGE-A4 expression.

Figure 3: Applicant – Tumor Burden In Vivo After Intravenous Inoculation with Afamitresgene Autoleucel



Source: 2.6.2 Pharmacology Written Summary, Figure 12.

A) Imaged tumor burden in NOG mice intravenously injected with A375+ cells was calculated using the mean relative flux (average luminescent flux as a percentage of the signal prior to A375luc+ cell injection on Day -1) beginning on Day 0, when mice were intravenously injected with non-transduced T-cells or 3 different doses of afamitresgene autoleucel. Data are plotted on a log scale. (B) NOG mice were subcutaneously implanted with A375+ cells 16 days prior to Day 0, when mice were intravenously injected with non-transduced T-cells or 3 different doses of afamitresgene autoleucel. Tumor volume was measured, and mice were euthanized when the tumor had reached 1000 mm³ or measured 15 mm in any direction. MAGE-A4^{c1032}T cells = afamitresgene autoleucel; NOG = NOD.Cg-Prkdc^{scid} Il2rg^{tm1Sug}/JicTac; ntd= non-transduced T-cells.

The FDA's Assessment:

[These studies demonstrate in vivo ADP-A2M4 activity against MAGE-A4 expressing systemic or local tumors when administered via the IV route of administration. Refer to FDA Pharmacology/Toxicology review memo for this BLA.]

Secondary Pharmacology

The Applicant's Position:

Molecular analysis of the response of afamitresgene autoleucel to homologous peptides derived from MAGE family member proteins (31 peptides) was performed to evaluate the cross-reactivity potential of the engineered TCR. An additional study to assess the potential for afamitresgene autoleucel to display cross-reactivity to homologous peptides derived from unrelated proteins was also performed. Together, these studies found 5 additional peptides to which the MAGE-A4 TCR may cross-react, including 2 additional MAGE proteins (MAGE-A8 and MAGE-B2) with very limited non-germline expression and 3 unrelated proteins that are not natively processed and presented at sufficient levels for T-cell activation. While the reactivity towards the two related MAGE proteins was detectable, the relative level of response was low

and is not expected to manifest in vivo. Hence, these potential cross-reactivities do not represent a clinical concern.

To complement the studies of cross-reactivity against defined peptides, a series of studies were conducted to evaluate whether afamitresgene autoleucel exhibits cross-reactivity to human cells that express HLA-A*02:01 but not MAGE-A4.

- Normal Primary Cells and Tumor Cell Lines: cross-reactivity was assessed by IFN γ secretion in a cell-based enzyme-linked immunosorbent assay (ELISA) following incubation with a variety of HLA-A*02:01 positive primary normal and tumor derived human cells covering a number of cell types from multiple organ systems including (b) (4) primary cell lines, (b) (4) primary blood products, and (b) (4) antigen negative tumor cell lines.
- iPS Human Cell Testing: Adult somatic cells from an HLA-A*02:01 donor underwent (b) (4) to generate iPS cells. The iPS cells were then differentiated into a panel of cell types that were used to test for the potential of cross-reactivity by afamitresgene autoleucel.
- (b) (4) Assay: To evaluate the theoretical risk of a cytokine storm, a (b) (4) assay was used to measure cytokine release following the addition of autologous afamitresgene autoleucel.

No clinically meaningful safety concerns due to the risk of cross-reactivity were found with these studies.

To screen for alloreactivity, afamitresgene autoleucel was tested against a panel of cell lines that endogenously expressed a range of HLA alleles or were transduced to express specific alleles (b) (4) cell lines; (b) (4) HLA-class I alleles), in the absence of MAGE-A4 expression. The population coverage achieved with the alloreactivity screen, as determined using a modified version of the algorithm detailed in [Bui et al. 2006](#), is summarized in [Table 4](#).

Table 4: Applicant – Population Coverage Achieved by Alloreactivity Screening

Population	Coverage
Worldwide	41%
US Total	52%
US Asian	48%
US Black	47%
US Caucasoid	82%
US Hispanic	52%

Source: 2.6.2 Pharmacology Written Summary, Table 11

Strong afamitresgene autoleucel responses were seen against cells expressing the HLA-A*02:05 allele. No alloreactivity was seen against cells expressing other HLA allelic variants. Afamitresgene autoleucel is therefore not indicated for patients expressing this HLA-A*02:05 subtype.

Overall, afamitresgene autoleucel is considered to have low potential for off-tumor reactivity and to have an acceptable safety profile, supporting its use in patients with advanced SS whose tumors express MAGE-A4 in the context of the appropriate HLA expression requested in the application.

The FDA's Assessment:

[Although there is potential for product-mediated activity against MAGE-A8 and MAGE-B2, the expression of both peptides is restricted to cancer and germline tissues.

An alloreactivity screen against a panel of cells expressing a range of HLA alleles indicated in vitro alloreactivity against HLA-A*02:05. Therefore, afamitresgene autoleucel is contraindicated for adults who are heterozygous or homozygous for HLA-A*02:05P.

Refer to FDA Pharmacology/Toxicology review memo for this BLA.]

Safety Pharmacology

No safety pharmacology studies were conducted, as there are no relevant animal models for the nonclinical safety assessment of afamitresgene autoleucel.

The FDA's Assessment:

[FDA concurs with the Applicant.]

5.4 ADME/PK

The Applicant's Position:

Afamitresgene autoleucel, cell suspension for infusion is an autologous T-cell product. Therefore, traditional pharmacokinetic and ADME studies are not considered relevant to this product.

The FDA's Assessment:

[FDA concurs with the Applicant.]

5.5 Toxicology

5.5.1 General Toxicology

Standard in vivo single-dose or repeat-dose toxicity studies were not conducted with afamitresgene autoleucel due to the lack of appropriate animal models for testing of human TCR engineered T-cells.

No immunogenicity studies have been performed on afamitresgene autoleucel, as there are no suitable animal models for assessment of the immunogenicity of human TCRs. While previous studies found that adoptive T-cell therapy using fully murine TCRs can induce anti-mouse TCR antibodies, albeit without apparent impact on durability, efficacy, or safety of the product [Davis 2010], the introduced MAGE-A4 TCR is derived from a wild-type human TCR and therefore would not be expected to be immunogenic.

The FDA's Assessment:

[FDA concurs with the Applicant.]

5.5.2 Genetic Toxicology

The Applicant's Position:

Conventional genotoxicity studies were not conducted with afamitresgene autoleucel, due to the lack of appropriate test models and pharmacologically relevant species.

To confirm that the integration site profile of afamitresgene autoleucel was as predicted, a study was performed to assess proviral integration sites in (b) (4) manufactured batches. All products were found to be highly polyclonal, with no evidence of selective insertion.

The FDA's Assessment:

[FDA concurs with the Applicant.]

5.5.3 Carcinogenicity

The Applicant's Position:

No carcinogenicity toxicology studies were conducted for afamitresgene autoleucel. Afamitresgene autoleucel is a human TCR engineered T-cell product, therefore conventional carcinogenicity studies were not performed due to the lack of relevant animal models.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

No developmental and reproductive toxicology studies were conducted with afamitresgene autoleucel. MAGE-A4 is known to be expressed in testes and placenta, and so there is a theoretical risk of embryotoxicity or toxicity to the testes. However, both these organs are highly immune privileged, and so this is not expected to manifest clinically. Because afamitresgene autoleucel is an autologous engineered-TCR T-cell therapy, there is a mismatch of MHC antigens between animal and human TCRs, so specificity cannot be assessed. Human T-cells in humanized mouse models would also result in lethal xenograft versus host disease

within 8 weeks, which masks evaluation of toxicity [Ito 2009, Nervi 2007]. Engineering an animal TCR for use in animal model testing would also not reflect the specificity/safety profile of the human TCR, and therefore would be uninformative. In addition, in vitro studies would not be expected to be informative as available primary placental, or testis cells do not express MAGE-A4 in vitro. Alongside this, the immune privileged nature of both the testis and placenta is, at least in part, due to the presence of tolerogenic immune cells and physical segregation of effector T-cells from the antigen site, neither of which would be readily recapitulated in vitro.

The proposed indicated population for afamitresgene autoleucel is patients with unresectable or metastatic SS who have received prior chemotherapy, therefore, all patients indicated for the therapy will have been exposed to chemotherapy as part of their previous therapy. Since first-line metastatic or neo-adjuvant/adjuvant systemic therapy for SS contains alkylating agents, patients would have undergone fertility counselling and offered gamete storage where indicated. In clinical trials, the clinical protocol included risk mitigation measures regarding effective birth control procedures and pregnancy monitoring, and no pregnancies have been reported in these studies. Also of relevance is the fact that no cases of orchitis or testicular inflammation have been reported in afamitresgene autoleucel clinical studies. In the post-marketing setting, this risk can be mitigated via labelling, and monitored via routine pharmacovigilance measures (follow-up and thorough evaluation of any reported pregnancy cases in the post-marketing setting).

The FDA's Assessment:

[FDA concurs with the Applicant.]

5.5.5 Other Toxicology Studies

The Applicant's Position:

None conducted.

The FDA's Assessment:

[FDA concurs with the Applicant.]

6. Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

[The proposed dosing regimen of a single dose of TECELRA administered by intravenous (IV) injection is acceptable. From a clinical pharmacology standpoint, the original BLA is approvable. Please see FDA Clinical Pharmacology reviewer's memo for this BLA.]

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

To characterize the cellular kinetic profile and cytokine response and evaluate exposure-response (E-R) relationships, a pooled analysis was performed using data from Studies ADP-0044-001 (CSR data cut-off 01Sep2020) and ADP-0044-002 (CSR data cut-off 29Mar2023). Noncompartmental analysis (NCA) was conducted in the group who received the recommended phase 2 dose range. E-R efficacy analyses were conducted in subjects with SS who received doses ranging from 2.68 to 10×10^9 transduced cells (N= 59). E-R safety analyses were conducted in both SS only (primary analysis, N=59) and overall (secondary, N=89).

The key clinical pharmacology attributes of afamitresgene autoleucel are summarized as follows:

- The observed afamitresgene autoleucel cellular kinetic profile, based on the measurement by PCR of integrated vector copy numbers (VCN) per microgram of PBMC genomic DNA, was as expected for a T-cell therapy, with an initial apparent expansion phase followed by contraction and then persistence.
- In subjects with SS treated in Study ADP-0044-002 Cohort 1, the median time to peak afamitresgene autoleucel exposure was 1.1 weeks (95% CI: 0.571, 2.00). In Study ADP-0044-001, all subjects had detectable levels of persistence throughout the interventional phase and LTFU phase. In Study ADP-0044-002, as of the 11Oct2021 data cut-off, all subjects had maintained persistence above the limit of quantitation for the entire duration of follow-up of at least 2 weeks and up to 20 months.
- Based on VCN/ μ g of PBMC genomic DNA, median afamitresgene autoleucel C_{max} and AUC increased with an increasing cell dose, although there was a substantial overlap in the ranges.
- Covariate analyses indicated that body weight (BW), gender, age, race, baseline tumor SLD, and ECOG status had no effect on afamitresgene autoleucel cell kinetics. There was a trend toward increasing median cell afamitresgene autoleucel AUC_{0-28D}, AUC_{0-3M}, and AUC_{0-6M} with increasing tumor H-scores; however, there was a marked overlap in the ranges.

- Subjects who received tocilizumab showed a trend toward higher afamitresgene autoleucel C_{max} , AUC_{0-7D} , and AUC_{0-28D} than those who did not. Tocilizumab use did not have a marked impact on later afamitresgene autoleucel AUC metrics (i.e., AUC_{0-3M} and AUC_{0-6M}). The use of bridging therapy, and the number of prior lines of systemic therapy had no effect on afamitresgene autoleucel cell kinetics.
- Higher VCN per transduced cell and the transduced VCN dose led to increased afamitresgene autoleucel C_{max} and AUC. CD4:CD8 content ratio led to an inverse trend in afamitresgene autoleucel C_{max} and AUC.
- Serum Cytokines (GM-CSF, IL-6, or IFN γ) C_{max} and AUC showed a wide range of elevated concentration after afamitresgene autoleucel infusion but did not increase with an increasing dose over the 1.41 to 9.99×10^9 dose range.
- No dose-response trends with ORR, DOR, or PFS were observed over the afamitresgene autoleucel dose range received by SS subjects.
- E-R relationships were observed between late afamitresgene autoleucel exposure metrics and the probability of response and PFS; however, the subgroup of SS subjects in the lowest quartiles of AUC_{0-3M} and AUC_{0-6M} also maintained a clinically meaningful ORR of 25%.
- A low incidence of Grade ≥ 3 CRS and any grade ICANS was observed over the proposed dose range.

The Applicant's Position:

Overall, the data from clinical pharmacology analyses, along with the efficacy and safety data, support the proposed recommended dose range of 2.68 to 10×10^9 MAGE-A4 TCR positive T-cells.

The FDA's Assessment:

[In general, the FDA agrees with the Applicant's assessment, except assessments of 1) impact of T cell product characteristics on afamitresgene autoleucel; and 2) dose/exposure-efficacy relationship analysis.]

Based on the reviewer's analysis, the exposure of afamitresgene autoleucel was positively associated with the administered dose. Therefore, dose was included for evaluation of potential impact of T cell product characteristics on afamitresgene autoleucel's pharmacokinetics (PK). The results showed that none of the T cell product characteristics except the administered dose had significant impact on afamitresgene autoleucel's expansion.

FDA re-analyzed dose/exposure-efficacy response relationships based on analysis of clinical data. The results support the proposed recommended dose range of 2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells. No dose adjustment is needed. Please refer to [Sections 6.2.2.1](#) and [6.2.2.2](#), and FDA Clinical Pharmacology reviewer's memo for detailed information.]

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

The recommended dose range for afamitresgene autoleucel, i.e. single intravenous infusion of 2.68 to 10×10^9 MAGE-A4 TCR positive T-cells, was based on the following:

- Among subjects with SS dosed in the ADP-0044-002 study (Cohort 1), the median transduced cell dose was as 8×10^9 and range: 2.68 to 9.99×10^9 . The ORR by independent review among the SS group was 38.6% (95% CI: 24.36, 54.50). Responses were observed at the lowest dose and at the highest dose administered in the study. The median DoR by independent review was 11.6 months (95% CI: 4.44, NE) and ranged from 2.7 to 32 months as of the 29Mar2023 data cut-off (ADP-0044-002-S2, Section 3).
- In the pooled data from subjects with SS across studies, the ORR by investigator assessment was 40.7% (95% CI: 28.07, 54.25), and the median DoR by investigator assessment was 12 months. Consistent with the data from ADP-0044-002, responses were observed across the dose range administered. There was a similar response rate among SS subjects who received $<7 \times 10^9$ transduced cells (9/25 subjects, ORR 36.0% [95% CI: (17.97, 57.48)]) and those who received $\geq 7 \times 10^9$ transduced cells (15/34 subjects, ORR 44.1% [95% CI: 27.19, 62.11]).
- A low incidence of Grade ≥ 3 CRS (n=3 SS subjects), and ICANS (n=2 SS subject with a Grade 1 event) was observed across this dose range (Safety Update, Section 3.3.3).
- No dose-response trends with ORR or DoR were observed over the afamitresgene autoleucel dose range received by subjects with SS. E-R relationships were observed between late afamitresgene autoleucel exposure metrics (AUC_{0-3M} and AUC_{0-6M}) and the probability of response and PFS; however, the subgroup of SS subjects in the lowest quartiles of AUC_{0-3M} and AUC_{0-6M} also maintained a clinically meaningful ORR of 25% (m2.7.2, Section 3.4.1).

The Applicant's Position:

The clinical efficacy and safety data along with the clinical pharmacology analyses provide evidence supporting the proposed afamitresgene autoleucel dose range is safe and efficacious for use in the indicated patient population.

The FDA's Assessment:

[FDA concurs with the Applicant. The Applicant proposed following dosing regimen of afamitresgene autoleucel: a single IV infusion of 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells. This is the same dose range of administered afamitresgene autoleucel in the Phase 2 Study ADP-0044-002 Cohort 1.]

The Applicant proposed dose range of afamitresgene autoleucel (a single IV infusion of 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells) has demonstrated clinical efficacy with a tolerable safety profile. The clinical pharmacology evaluation based on clinical reviewer's efficacy and safety analysis supports this proposed dose range for use in the indicated patient population. Please refer to [Section 6.3.1](#) and Clinical Pharmacology reviewer's memo for additional detailed information.]

6.2.2.2 Therapeutic Individualization

Data:

The effect of Intrinsic and extrinsic factors on afamitresgene autoleucel PK parameters was evaluated in a covariate analysis.

Effect of Intrinsic Factors

Gender: Gender had no impact on afamitresgene autoleucel cell kinetics (m2.7.2 Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). No differences in safety and efficacy outcomes of afamitresgene autoleucel based on and E-R analyses and gender were identified.

Age: Age had no impact on afamitresgene autoleucel cell kinetics (m2.7.2. Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report).

Body Weight (BW): BW had no impact on afamitresgene autoleucel cell kinetics (m2.7.2. Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). No differences in safety outcomes of afamitresgene autoleucel based on BW were identified.

Race: Race (White versus non-White) had no impact on afamitresgene autoleucel cell kinetics (m2.7.2. Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). No differences in safety and efficacy outcomes of afamitresgene autoleucel based on race were identified.

Organ Impairment: No dedicated renal or hepatic impairment studies were conducted with afamitresgene autoleucel. Given the nature of the therapeutic product, varying degrees of renal and hepatic impairment are not expected to have any clinically relevant impact on the cellular expansion, safety, or efficacy of afamitresgene autoleucel. The recommended dose range of afamitresgene autoleucel for the general subject population is acceptable for use in subjects with renal or hepatic impairment.

Disease Characteristics: Baseline tumor SLD had no impact on afamitresgene autoleucel cell kinetics (m2.7.2 Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). Consistent with the expectation that the interaction between afamitresgene autoleucel and the MAGE-A4 expressing cells may impact afamitresgene autoleucel expansion kinetics, a trend toward higher afamitresgene autoleucel AUC_{0-28D}, AUC_{0-3M}, and AUC_{0-6M} with higher H-scores was observed (m2.7.2. Section 3.1.5). This finding is hypothesized to be due to antigen interaction-driven expansion, particularly of the CD8 T-cell component of afamitresgene autoleucel. There was, however, no effect of an H-score on post-afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report).

Lower baseline SLD and higher tumor H-scores showed a trend toward a higher probability of response and longer PFS based on graphical analyses, although these were not identified as statistically significant covariates in the logistic regression and CPH models. While the observed impact of lower baseline tumor SLD may be indicative of less advanced or aggressive disease, the observed effect of higher H-scores is hypothesized to be a combined effect of higher afamitresgene autoleucel exposures in subjects with higher H-scores and a direct effect of higher target expression potentiating cell killing.

ECOG status (0 versus ≥ 1) had no impact on afamitresgene autoleucel cell kinetics (m2.7.2. Section 3.1.5) or post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). No differences in safety and efficacy outcomes of afamitresgene autoleucel based on ECOG were identified.

Effect of Extrinsic Factors

T-Cell Product-Related Parameters: Higher VCN per transduced cell and the transduced VCN dose (the number of administered copies, (b) (4) [REDACTED]) led to increased afamitresgene autoleucel C_{max} and AUC metrics (m2.7.2. Section 3.1.4). This finding is likely attributable to the bioanalytical approach used to assess afamitresgene autoleucel cell kinetics. Cell kinetics of transduced T cells post-infusion was assessed using a quantitative polymerase chain reaction specific for the packaging signal sequence present in the vector genome and is expressed as the number of vector copies per microgram of genomic DNA from PBMC. Therefore, a higher VCN input into systemic circulations is expected to lead to higher measured systemic VCN per microgram of DNA (i.e., higher exposures). CD4:CD8 content ratio led to an inverse trend in afamitresgene autoleucel C_{max} and AUC. The underlying rationale for this observation is unclear. However, a hypothetical explanation might be that the transduced CD8 T-cells engage more effectively than CD4 T-cells with the HLA class I peptide-MHC complex and are therefore more likely to undergo antigen-driven expansion than CD4 T-cells. However, these T-cell product-related parameters did not have an impact on post afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). In addition, these

findings did not translate into clinically relevant effects as no differences in safety and efficacy outcomes of afamitresgene autoleucel based on T-cell product characteristics were identified.

Bridging Therapies: Antitumor bridging therapy was administered between leukapheresis and the start of lymphodepletion if a subject had a disease that was clinically progressing, and systemic therapy was in the best interest of the subject. Treatment with bridging therapies had no impact on afamitresgene autoleucel cell kinetics (m2.7.2. Section 3.1.5) or post-afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report).

Concomitant Use of Tocilizumab: Tocilizumab was used for the management of CRS and ICANS events after treatment with afamitresgene autoleucel. Afamitresgene autoleucel exposure was maintained in subjects who received tocilizumab. There was a correlation between median afamitresgene autoleucel C_{max} or AUC metrics and use of tocilizumab (m2.7.2. Section 3.1.5). Post-afamitresgene autoleucel exposures of GM-CSF, IL-6 and IFN γ were higher in subjects who received tocilizumab compared to those who did not, that is, elevated concentrations of all 3 cytokines were predictive of tocilizumab usage (Section 3.4.2 and ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). Further, as expected, tocilizumab use was correlated with the incidence of Grade ≥ 3 CRS. These findings are consistent as subjects with higher IL-6 exposure are more likely to experience CRS events (m2.7.2. Section 3.5.2), which would indicate the use of tocilizumab for management.

Concomitant Use of G-CSF for Neutropenia Prophylaxis: In the clinical protocols G-CSF was recommended for neutropenia prophylaxis, in accordance with American Society of Clinical Oncology (ASCO) guidelines [Smith 2015]. This approach was not employed in prior studies with approved chimeric antigen receptor (CAR) T-cell therapies. The coadministration of G-CSF may potentially increase AEs associated with engineered T-cell therapies, including CRS and ICANS, or alter the cellular expansion of T-cell therapies. Therefore, the effect of concomitant G-CSF use on the cell kinetics, cytokine exposure, safety, and efficacy of afamitresgene autoleucel treatment was evaluated. Concomitant treatment with G-CSF was associated with a trend toward lower median afamitresgene autoleucel C_{max} , AUC_{0-7D} , and AUC_{0-28D} (m2.7.2 Section 3.1.5), albeit with a marked overlap in range. There was no impact of G-CSF use on post-afamitresgene autoleucel cytokine exposures (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). Concomitant G-CSF use was not found to be associated with an increased incidence of Grade ≥ 3 CRS based on univariate analyses in the graphical E-R analyses with safety (m2.7.2 Section 3.4.2), and no trend for differences in efficacy outcomes of afamitresgene autoleucel based on G-CSF use was identified. Overall, concomitant use of G-CSF did not lead to clinically meaningful differences in the cell kinetics, safety, or efficacy profile of afamitresgene autoleucel.

The Applicant's Position:

None of the demographic and disease factors evaluated impacted afamitresgene autoleucel PK parameters. Therefore, no dose adjustment is recommended based on any of these factors.

The FDA's Assessment:

[FDA concurs with the Applicant and no dose adjustment of the proposed recommended dose range is needed.]

6.2.2.3 Outstanding Issues

Data:

Not applicable.

The Applicant's Position:

None based on Applicant's assessment.

The FDA's Assessment:

[FDA concurs with the Applicant.]

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Afamitresgene autoleucel pharmacology information is based on the pooled analyses across studies ADP-0044-001 (data cut-off date: 01Sep2020) and ADP-0044-002 (data cut-off date: 11Oct2021). Based on the doses administered, a pooled treatment group was generated from ADP-0044-001 Group 3 (transduced cell dose range >1.2 to 6×10^9) and Expansion Group (dose range: 1.2 to 10×10^9) and all subjects from ADP-0044-002 (1 to 10×10^9 transduced cells). This pooled treatment group included all tumor types and was used when assessing covariate relationships for afamitresgene autoleucel cellular kinetic NCA parameters and serum cytokine NCA parameters. E-R analyses with efficacy were conducted only in subjects with SS treated with afamitresgene autoleucel in all dose groups of Study ADP-0044-001 and Cohort 1 of ADP-0044-002. SS subjects received doses ranging from 2.68 to 9.99×10^9 transduced cells across these studies. E-R analyses with safety were conducted in subjects with SS only (primary analysis) or with any tumor type (secondary), treated with afamitresgene autoleucel in all dose groups of Study ADP-0044-001 and Cohort 1 of ADP-0044-002.

Cellular Kinetic Profile

Study ADP-0044-002

Circulating afamitresgene autoleucel, measured as VCN per microgram of PBMC genomic DNA, was observed post-infusion in all subjects in the mITT population (data cut-off date: 11Oct2021). The post-infusion profile of afamitresgene autoleucel was characterized by an increase in cell exposure to a peak, followed by a bi-exponential decline. The median time to the peak afamitresgene autoleucel exposure was 1.1 weeks (95% CI: 0.571, 2.00). Persistence of transduced T-cells showed large variations of peak and duration among subjects (Study ADP-0044-002 CSR, Section 10.3.1). As of the data cut-off date, all subjects had maintained persistence above the limit of quantitation for the entire duration of follow-up of at least 2 weeks and up to 20 months.

Pooled Analysis

The observed afamitresgene autoleucel cellular kinetic profile was consistent with that expected for a T-cell therapy, with an initial apparent expansion phase followed by contraction and then persistence. A summary of the afamitresgene autoleucel cellular kinetic parameters in the SS group are summarized in [Table 5](#).

Table 5: Applicant – Pharmacokinetics (PK) of afamitresgene autoleucel in subjects with SS

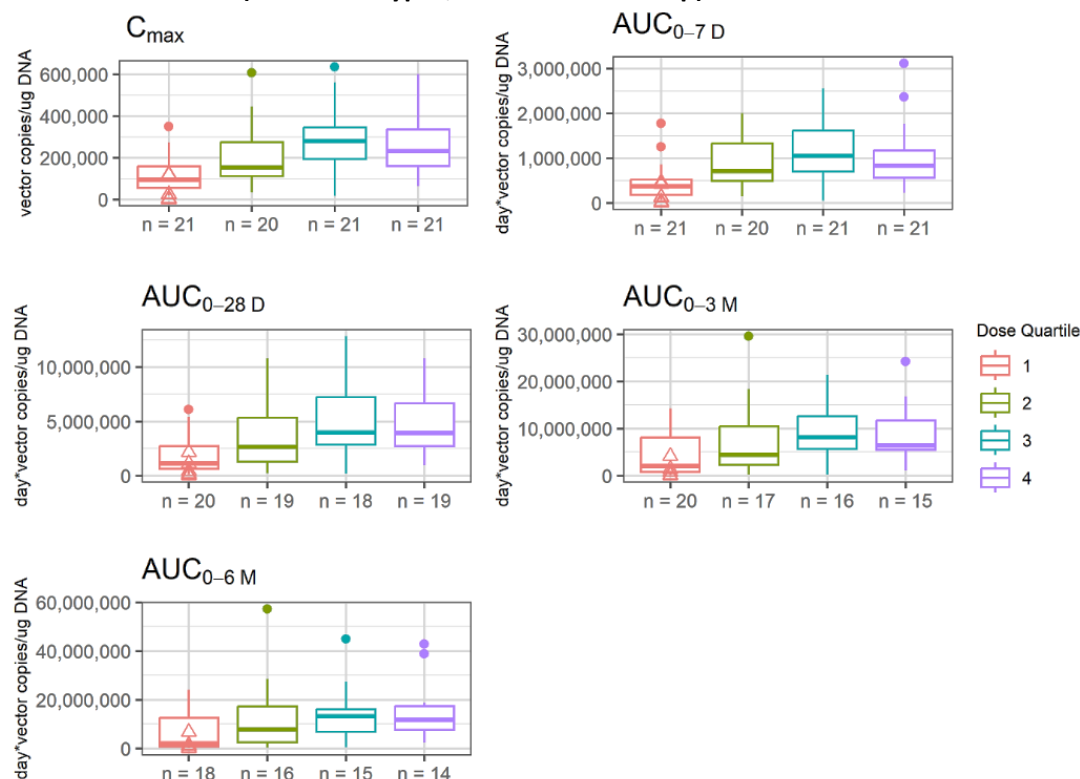
PK Parameter	Statistics	Dose Range: 2.68 to 9.99 x10 ⁹ (N=59)
t _{max} (day)	Median (range)	7 (1-89)
C _{max} (DNA copies/μg)	Geometric mean (CV%)	170000 (111.1%)
AUC _{0-7D} (day*DNA copies/μg)	Geometric mean (CV%)	666000 (117.3%)
AUC _{0-28D} (day*DNA copies/μg)	Geometric mean (CV%)	2650000 (169.6%)
AUC _{0-3M} (day*DNA copies/μg)	Geometric mean (CV%)	4290000 (243.5%)
AUC _{0-6M} (day*DNA copies/μg)	Geometric mean (CV%)	6280000 (310.4%)

Source: m2.7.2 Summary of Clinical Pharmacology Studies, Table 7.

Dose and Cellular Kinetics Relationship

Across the dose range evaluated, there was an increase in median afamitresgene autoleucel C_{max}, AUC_{0-7D}, and AUC_{0-28D} for all tumor types ([Figure 4](#)), and these findings were consistent in the SS-only subgroup.

Figure 4: Applicant – Box Plot of Afamitresgene Autoleucel Cell Kinetic Parameters by Quartiles of Dose Administered (All Tumor Types, Pooled Dose Group)



Source: adap-PersistentCovariate20Feb2023.Rmd, Reference: fb3294:44d3e4; m2.7.2 Figure 4

Note: Transduced cell dose quartiles: 1 = 2.12 to 5.10×10^9 ; 2 ≥ 5.10 to 8.02×10^9 ; 3 ≥ 8.02 to 9.88×10^9 ; 4 ≥ 9.88 to 9.99×10^9 transduced cells.

Triangle and closed circle symbols represent values from subjects in Study ADP-0044-001 Groups 1 and 2 who were not included in the statistical analysis but are overlaid on the plot for reference.

Factors Impacting Cellular Kinetics/Pharmacokinetics of Afamitresgene Autoleucel

Details on the intrinsic and extrinsic factors evaluated as part of the covariate assessment in the afamitresgene autoleucel cellular kinetic analyses are provided above in [Section 6.2.2.2. Therapeutic Individualization](#).

Pharmacodynamics

Serum Cytokines (GM-CSF, IL-6, and IFN γ): After lymphodepletion therapy and prior to afamitresgene autoleucel infusion, serum concentrations of GM-CSF, IL-6, and IFN γ were not markedly increased relative to baseline. Following afamitresgene autoleucel infusion, elevations in concentrations of GM-CSF, IL-6, and IFN γ relative to pre-dose concentrations were observed. [Table 6](#) presents the median serum concentration at key time points for GM-CSF, IL 6, and IFN γ , respectively, relative to afamitresgene autoleucel infusion in the pooled dose group (m2.7.2 Section 3.2).

Table 6: Applicant – Summary of Pharmacodynamic Biomarkers (All Tumor Types, Pooled Dose Group)

Cytokine	Baseline	Day 1	Peak	Week 4
Median (Range; ng/L) [n]				
GM-CSF	0.520 (0.390 - 2.50) [76]	1.57 (0.390 - 558) [76]	3.86 (0.520 - 610) [81]	0.610 (0.390 - 2.50) [68]
IL-6	1.67 (0.340 - 55.9) [81]	6.29 (0.650 - 1370) [79]	58.1 (0.390 - 11200) [81]	5.39 (0.340 - 658) [71]
IFN γ	3.61 (0.770 - 231) [80]	16.6 (2.48 - 5660) [80]	125 (4.78 - 38800) [81]	12.4 (2.48 - 602) [71]
Median (Range; Fold Change) [n]				
GM-CSF	1.00 (1.00 - 1.00) [75]	2.31 (1.00 - 801) [73]	6.54 (1.00 - 1170) [77]	1.00 (0.236 - 4.13) [64]
IL-6	1.00 (0.358 - 1.00) [80]	2.93 (0.287 - 174) [78]	18.6 (0.271 - 6080) [80]	2.25 (0.257 - 385) [70]
IFN γ	1.00 (1.00 - 1.21) [79]	4.87 (0.0650 - 2390) [79]	41.2 (0.231 - 15700) [79]	3.13 (0.152 - 208) [69]

Source: ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report Table 16.

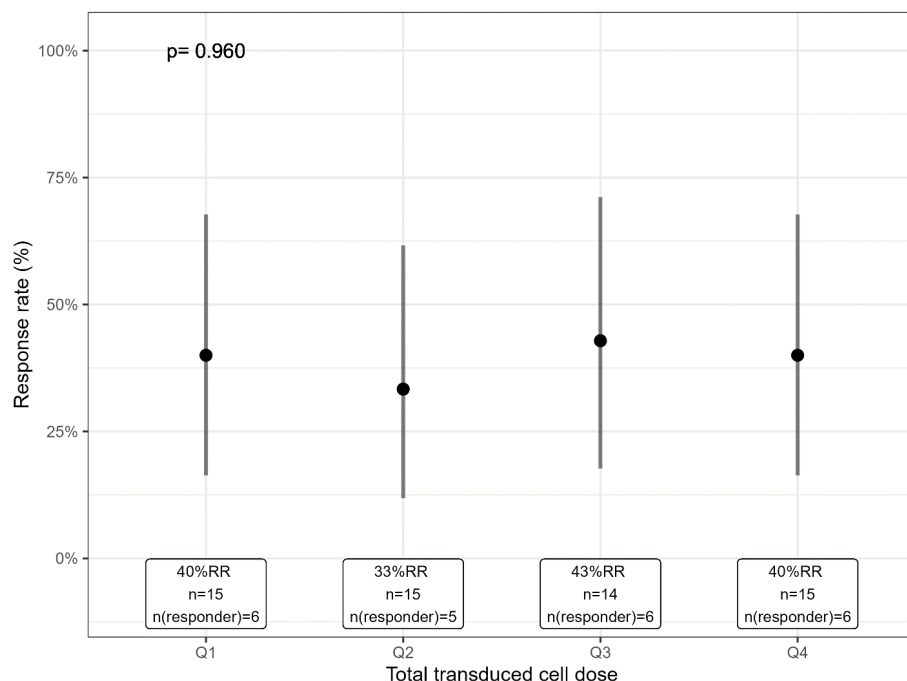
Abbreviations: GM-CSF=granulocyte macrophage colony-stimulating factor; IFN γ =interferon γ ; IL-6=interleukin-6; n= sample size. Note: Baseline = pre-lymphodepletion therapy, Day 1 = pre-afamitresgene autoleucel infusion

There was no increase in cytokine exposure (C_{max} and AUC) across quartiles of the administered dose range in the pooled group in all tumor types. Findings were consistent in the SS-only subject subgroup of the pooled dose group.

Dose Relationship with Efficacy and Safety

Dose-Efficacy Relationships (m2.7.2 Section 3.3.1): The analysis of clinical efficacy across quartiles of afamitresgene autoleucel dose was conducted in the efficacy E-R analysis population (SS-only subjects). No dose-response was observed with ORR across quartiles of transduced cell dose ([Figure 5](#)). TTR, DOR, and PFS were also similar across quartiles of viable transduced cell dose (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report) in the efficacy E-R analysis population. Overall, dose-efficacy analyses suggest that a dose over the range of 2.68 to 9.99×10^9 transduced cells does not have a marked impact on clinical efficacy outcomes.

Figure 5: Applicant – Response Rate by Quartiles of Afamitresgene Autoleucel Dose (Efficacy E-R Population)



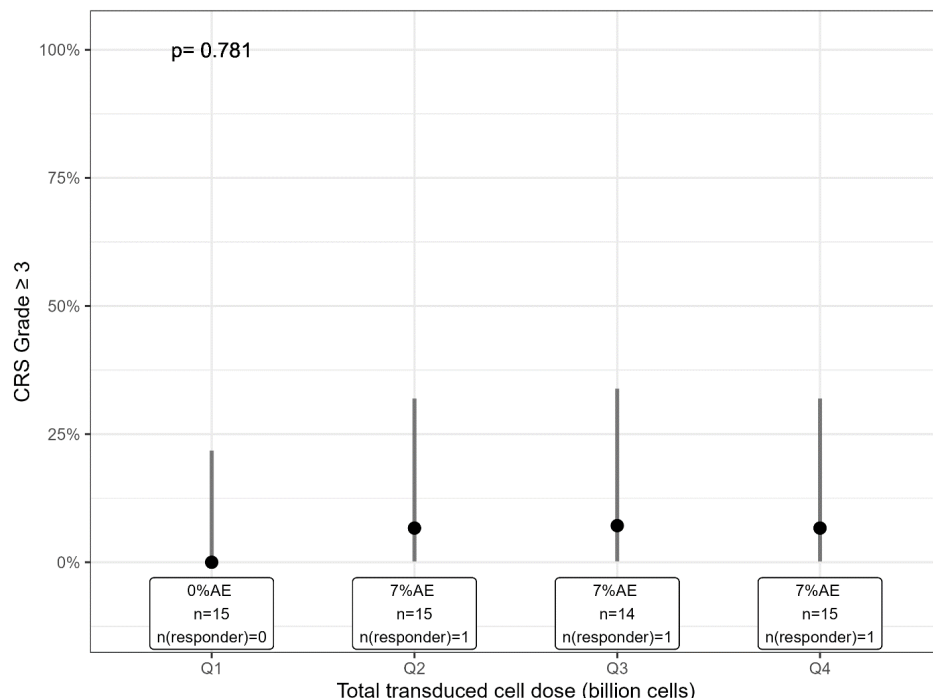
Source: adap-adpa2m4-orr-ss-v20.Rmd, Reference: 471a88; m2.7.2 Figure 19.

Note: Cell dose quartiles: 1 = 2.68 to 5.13×10^9 ; 2 ≥ 5.13 to 8.38×10^9 ; 3 ≥ 8.38 to 9.90×10^9 ; 4 ≥ 9.90 to 9.99×10^9 transduced cells.

Abbreviations: E-R=exposure-response; n=sample size; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; RR=response rate

Dose-Safety Relationships (m2.7.2 Section 3.3.2): Analyses of select safety endpoints by quartiles of afamitresgene autoleucel transduced dose were conducted in the primary safety E-R analysis population (SS only). These analyses suggested that the probability of Grade ≥ 3 CRS was higher in the upper quartiles of dose ($>5.13 \times 10^9$ transduced cells) compared to the lower quartiles ([Figure 6](#)). However, this finding is interpreted with caution due to the limited number of subjects in this analysis who developed Grade ≥ 3 CRS ($n = 3$). There was similar a trend toward an increased probability of CRS requiring tocilizumab in the upper two quartiles of viable transduced cell dose.

Figure 6: Applicant – Grade ≥ 3 CRS by Quartiles of Afamitresgene Autoleucel Dose (Primary Safety E-R Population)



Source: adap-adpa2m4-safety-eda-ss-v7.Rmd, Reference: bec9bb; m2.7.2 Figure 20.

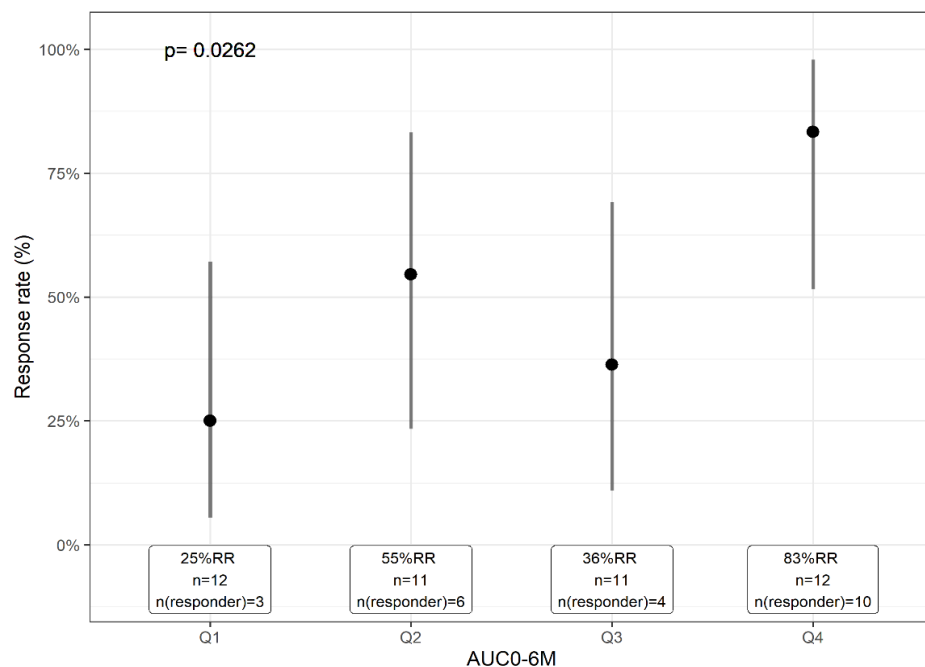
Note: Cell dose quartiles: 1 = 2.68 to 5.13 × 10⁹; 2 ≥5.13 to 8.38 × 10⁹; 3 ≥8.38 to 9.90 × 10⁹; 4 ≥9.90 to 9.99 × 10⁹ transduced cells.

Abbreviations: CRS=cytokine release syndrome; E-R=exposure-response; Efficacy=E-R Analyses

E-R analyses with efficacy were conducted in subjects with SS treated with afamitresgene autoleucel in all dose groups of Study ADP-0044-001 (data-cut: 01Sep2020) and Cohort 1 of Study ADP-0044-002, as of data-cut: 11Oct2021 (m2.7.2 Section 3.4.1).

ORR: A trend was identified between afamitresgene autoleucel AUC_{0-3M} or AUC_{0-6M} and the probability of response. No trend was observed between early afamitresgene autoleucel exposure metrics (i.e., C_{max}, AUC_{0-7D}, and AUC_{0-28D}) and the probability of response. Afamitresgene autoleucel median C_{max}, AUC_{0-7D}, AUC_{0-28D}, AUC_{0-3M}, and AUC_{0-6M} in responders were 1.1-, 1.2-, 1.3-, 2.6-, and 3.1-fold than that in non-responders (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report). These findings were consistent with the observation that the response rate in the highest quartile of AUC_{0-6M} was 83% (n = 10/12) versus 25% (n = 3/12) in the lowest quartile ([Figure 7](#)).

Figure 7: Applicant – Response Rate by Afamitresgene Autoleucel Quartiles of AUC_{0-6M} (Efficacy E-R Population)



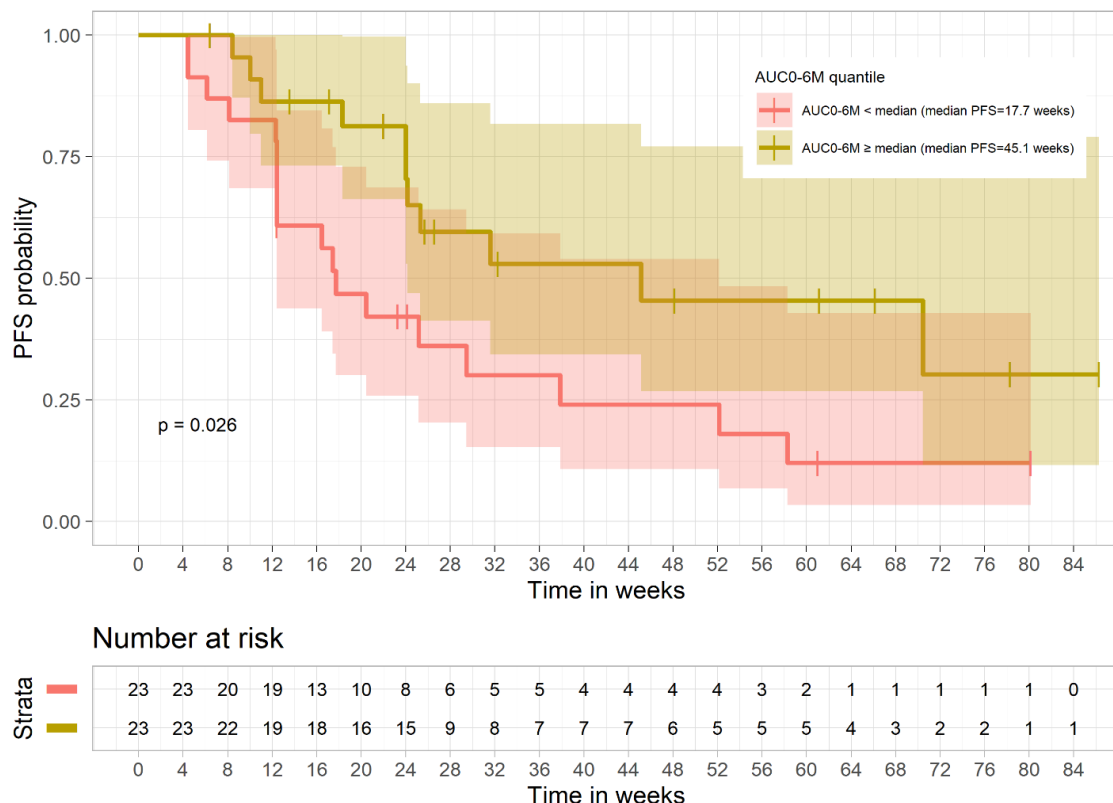
Source: adap-adpa2m4-orr-ss-v20.Rmd, Reference: ddfd8c; m2.7.2 Figure 22.

Abbreviations: AUC_{0-6M}= area under the curve from time zero to 6 months postinfusion; E-R=exposure-response; n=sample size; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; RR=response rate.

TTR and DOR: No relationships between afamitresgene autoleucel exposures, and TTR or DOR were observed in graphical analyses (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report).

Progression-Free Survival (PFS): Similar to ORR, a trend was identified between afamitresgene autoleucel AUC_{0-3M} or AUC_{0-6M} ([Figure 8](#)) and PFS based on exploratory analyses. No trend was observed between early afamitresgene autoleucel exposure metrics (i.e., C_{max}, AUC_{0-7D}, and AUC_{0-28D}) and PFS.

Figure 8: Applicant – PFS by Quantiles of Afamitresgene Autoleucel AUC_{0-6M} (Efficacy E-R Population)



Source: adap-adpa2m4-pfs-ss-v18.Rmd, Reference: 1882d6; m2.7.2 Figure 25.

Abbreviations: AUC=area under the curve; AUC_{0-6M}= area under the curve from time zero to 6 months postinfusion; E-R=progression-free survival; PFS=progression-free survival

In the same population as that used for efficacy E-R analyses with afamitresgene autoleucel cell kinetic exposure, a correlative analysis was conducted to assess the relationship between GM-CSF, IL-6, and IFN γ exposures and efficacy of afamitresgene autoleucel treatment. No clinically meaningful or actionable associations were identified between any cytokine exposure metrics and efficacy endpoints including ORR, TTR, DOR, and PFS (ADAP-PMX-ADPA2M4-2966 Modeling and Simulation Report).

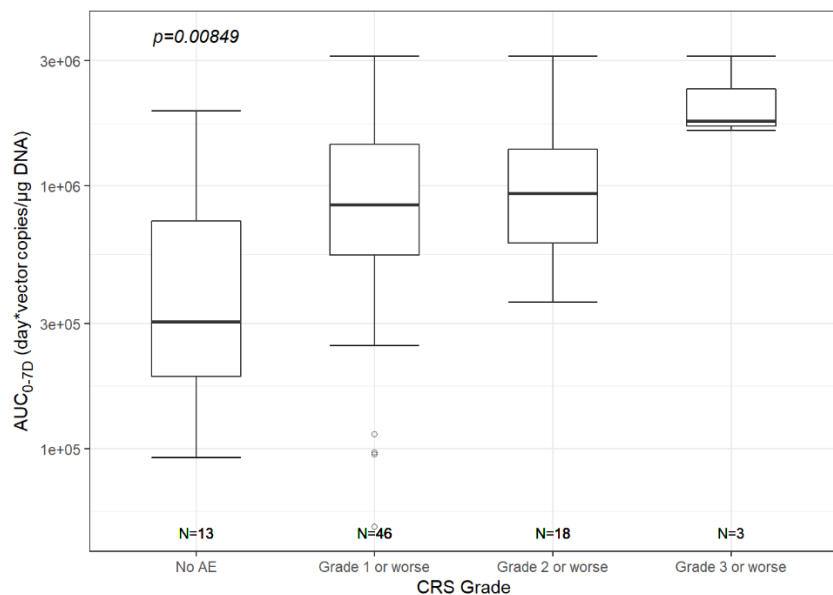
Safety E-R Analyses

E-R analyses with safety were conducted in subjects with SS only (primary analysis) or with any tumor type (secondary), treated with afamitresgene autoleucel in all dose groups of Study ADP 0044-001 and Cohort 1 of Study ADP-0044-002, as of data cut-off: 11Oct2021 (m2.7.2 Section 3.4.2).

Cytokine Release Syndrome (CRS): A limited number of SS subjects in the primary safety E-R analysis population developed Grade ≥ 3 CRS (N = 3). All subjects with Grade ≥ 3 CRS were in the 2 upper quartiles of afamitresgene autoleucel C_{max} and in the highest quartile of AUC_{0-7D}. In

addition, afamitresgene autoleucel exposure appeared to correlate with worsening grade of CRS ([Figure 9](#)). A logistic regression analyses was also conducted, and a statistically significant trend was identified between the probability of Grade ≥ 3 CRS and afamitresgene autoleucel AUC_{0-7D}. A trend toward an increased probability of CRS requiring tocilizumab was also observed in the 2 upper quartiles of afamitresgene autoleucel exposures (C_{max} and AUC_{0-7D}).

Figure 9: Applicant – Afamitresgene Autoleucel AUC_{0-7D} by CRS Grade (Primary Safety E-R Population)



Source: ordinal_regression_safety_script_v2.R, Reference: f66b95; m2.7.2 Figure 28

Abbreviations: AE=adverse event; AUC=area under the curve; AUC_{0-7D}= area under the curve from time zero to 7 days postinfusion; CRS=cytokine release syndrome; E-R=exposure-response; N=sample size.

An ordinal regression analysis was also conducted to further investigate the relationship between exposure and CRS. Relationships were identified between increasing afamitresgene autoleucel AUC_{0-7D} and increasing probability of CRS. In addition, this analysis indicated that throughout the exposure range achieved with the proposed dose range of 2.68 to 9.99×10^9 transduced cells, the probability of experiencing a Grade 2 or 3 CRS event remains lower than the probability of experiencing a Grade 1 CRS event.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): Only 1 subject with SS in the primary safety E-R analysis population experienced an ICANS event as of the cut-off for analysis. In this subject, afamitresgene autoleucel C_{max} and AUC metrics were within the range of exposure in subjects who did not experience ICANS. Three subjects in the secondary safety E-R analysis population (all tumor types), including the subject with SS as described, experienced ICANS events. Afamitresgene autoleucel median C_{max} , AUC_{0-7D}, and AUC_{0-28D} in these 3 subjects was 1.86-, 2.44-, and 1.96-fold that in subjects who did not have an ICANS event.

Serum Cytokines (m2.7.2 Section 3.5): In the same population as that used for safety E-R analyses with afamitresgene autoleucel cell kinetic exposure, a correlative analysis was conducted to assess the relationship between GM-CSF, IL-6, and IFN γ exposures and safety of afamitresgene autoleucel treatment. Markedly higher C_{max} , AUC_{0-7D}, and AUC_{0-28D} of all 3 evaluated cytokines were observed in subjects who developed Grade ≥ 3 CRS (n = 3) compared to subjects without Grade ≥ 3 CRS (n = 56). [Table 7](#) summarizes the ratio of cytokine exposures in subjects who experienced Grade ≥ 3 CRS versus those who did not. A logistic regression analysis was also conducted with cytokine exposures and CRS requiring tocilizumab, which identified a relationship between exposure of all three cytokines and CRS requiring tocilizumab.

Table 7: Applicant – Cytokine Exposures by CRS Incidence (Primary Safety E-R Population)

Cytokine	Exposure Parameter	Exposure Ratio in Subjects With Grade ≥ 3 CRS to Subjects With Grade < 3 CRS
GM-CSF	C_{max} (ng/L)	35.58
	AUC _{0-7D} (day• ng/L)	37.68
	AUC _{0-28D} (day• ng/L)	15.57
IL-6	C_{max} (ng/L)	19.17
	AUC _{0-7D} (day• ng/L)	36.00
	AUC _{0-28D} (day• ng/L)	60.66
IFN γ	C_{max} (ng/L)	24.52
	AUC _{0-7D} (day• ng/L)	23.42
	AUC _{0-28D} (day• ng/L)	12.04

Source: adap-adpa2m4-safety-cytokine-eda-ss-v7.Rmd, Reference: 8b98b0, adap-adpa2m4-safety-cytokine-eda-ss-v7.Rmd, Reference: 44aa65 and adap-adpa2m4-safety-cytokine-eda-ss-v7.Rmd, Reference: 315cd3; m2.7.2 Table 11.
Abbreviations: C_{max} =maximum concentration in circulation; CRS=cytokine release syndrome; E-R=exposure-response; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN γ =interferon γ ; IL-6=interleukin-6; n=sample size

Three subjects in the secondary analysis population (all tumor types), including 1 subject with SS, experienced ICANS events. Higher levels of GM-CSF, IL-6 and IFN γ were observed in these 3 subjects than in those who did not have an ICANS event.

The Applicant's Position:

Overall, the clinical pharmacology analyses support the proposed recommended afamitresgene autoleucel dose range of 2.68 to 10 x 10⁹ MAGe-A4 TCR positive T-cells.

The FDA's Assessment:

[FDA clinical pharmacology review focused on the Phase 2 Study ADP-0044-002 Cohort 1 (data cut-off date: March 29, 2023). Phase 1 Study ADP-0044-001 (data cut-off date: September 1, 2020) was reviewed as supportive data.]

General Pharmacokinetics/Cellular Kinetics

Following a single intravenous infusion, afamitresgene autoleucel exhibited an initial engraftment and expansion phase followed by contraction, and then persistence. The median

time to achieve peak levels in blood was 7 days (range: Day 1 to Day 89) post-dosing. However, high inter-individual variability was observed for afamitresgene autoleucel transgene exposures including C_{max} and AUCs. In general, afamitresgene autoleucel expansion increased with increasing administered dose.

Patients who received tocilizumab showed a trend toward higher afamitresgene autoleucel C_{max} , AUC_{0-7D} , and AUC_{0-28D} than those who did not. Tocilizumab use did not have a marked impact on later afamitresgene autoleucel AUC metrics, that is, AUC_{0-3M} and AUC_{0-6M} . The observations are in line with the observation that higher TECELRA expansion levels are associated to more severe adverse events that require management with medications.

The use of G-CSF for neutropenia prophylaxis, bridging therapy, and the number of prior lines of systemic therapy had no effect on afamitresgene autoleucel cell kinetics.

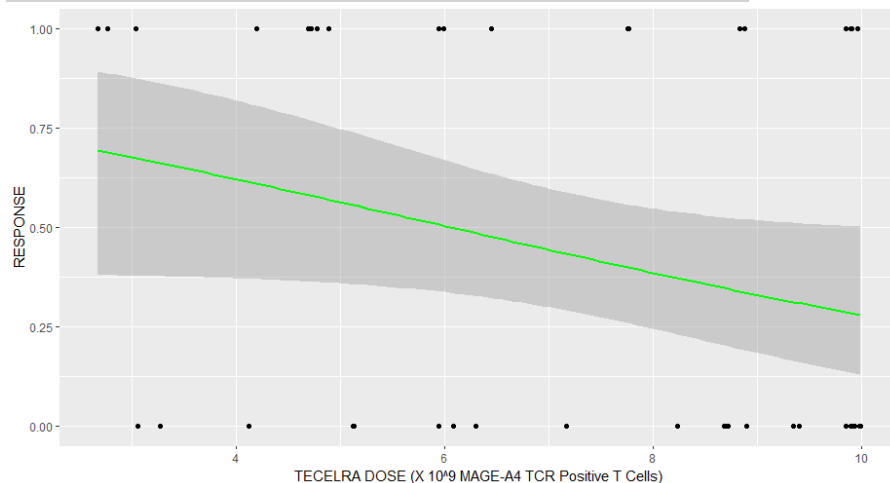
Pharmacodynamics

In patients with synovial sarcoma who were treated with afamitresgene autoleucel, serum concentrations of cytokines and other soluble factors involved in cellular homeostasis, T cell activation and inflammation (e.g., IFN γ , IL-6, IL-8, IL-15, and IL-2R α) increased post-infusion, generally peaking between Days 3 and 8.

Dose-Response Analysis

The overall response rate was evaluated in 4 dose subgroups across the dose range (2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells) for Study ADP-0044-002 Cohort 1 patients with SS. The overall response rate (ORR) for the highest dose subgroup ($8.13 - 10.0 \times 10^9$ MAGE-A4 TCR positive T cells) was 27.3%. The ORR in patients who received less than 8.0×10^9 MAGE-A4 TCR positive T cells was higher than that in the highest dose subgroup ($8.13 - 10.0 \times 10^9$ MAGE-A4 TCR positive T cells) (Figure 10). Kaplan-Meier analysis was conducted to assess the relationship between afamitresgene autoleucel dose and duration of response (DOR). The results of Kaplan-Meier analysis suggested that patients received more than 8.13×10^9 MAGE-A4 TCR positive T cells had higher probability of longer duration of response (DOR) (Figure 11). Given the small sample size in the subgroups of different dose ranges, the results should be interpreted with caution and no definitive conclusion can be made. The relationship between dose and clinical efficacy endpoints (ORR and DOR) supported the Applicant proposed dose range of afamitresgene autoleucel: 2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells.]

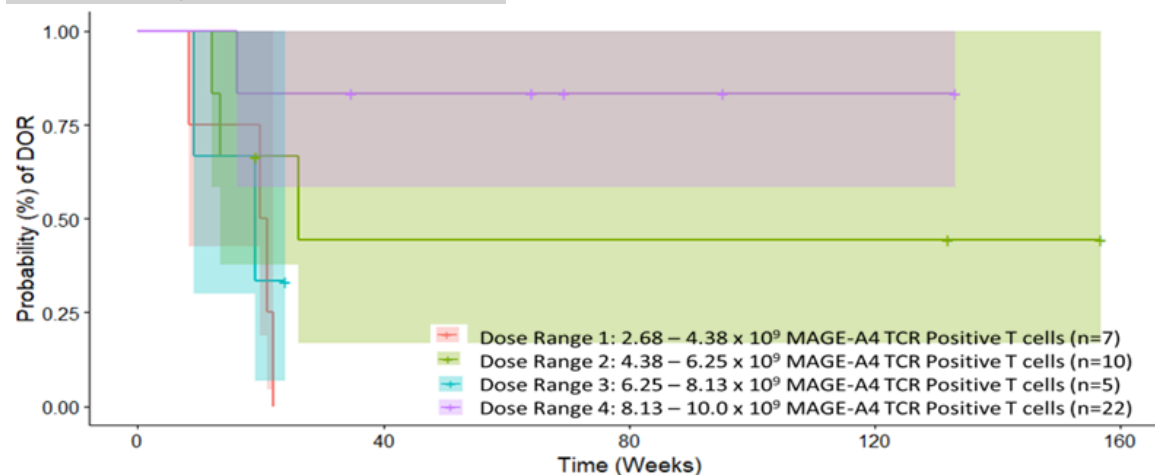
Figure 10. FDA – Afamitresgene Autoleucel (TECELRA) Dose-Efficacy (Overall Response Rate) Response Relationship, Study ADP-0044-002, Cohort 1 Patients With SS



Source: FDA Clinical pharmacology reviewer's analysis

Abbreviations: MAGE = melanoma-associated antigen, ORR = overall response rate, SS = synovial sarcoma, TCR = T cell receptor

Figure 11. FDA – Duration of Response by Afamitresgene Autoleucel Dose Quantile Groups, Study ADP-0044-002, Cohort 1 Patients With SS



Source: FDA Clinical pharmacology reviewer's analysis

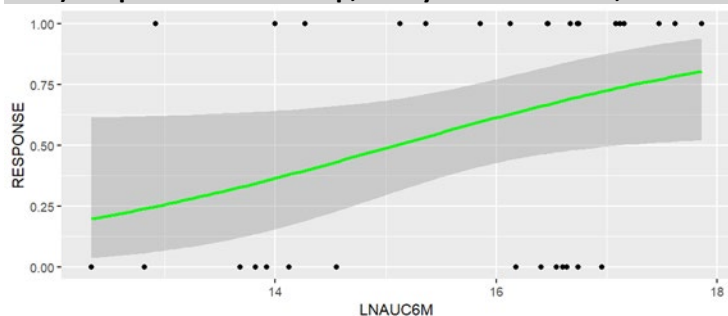
Abbreviations: DOR = duration of response, MAGE = melanoma-associated antigen, n = number of patients in the specified group, SS = synovial sarcoma, TCR = T cell receptor

There were very limited numbers of adverse events of CRS Grade ≥ 3 ($n=3$) and adverse events of ICANS any grade ($n=$ one adverse event of Grade 1) observed within the recommended dose range in patients with SS. Due to the limited number of adverse events of CRS Grade ≥ 3 and ICANS any grade, there was no clear relationship established between the dose of afamitresgene autoleucel and the risks of CRS Grade ≥ 3 and ICANS any grade. In addition, the administered doses of afamitresgene autoleucel in patients who had CRS Grade ≥ 3 or ICANS any grade were less than 8.0×10^9 MAGE-A4 TCR-positive T cells.

Exposure-Response Analysis

Afamitresgene autoleucel PK parameter, AUC_{0-6M} appeared to be positively associated with ORR ([Figure 12](#)). Patients with the highest quantile of afamitresgene autoleucel exposure (C_{max} and AUCs) tended to have higher probability of longer duration of response ([Figure 13](#)).]

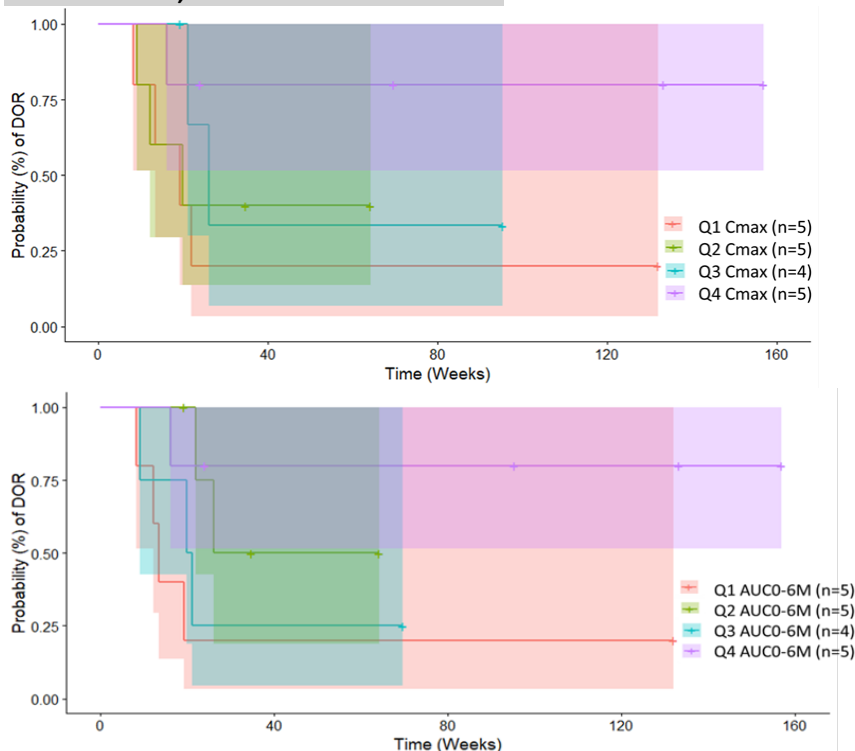
Figure 12. FDA – Afamitresgene Autoleucel (TECELRA) Exposure (AUC_{0-6M})-Efficacy (Overall Response Rate) Response Relationship, Study ADP-0044-002, Cohort 1 Patients With SS



Source: FDA Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-6M} = Area under the concentration-time curve from Day 0 to Month 6, SS = synovial sarcoma

Figure 13. FDA – Duration of Response by Afamitresgene Autoleucel Exposure Quantile Groups, Study ADP-0044-002, Cohort 1 Patients With SS



Source: FDA Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-6M} = Area under the concentration-time curve from Day 0 to Month 6, C_{max} = maximum concentration in circulation, DOR = duration of response, n = number of patients in the specified group, SS = synovial sarcoma

There were very limited numbers of adverse events of CRS Grade ≥ 3 and one adverse event of ICANS (Grade 1) observed within the recommended dose range in patients with SS. Due to the limited number of incidences of ICANS and severe CRS, there was no clear relationship established between the exposure of afamitresgene autoleucel and the risks of ICANS and CRS ≥ 3 . In summary, based on the dose/exposure-response (efficacy and safety) relationship analysis, the Applicant proposed recommended dose range (2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells) appears to be acceptable. Please refer to Clinical Pharmacology reviewer's memo for details.]

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

See [Section 6.2.2.1](#) and [Section 6.3.1](#).

The Applicant's Position:

Overall, the clinical pharmacology properties of afamitresgene autoleucel support the use of afamitresgene autoleucel in the intended indication at the proposed recommended dose range.

The FDA's Assessment:

[FDA agrees that data from Study ADP-0044-002 Cohort 1 and Study ADP-0044-001 support the Applicant's proposed dose range (2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells) of afamitresgene autoleucel for the intended indication. Please refer to FDA Clinical Pharmacology reviewer's memo for detailed information.]

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

See [Section 6.2.2.1](#) and [Section 6.3.1](#).

The Applicant's Position:

Among subjects with SS dosed in the ADP-0044-002 study (data cut-off 29Mar2023), the infused dose range was 2.68 to 9.99×10^9 transduced cells (median 8×10^9), and responses were observed at the lowest and highest dose administered. By independent review, the ORR was 38.6% (95% CI: 24.36, 54.50), and median DoR was 11.6 months (95% CI: 4.4, NE) and ranged from 2.7 to 32 months as of the data cut-off.

In the pooled SS subjects dosed across ADP-0044-002 and ADP-0044-001 (at the RP2D range), no dose-response trends with ORR, DOR, or PFS were observed over the afamitresgene autoleucel dose range received.

In the pooled analysis, the probability of Grade ≥ 3 CRS was higher in the upper quartiles of dose ($>5.13 \times 10^9$ transduced cells) compared to the lower quartile. There was similar trend towards an increased probability of CRS requiring tocilizumab in the upper two quartiles of cell dose. However, a low incidence of Grade ≥ 3 CRS was observed at the recommended dose range ($n=3$). A low incidence of ICANS was also observed across this dose range.

The FDA's Assessment:

[FDA agrees with the Applicant's proposed dose range (2.68×10^9 to 10.0×10^9 MAGE-A4 TCR positive T cells) of afamitresgene autoleucel for the treatment of adult patients with unresectable or metastatic synovial sarcoma (SS). Please refer to FDA's assessment in [Section 6.3.1](#) for detailed information.]

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

See [Section 6.2.2.2](#).

The Applicant's Position:

None of the demographic and disease factors evaluated impacted afamitresgene autoleucel pharmacokinetics parameters. Therefore, no dose adjustment is recommended based on any of these patient factors.

The FDA's Assessment:

[FDA agrees with the Applicant's position.]

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

See [Section 6.2.2.2](#).

Food-drug studies are not applicable, as afamitresgene autoleucel is a genetically modified T-cell immunotherapy administered by intravenous infusion.

The Applicant's Position:

No alternative dosing recommendations are proposed for patients who receive bridging therapy, tocilizumab for management of CRS, or G-CSF for neutropenia prophylaxis.

The FDA's Assessment:

[FDA concurs with the Applicant.]

7. Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

The afamitresgene autoleucel clinical development program was initiated with the ADP-0044-001 phase 1 study to evaluate the safety, tolerability, and anti-tumor activity of afamitresgene autoleucel in HLA-A*02 positive subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors. ADP-0044-001R, a sub-study of ADP-0044-001, aimed to characterize safety and tolerability and assess anti-tumor activity of low dose radiation in combination with afamitresgene autoleucel across the tumor types included in the main protocol. Both ADP-0044-001 and ADP-0044-001R studies have long-term follow-up (LTFU) phase ongoing.

Evidence on safety, tolerability, and antitumor activity from the ADP-0044-001 study, provided the rationale to conduct Study ADP-0044-002 (registration-directed trial), a phase 2, single-arm, open-label clinical trial to evaluate efficacy of afamitresgene autoleucel in HLA-A*02 positive MAGE-A4 expressing advanced SS or myxoid/round cell liposarcoma (MRCLS). The study is composed of 2 independent and serially enrolled Cohorts (Cohort 1 and 2). The primary endpoint was ORR per RECIST v1.1 by independent review in Cohort 1. Secondary endpoints included safety, ORR, TTR, DOR, BOR, PFS and OS. The study has met its pre-specified threshold for demonstrating efficacy, i.e., the lower bound of the 95% CI exceeded the historical ORR of 18% in Cohort 1. The study is ongoing. Details for these studies are provided in [Table 8](#).

NDA/BLA Multi-disciplinary Review and Evaluation BLA 125789
TECELRA (afamitresgene autoleucel)

Table 8: Applicant – Listing of Clinical Trials Relevant to this BLA

Trial Identity/ NCT Nr	Trial Design	Regimen/ Schedule/ Route	Primary and Key Secondary Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers and Countries
Open-label Studies to Support Efficacy and Safety							
Main Study: ADP-0044-002 NCT 04044768	Phase 2 single- arm, open- label study	Lymphodepletion Fludarabine 30 mg/m ² /day for 4 days (Days -7, -6, -5, -4) and cyclophosphamide 600 mg/m ² /day for 3 days (Days -7, -6, - 5). Afamitresgene autoleucel Single IV infusion at a dose range of 1–10 x 10 ⁹ transduced cells.	Primary: ORR by RECIST v1.1 per independent review in Cohort 1. Secondary: AEs, SAEs, incidence, severity, and duration of the AESIs, RCL, T- cell clonality and insertional oncogenesis. ORR (across cohorts), TTR, DoR, BOR, PFS, OS. Development and validation of the MAGE-A4 antigen expression companion diagnostic assay. Peak persistence and other relevant PK parameters of afamitresgene autoleucel.	Single IV infusion of afamitresgene autoleucel. Subjects are followed for 15 years post-infusion for delayed gene therapy related AEs.	N=52 (Cohort 1) SS patients: 44 (Cohort 1; data cut-off: 29Mar2023) N=36 (Cohort 2) SS patients: 36; safety, data cut-off 29Mar 2023	HLA- A*02:01P, HLA- A*02:03P or HLA- A*02:06P positive patients (and HLA- A*02:05P negative) with MAGE- A4 expressing metastatic or inoperable (advanced) SS or MRCLS.	25 sites United States, Canada, United Kingdom, France, and Spain.
Supportive Study: ADP-0044-001 NCT 03132922	Phase 1, open- label, dose escalation study	Lymphodepletion Groups 1 and 2: Cyclophosphamide 600 mg/m ² /day + fludarabine 30 mg/m ² /day on Days 7, -6, and -5. Group 3 and Expansion group:	Primary: AEs, serious adverse event (SAEs); laboratory assessments, incidence of DLTs and determination of optimally tolerated dose range. Persistence of afamitresgene autoleucel and RCL over time.	Single IV infusion of afamitresgene autoleucel. A second infusion was allowed under protocol specified conditions. Subjects are followed for 15	N=38 (2 received a second infusion) SS patients: 16	HLA-A*02 positive (and HLA- A*02:05P negative) adult patients with MAGE-A4 inoperable	10 sites United States and Canada.

NDA/BLA Multi-disciplinary Review and Evaluation BLA 125789
TECELRA (afamitresgene autoleucel)

Trial Identity/ NCT Nr	Trial Design	Regimen/ Schedule/ Route	Primary and Key Secondary Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers and Countries
		<p>Cyclophosphamide 600 mg/m²/day on Days -7, -6, -5 and fludarabine 30 mg/m²/day on Days 7, -6, -5, and -4. or Cyclophosphamide (1800 mg/m²/day) on Days -3 and -2 + fludarabine (30 mg/m²/day) on Days -5, -4, -3, and -2</p> <p>Afamitresgene autoleucel (IV infusion) Group 1: (0.08 to 0.12) ×10⁹ transduced cells Group 2: (0.5 to 1.2) ×10⁹ transduced cells Group 3: (1.2 to 6) ×10⁹ transduced cells Expansion group: (1.2 to 10) ×10⁹ transduced cells</p>	<p>Secondary: ORR by RECIST v1.1, BOR, TTR, DoR, duration of stable disease, PFS, OS. Presence of gene therapy-related delayed AEs in LTFU.</p>	years post-infusion for delayed gene therapy related AEs.		locally advanced or metastatic tumors.	

NDA/BLA Multi-disciplinary Review and Evaluation BLA 125789
TECELRA (afamitresgene autoleucel)

Trial Identity/ NCT Nr	Trial Design	Regimen/ Schedule/ Route	Primary and Key Secondary Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers and Countries
Studies to Support Safety							
ADP-0044-001R	Multi-center sub-study of ADP-0044-001 (phase 1)	<u>Radiation</u> 3-5 days beginning 5 days prior to lymphodepletion, at a dose of 1.4Gy/lesion/day (total up to 7Gy per lesion/ isocenter). <u>Lymphodepletion</u> Cyclophosphamide 600 mg/m ² /day on Days -7, -6, and -5 + fludarabine 30 mg/m ² /day on Days -7, -6, -5, and -4. <u>Afamitresgene autoleucel</u> Single IV infusion at a dose range of 1.2 ×10 ⁹ – 10 ×10 ⁹ transduced cells.	Primary: AEs, SAEs, incidence of DLTs, persistence of afamitresgene autoleucel and RCL over time Secondary: ORR by RECIST v1.1, BOR, TTR, DoR, duration of stable disease, PFS, OS. Presence of gene therapy-related delayed AEs in LTFU.	Single IV infusion of afamitresgene autoleucel. Subjects are followed for 15 years post-infusion for delayed gene therapy related adverse events.	N=5 ^a SS patients: 1	HLA-A*02 positive (and HLA-A*02:05P negative) adult patients with MAGE-A4 expressing tumors	2 sites United States and Canada.

a. 5 subjects received low-dose radiation (1 with SS), and 4 received low-dose radiation and afamitresgene autoleucel in the sub-study).

Abbreviations: AEs – adverse events; BOR- best overall response; DLTs- dose limiting toxicities; DOR- Duration of response; IV- intravenous; LTFU- long-term follow-up; ORR- overall response rate; OS- overall survival; PFS- progression free survival; RCL-replication competent lentivirus; RECIST- Response Evaluation Criteria in Solid Tumors; SAEs- serious adverse events; TTR- time to response; SS- synovial sarcoma.

The Applicant's Position:

The primary evidence to support the efficacy and safety of afamitresgene autoleucel in the proposed indicated population is provided by the registration-directed study ADP-0044-002 (Cohort 1). The ADP-0044-001 study provides supportive efficacy evidence in subjects with advanced SS (N=16 subjects) dosed at the same afamitresgene autoleucel dose range as in the phase 2 study, as well as supportive safety data from subjects with SS and subjects with other indications. The ADP-0044-001R sub-study provide additional supportive safety data.

The FDA's Assessment:

[FDA's efficacy analysis is based on patients with SS who enrolled and received afamitresgene autoleucel in Cohort 1 of Study ADP-0044-002 (n=44) with a data cut-off date of March 29, 2023.]

8. Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 ADP-0044-002

Trial Design

The Applicant's Description:

The primary evidence of efficacy for afamitresgene autoleucel is based on data from subjects with SS dosed in Cohort 1 of Study ADP-0044-002 (data cut-off: 29Mar2023).

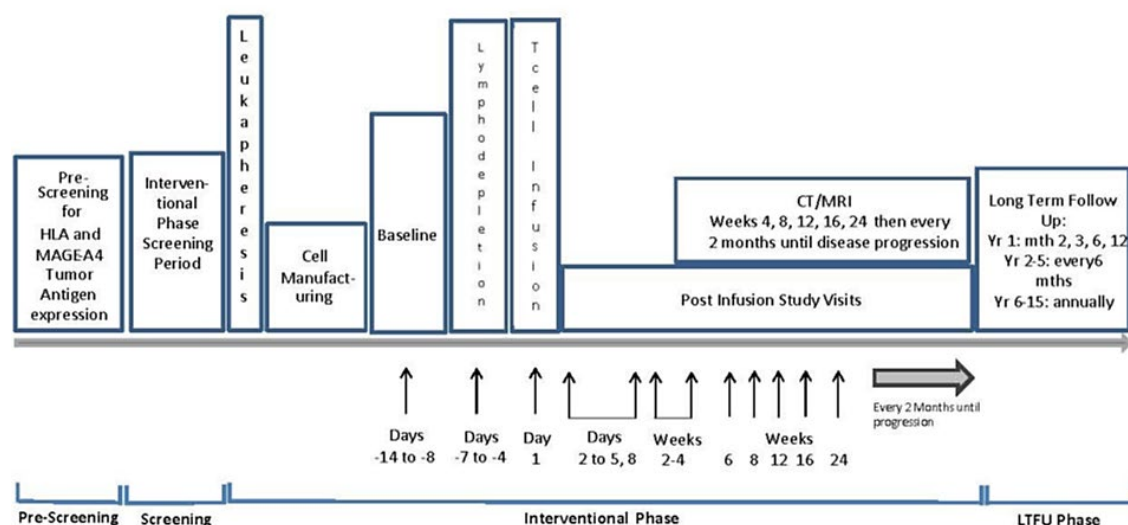
ADP-0044-002 is a phase 2, single-arm, open-label clinical study of afamitresgene autoleucel in HLA-A*02 positive subjects with MAGE-A4 expressing advanced SS or myxoid/round cell liposarcoma (MRCLS), who have received at least one line of prior systemic therapy. The study comprises of 2 separate, independent, and serially enrolled cohorts: Cohorts 1 and 2.

Once afamitresgene autoleucel was available at the respective sites, subjects underwent lymphodepleting chemotherapy with fludarabine 30 mg/m²/day for 4 days (Days -7 to -4) and cyclophosphamide 600 mg/m²/day for 3 days (Days -7 to -5) followed by infusion of afamitresgene autoleucel cells on Day 1. Subjects remained hospitalized for observation for at least 24 hours post-T-cell infusion. Discharge following T-cell infusion was at the discretion of the investigator. All subjects were reviewed by the investigator (or a designated study physician) prior to discharge.

Efficacy was assessed by both local and independent review using RECIST v1.1. To allow time for the immune response to become apparent and for potential transient inflammatory reactions of the disease to the treatment (“tumor flare”), disease progression was not determined before 4 weeks (28 days) post-infusion of afamitresgene autoleucel unless there was unequivocal clinical evidence of deterioration. Subjects were evaluated in the clinic according to the Interventional Phase schedule until disease progression. Upon completion of the Interventional Phase, subjects followed the Long-term Follow-up (LTFU) schedule. Subjects were to be followed for 15 years after treatment. During the LTFU Phase, subjects were only monitored for the following potential gene therapy-related delayed AEs: new malignancies; new incidence or exacerbation of a pre-existing neurological disorder; new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder; new incidence of hematologic disorder; opportunistic and/or serious infections; unanticipated illness and/or hospitalization deemed related to gene-modified cell therapy.

The study schematic is presented as presented in [Figure 14](#).

Figure 14: Applicant – Schematic for Study ADP-0044-002



Source: ADP-0044-002 CSR, Section 6.1

ADP-0044-002 was designed to demonstrate a substantial improvement in ORR over available second-line therapies in subjects with advanced disease previously treated (Cohort 1). To meet the pre-specified threshold for demonstrating efficacy, the lower bound of the 95% CI must exceed the historical ORR of 18%, for available second-line therapies, such as pazopanib and trabectedin ([Table 1](#)).

The FDA's Assessment:

[The primary evidence to support efficacy of afamitresgene autoleucel comes from patients with SS treated in Cohort 1 of Study ADP-0044-002. The primary endpoint of the study was ORR per RECIST v1.1 by independent review.]

Per protocol, the pre-specified cut-off for the primary analysis was planned to occur once the last patient dosed in Cohort 1 (including patients with SS and patients with MRCLS) had up to 6 months follow-up post T cell infusion or had ended the interventional phase of the study. Thus, the Applicant originally proposed an efficacy data cut-off of August 29, 2022. At FDA's request, the Applicant submitted an efficacy update with additional duration of response follow up for Cohort 1. Therefore, the FDA's data cut-off to support the efficacy analysis is March 29, 2023.

The Applicant's pre-specified threshold for demonstrating efficacy was the lower bound of the 95% CI exceeding an ORR of 18%, based on historical data for available second-line therapies, such as pazopanib and trabectedin. FDA notes the following issues with the proposed pre-specified threshold for demonstrating efficacy:

- The null hypothesis regarding ORR (18%) for Study ADP-004-002 (SPEARHEAD-1) is based on estimated ORR in the second-line setting (e.g., disease progression after first-line treatment for metastatic disease) using historic data.
- The reported ORR of pazopanib for metastatic SS in the second line and greater setting from clinical trials and real-world data ranges from 13% to 20% with wide confidence intervals given the small sample sizes. ([Carroll et al. 2022](#)).

A limitation of the ADP-0044-002 study design is that the protocol allowed on-study tumor biopsies for exploratory biomarker objectives at baseline and approximately Week 4. Specifically, protocol section 8.6.1 states, "tumor tissues should either be taken from non-target lesions or from target lesions where sampling can be done without impacting lesion measurement." Biopsies of target lesions by independent review may confound response assessment. Detailed information on the patients who underwent on-study tumor biopsies, including implication on response assessment, are provided in [Section 8.1.2, Study Results](#).]

Eligibility Criteria

The Applicant's Description:

Key Inclusion Criteria:

- Age ≥ 16 and ≤ 75 years at the time the pre-screening informed consent/assent is signed.
- Diagnosis of advanced (metastatic or inoperable) SS or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics.
- Must have previously received either an anthracycline or ifosfamide containing regimen. Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy.

- Measurable disease according to RECIST v1.1.
- Positive for HLA-A*02:01, HLA-A*02:03 or HLA-A*02:06 allele via Adaptimmune designated central laboratory testing. HLA-A*02 alleles having the same protein sequence in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the sponsor (note: HLA-A*02:02P was also considered eligible based on preclinical data)
- Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of $\geq 2+$ staining in $\geq 30\%$ of the cells by immunohistochemistry. All samples must have been pathologically reviewed by an Adaptimmune designated central laboratory confirming expression.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Left ventricular ejection fraction (LVEF) $\geq 50\%$.
- Female subjects of childbearing potential must have a negative urine or serum pregnancy test and must agree to use an effective method of contraception starting at the first dose of chemotherapy and continuing for at least 12 months, or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer. Male subjects must be surgically sterile or agree to use a double barrier contraception method or abstain from heterosexual activity with a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).
- Must have adequate organ function as indicated by hematological, coagulation, renal, and hepatic laboratory values.

Key Exclusion Criteria:

- Positive for HLA-A*02:05 (including P group) in either allele via Adaptimmune designated central laboratory testing.
- Received or planned to receive allogeneic hematopoietic stem cell transplant or gene therapy using an integrating vector prior to leukapheresis or lymphodepleting chemotherapy: or. Subject who received cytotoxic chemotherapy, tyrosine kinase inhibitor, immune therapy, anti-cancer vaccine, corticosteroids, radiotherapy, major surgery or other investigational treatment must follow specified wash-out periods.
- Toxicity from previous anti-cancer therapy must have recovered to \leq Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that were deemed stable or irreversible (e.g., peripheral neuropathy) could have been enrolled.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide, or other agents used in the study.
- History of autoimmune or immune mediated disease.
- Symptomatic CNS metastases including leptomeningeal disease.

- Uncontrolled intercurrent illness including: ongoing or active infection; clinically significant cardiac disease defined by congestive heart failure New York Heart Association Class 3 or Class 4; uncontrolled clinically significant arrhythmia; Acute Coronary Syndrome in last 6 months; interstitial lung disease; congenital or family history of long QT syndrome; uncontrolled hypertension despite optimal medical therapy; history of stroke or central nervous system bleeding; transient ischemic attack or reversible ischemic neurologic deficit in last 6 months; incipient compression/occlusion of a vital structure which cannot undergo prophylactic stenting; COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy.
- Active infection with HIV, HBV, HCV or HTLV.
- Pregnant or breastfeeding.

The FDA's Assessment:

[The protocol-defined inclusion criteria require prior treatment with an anthracycline- and/or ifosfamide-containing regimen. Patients, who were intolerant of both an anthracycline and ifosfamide, were eligible as long as they received one prior line of systemic therapy. Given that patients who are intolerant to standard of care doxorubicin and/or ifosfamide may have a different prognosis compared to patients who have received prior doxorubicin and/or ifosfamide, this inclusion criteria may introduce a heterogeneous population and may make interpretation of ORR challenging.]

Progression following first-line therapy was not required. Additionally, the eligibility criteria were revised in the most recent amendment of the protocol (Amendment 3, February 5, 2021) to allow first-line metastatic treatment with afamitresgene autoleucel if ifosfamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting. This inclusion criteria may potentially include a heterogeneous study population, particularly for Cohort 2 and 3.

ADP-0044-002 Cohort 1 also included patients with myxoid liposarcoma/MRCLS; however, patients with MRCLS are not included in the primary efficacy analysis. In addition, the protocol allowed inclusion of pediatric patients 16 years or older. However, no pediatric patients were enrolled in Cohort 1.

Patients were required to meet all eligibility criteria prior to leukapheresis and prior to lymphodepleting (LD) chemotherapy.]

Study Endpoints

The Applicant's Description:

The primary endpoint of the study was ORR per RECIST v1.1 by independent review in Cohort 1.

The secondary endpoints were (for Cohort 1 and across Cohorts): safety – adverse events (Aes) including serious adverse events (SAEs), incidence, severity and duration of the Aes of special interest (AESIs), Replication Competent Lentivirus (RCL), T-cell Clonality and Insertional oncogenesis (IO); efficacy – time to response (TTR), duration of response (DoR), best overall response (BOR), progression free survival (PFS), overall survival (OS), and ORR per RECIST v1.1 by independent review across Cohorts; retention of additional tumor tissue during pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay; peak persistence and other relevant PK parameters of afamitresgene autoleucel.

The FDA's Assessment:

[The primary endpoint of the study was ORR per RECIST v1.1 by IRC. The FDA's primary determination of efficacy is based on confirmed ORR by IRC re-review, further supported by DOR. See [Section 8.1.2, Data Quality and Integrity](#), for additional details on the re-review of response assessment by a new IRC that was requested by FDA.

Taking into account the rarity of the disease and the lack of alternative treatment options for advanced unresectable and/or metastatic SS, the endpoint of ORR supported by DOR is reasonably likely to predict clinical benefit that can support a marketing application of afamitresgene autoleucel in the proposed indication under accelerated approval.]

Statistical Analysis Plan and Amendments

The Applicant's Description:

The first version of the Statistical Analysis Plan (SAP) was issued on 02 April 2021, amended to version 2.0 on 19 Oct 2021 (ADP-0044-002 Appendix 16.1.9). A separate SAP dated 09Feb2023, was also created to incorporate additional analysis for the CSR Supplement (Efficacy; ADP-0044-002-S1 Appendix 16.1.9). The changes in each version are summarized in [Table 9](#).

Table 9: Applicant – Study ADP-0044-002 SAP and Amendments

SAP Version	Version Date	Summary of Changes	Rationale for Changes
1.0	02Apr2021	New document	Not applicable.
2.0	19Oct2021	<ul style="list-style-type: none">Sensitivity analyses for secondary efficacy endpoints are not required to be performed.Update to missing date imputation algorithm.Replace one-sided 97.5% confidence intervals with two-sided 95% confidence intervals	<ul style="list-style-type: none">To test the robustness of the secondary efficacy endpoints, sensitivity analyses maybe performed as data permits.Update to the imputation algorithm to conform to Company standard.Change to two-sided 95% cIs to provide the estimation of the upper bound for primary endpoint.Summary of the Immune Effector

SAP Version	Version Date	Summary of Changes	Rationale for Changes
		<p>for primary endpoint.</p> <ul style="list-style-type: none"> Add additional safety summaries. Definitions of H Score/ P Score added. Discordance analysis added. PFS/ DOR definitions and censoring rules updated. Update to summarize TTR using regular descriptive statistics. 	<p>Cell-Associated Encephalopathy neurological assessment results is added. Details of CARTOX scores are added.</p> <ul style="list-style-type: none"> The definitions of H Score/ P Score were not provided in version 1.0. To assist in the interpretation of DoR. Update the PFS/DoR definition to ensure the accuracy. <p>Adding more details of prohibited concomitant medications in time to event censoring rules.</p> <ul style="list-style-type: none"> No censoring rules will be applied to TTR, thus Kaplan-Meier method is replaced with regular summary of statistics.
Additional Analysis for CSR Supplement	09Feb2023	<ol style="list-style-type: none"> Update to include summary of BOR and ORR for ITT population. Update to include summary of concordance between BOR per Independent Reviewer and BOR per Investigator using RECIST v1.1. Update to include summary of BOR by subgroup. Update to include summary of viable transduced dose cells. 	<ol style="list-style-type: none"> To provide the efficacy assessment of the primary endpoint in the ITT population. To assist in the interpretation and the robustness of the BOR analysis. To have consistent summary with integrated summary of efficacy. To provide an exploratory assessment of dose (incorporating cell viability).

Analysis populations

The following analysis populations were used in the study:

- Intention-to-treat population (ITT): All subjects who were enrolled in the trial. The ITT population will be used to assess the safety of the end-to-end autologous T-cell therapy procedure.
- Modified intention-to-treat population (mITT): This is the population of all ITT subjects who received T cell infusion. The mITT population is the primary analysis population for safety and efficacy evaluations following T-cell infusion.

Examination of subgroups

Efficacy and safety summaries will be displayed across both SS and MRCLS tumor types (overall) and by tumor type.

Power and Sample Size

Sample size estimation was based on the primary efficacy endpoint, i.e. ORR, defined as the proportion of subjects with a confirmed complete response or partial response via independently reviewed RECIST v1.1 relative to the total number of subjects in the mITT population in Cohort 1.

The clinical and statistical assumptions, hypothesis test, and sample size for this study were based on the following factors:

- Historical ORR was $\leq 13\%$ for SS and $< 10\%$ for MRCLS.
- The ORR for historical control for hypothesis testing was 18%.
- The mechanism of action for the TCR was assumed to be the same for SS and MRCLS.
- The assumed ORR for afamitresgene autoleucel was 0.40.

Statistical design assumptions were as follows:

- The assessment for efficacy was based on the mITT population using confirmed ORR via RECIST v1.1 per independent review.
- The 2-sided type I error (α) for this test was no more than 0.05.
- The type II error (β) did not exceed 0.1.
- Exact binomial method was used to test the hypothesis.
- Cohort 1 is independent.

The hypothesis of interest for the primary endpoint is:

(Null Hypothesis) $H_0: p \leq p_0$, vs. (Alternate Hypothesis) $H_1: p > p_0$, where p_0 (historical control rate) = 0.18.

Based on the above assumptions, a sample size of 45 subjects in Cohort 1 was targeted, in order to provide at least 90% power to reject the null hypothesis if the true ORR is at least 40%. No hypothesis testing was planned for the secondary endpoints.

Handling of Dropouts or Missing Data

In general, imputed partial dates were not used to derive study day, duration (eg, duration of Aes), or elapsed time variables. In addition, imputed dates were not used for deriving the last contact date in the OS analysis dataset.

For AEs, prior/concomitant medications, medical history, and initial diagnosis, partially missing start and stop dates were imputed. In general, AEs were assumed to be treatment-emergent unless there was clear evidence (through comparison of partial dates) to suggest that the AE started before the date of lymphodepletion.

Partial dates were imputed according to analysis data model conventions.

The FDA's Assessment:

[FDA concurs with the Applicant's assessment.]

The Applicant's ORR for historical control for hypothesis testing is 18%, which is estimated for therapies administered in the second-line setting for SS. See [Section 8.1.1, Trial Design](#), for FDA comments on the Applicant's null hypothesis.]

Protocol Amendments

The Applicant's Description:

The original global protocol (25-Feb-2019) was amended 3 times. Important changes in the conduct of the study that were implemented by global protocol amendment are summarized in [Table 10](#).

Table 10: Applicant – Study ADP-0044-002: Global Protocol Amendments Summary

Version	Main Reasons for Amendment
Amendment 1 04-Jun-2019	<ul style="list-style-type: none">• Changed the lymphodepletion regimen• Added ECG at Day 5• Added upper age limit• Increased entry criteria for ANC, platelets, and glomerular filtration rate• Added exclusion criteria under uncontrolled intercurrent illness• Added emerging data for afamitresgene autoleucel• Updated study physician
Amendment 2 26-Mar-2020	<ul style="list-style-type: none">• Updated Sponsor contacts• Updated and clarified HLA criteria• Removed futility analysis and associated protocol aspects• Updated number of subjects• Decreased duration of enrollment• Increased LVEF criteria• Clarified washout for prior gene therapy• Added updated data from the current afamitresgene autoleucel Investigator's Brochure (IB)• Updated CRS management guidelines• Updated grading for CRS and neurologic toxicity associated with immune effector cells
Amendment 3 05-Feb-2021	<ul style="list-style-type: none">• Updated Sponsor contacts• Added Cohort 2 (45 SS subjects)• Updated safety and efficacy information to align with current IB• Added information for COVID-19 requirements• Added exclusion criterion for compression/occlusion of a vital structure• Added EORTC-QLQ-C30 (Cohort 2 only)• Removed companion diagnostic and per-protocol population definitions• Updated template language

Source: ADP-0044-002 CSR, Section 6.11

The FDA's Assessment:

[In addition to the Applicant's summary of protocol amendments above, Amendment 3 (February 5, 2021) revised the eligibility criteria to allow first-line metastatic treatment with afamitresgene autoleucel if ifosfamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting. The revised eligibility criteria introduce the potential for enrolling a heterogenous study population.

Additional amendments to protocol ADP-0044-002 since February 5, 2021, are summarized below in [Table 11](#).

In "Amendment 3 Pediatric Version 1," the Applicant submitted a pediatric version of ADP-0044-002 to allow enrollment of eligible children and adolescents 10 years old and older alongside adults (b) (4)

Table 11: FDA – Summary of Additional Protocol Amendments (After February 5, 2021)

Version	Main Reasons for Amendment
Amendment 3 Pediatric Version 1 August 13, 2021	<ul style="list-style-type: none"> • Update to Sponsor contact • Minimum age for enrollment updated to include patients ≥10 years old with actual body weight ≥40 kg (Cohort 2). • Addition of Lansky Performance Status for patients under 16 years old. • Addition of CAPD scoring for patients under 12 years old. • Addition of PedsQL
Amendment 4 April 14, 2023	<ul style="list-style-type: none"> • Update to sponsor contacts • Addition of Cohort 3 (approximately 30 synovial sarcoma patients) • Modification of inclusion criteria 6; measurable disease according to RECIST v1.1 required prior to lymphodepletion only • Modification of inclusion criteria 7; adding HLA-A*02:02 • Modification of exclusion criteria 2; Gene therapy using a lentiviral vector • Additional safety and efficacy data from ADP-0044-002 Cohort 1 • Update to number of patients • Update to number of clinical sites • Statistical hypothesis for adding Cohort 3 (approximately 30 synovial sarcoma patients) • Additional DSMB meeting information • Update to Persistence flow chart
Amendment 5 August 7, 2023	<ul style="list-style-type: none"> • Updated inclusion #8 to include statement that patients must not be oxygen dependent in response to FDA request following SUSAR 2023-ADP-000016

Source: Protocol amendments

Abbreviations: CAPD = Cornell Assessment Pediatric Delirium, DSMB = Data and Safety Monitoring Board, FDA = Food and Drug Administration, HLA = human leukocyte antigen, kg = kilogram, PedsQL = Pediatric Quality of Life Inventory, RECIST = Response Evaluation Criteria in Solid Tumors, SUSAR = serious and unexpected adverse reaction

8.1.2 Study Results

Compliance with Good Clinical Practices

Data:

A risk-based approach to quality management of study ADP-0044-002 was executed using a Risk Assessment and Categorization Tool (RACT). The RACT identified risks, risk owner(s), and appropriate mitigations for each identified risk factor. Adaptimmune also follows the Data Review Guidelines for ongoing and contemporaneous review of study data to assess any data or data quality issues, assess data trends and review key study efficacy and safety data points. Quality assurance activities were planned and executed by Adaptimmune via audits of study sites and vendors at various times throughout the life cycle of the study. A list of audited study sites is provided in [Table 12](#), and vendors is provided in [Table 13](#). No serious breaches were identified nor were any sites closed due to non-compliance.

Table 12: Applicant – ADP-0044-002: Site Audits

Site	Date of Site Audit
Moffitt Cancer Center	10-11 Jun 2020
Centre Leon Berard	15-16 Sep 2021
Hospital Virgin del Rocio	16-17 Sep 2021
Memorial Sloan Kettering Cancer Center	30 Aug – 01 Sep 2021
University Health Network Princess Margaret Cancer Center	09-10 Sep 2021
University College London Hospital Cancer Clinical Trials Unit	10-11 Aug 2021
Washington University School of Medicine	23-24 Aug 2021

Source: ADP-0044-002 CSR, appendix 16.1.8

Table 13: Applicant – ADP-0044-002 Study: Vendor Audits

Name of Vendor	Title	Audit Date(s)
(b) (4)	Clinical safety database	24-25Nov2021
(b) (4)		16-17Sep2019
(b) (4)	Central laboratory	02-03Nov2021

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Name of Vendor	Title	Audit Date(s)
(b) (4)	Central laboratory for block and slide samples only	28-29Jan2019
(b) (4)	Central laboratory for formalin biopsy sample only	11-12Oct2021
(b) (4)	Laboratory supplies	19-20Feb2019
(b) (4)	Central laboratory	05-06Mar2019 29-31Mar2022
(b) (4)	Central imaging	18-19Sep2018 15-16Mar2022
(b) (4)	Central laboratory for French site	31Jul-01Aug2019
(b) (4)	Laboratory supplies	07-08Apr2020
(b) (4)	Safety management	14-15Aug2019 08-09Feb2022
(b) (4)	Drug Substance Manufacture	18-19Oct2021
(b) (4)	Site of Lentiviral Vector Manufacture	1-2Jun2022
(b) (4)	Lentiviral Vector Release Testing Location	09Nov2021
(b) (4)	Site of Lentiviral Vector and T cell release testing	12-13Oct2021

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Name of Vendor	Title	Audit Date(s)
(b) (4)	Site of LV and T cell release testing	27-28Oct2020
(b) (4)	Site of LV testing	12Sep2019
(b) (4)	IMP Importation	24Oct2022

Source: ADP-0044-002 CSR, Quality Supplement, Appendix 1.

The Applicant's Position:

The study was conducted in accordance with the International Council for Harmonisation (ICH) GCP and all applicable subject privacy requirements and the ethical principles as outlined in the Declaration of Helsinki. The study protocol and amendments were reviewed by Institutional Review Boards or Ethics Committees. Subjects (or legally authorized representative) provided written informed consent to participate in the study. The study was monitored in accordance with ICH E6 R2, Section 5.18.

The FDA's Assessment:

[The Applicant has made an explicit statement of Good Clinical Practice, affirming that all studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures.]

Financial Disclosure

Data:

Principal investigators and sub-investigators participating in Study ADP-0044-002 were assessed for financial disclosures as defined in 21 CFR Part 54, and no investigator had disclosable financial interests or arrangements. Further details of financial disclosure are provided in [Section 19.2](#).

The Applicant's Position:

No investigator participating in the above covered study had disclosable financial interests or arrangements.

The FDA's Assessment:

[The FDA concurs with the Applicant's assessment of financial disclosures of study investigators.

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, as well as if and when the information was updated. The information submitted to the BLA was verified for each of the inspected clinical study sites.

Based on the financial data returned, no investigators in ADP-0044-002, ADP-0044-001, and ADP-0044-001R studies exceeded the \$50,000 threshold for equity interest. Adaptimmune relied upon payments of other sorts of data provided by the clinical investigators, as well as records of non-study-related payments made to clinical investigators by Adaptimmune to determine if the \$25,000 threshold was exceeded in the case of any individual clinical investigator. There are no disclosures to report in this category.]

Patient Disposition

Data:

A total of 63 subjects, 51 subjects with SS and 12 with MRCLS, were enrolled in Cohort 1 of the study and underwent leukapheresis (ITT population), 11 of whom (7 with SS) did not receive afamitresgene autoleucel due to: death from cancer under study (6 subjects, 3 with SS), loss of eligibility prior to lymphodepleting chemotherapy (3 subjects, 2 with SS), withdrawal by subject (1 subject with SS), and investigator decision (1 subject with SS).

Fifty-two subjects, 44 with SS, underwent lymphodepletion chemotherapy and received afamitresgene autoleucel (mITT population) at the recommended dose range. Subject disposition is summarized in [Table 14](#).

Table 14: Applicant – Study ADP-0044-002 – Disposition of Subjects as of CSR Supplement 2; Cut-Off Date 29Mar2023 (Updated Efficacy; ADP-0044-002-S2)

Status	Synovial Sarcoma n (%)	Overall n (%)
Subjects in the ITT population ^a	51 (100.0)	63 (100.0)
Subjects underwent leukapheresis	51 (100.0)	63 (100.0)
Subjects lymphodepleted	45 (88.2)	53 (84.1)
Subjects in the mITT population ^b	44 (86.3)	52 (82.5)
mITT population	N=44	N=52
Subjects ongoing in Interventional Phase	6 (13.6)	6 (11.5)
Subjects ended Interventional Phase in mITT population (had T-cell infusion) ^c	38 (100.0)	46 (100)
Primary reason for ending Interventional Phase		
Clinical progression ^d	3 (7.9)	4 (8.7)

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Status	Synovial Sarcoma n (%)	Overall n (%)
Death	4 (10.5)	4 (8.7)
Noncompliance with study requirements ^e	1 (2.6)	1 (2.2)
Progressive disease	30 (78.9)	37 (80.4)
Subjects who entered LTFU	31 (70.5)	37 (75.0)
Subjects who completed the study ^f	24 (54.4)	31 (59.6)
Subjects discontinued from study	28 (63.6)	35 (67.3)
Primary reason for discontinuation from study		
Death	24 (54.5)	31 (59.6)
Lost to follow-up	1 (2.3)	1 (1.9)
Noncompliance with study requirements ^e	1 (2.3)	1 (1.9)
Withdrawal by subject	2 (4.5)	2 (3.8)

Source: Tables SUR-14.1.1_C1 and SUR-14.1.1.1_C1 ADaM: ADSL

a. The ITT population included all subjects who were enrolled in the study (ie, signed consent and met eligibility criteria). The text of Clinical Study Report ADP-0044-002-S2 Section 2.1 Subject Disposition is correct; there were 51 subjects with synovial sarcoma who underwent leukapheresis in Cohort 1. Table 1 within Clinical Study Report ADP-0044-002-S2 is incorrect and inadvertently includes one additional subject (b) (6) within Cohort 1. Subject (b) (6) was included in Cohort 2.

b. The mITT population included all subjects who received the T-cell infusion.

c. Percentages were calculated using the number of subjects discontinued.

d. Clinical progression was determined by the PI evaluation when a subject had clear disease progression in the absence of radiological confirmation of PD per RECIST v1.1.

e. The term unable/unwilling to comply with study requirements was specified in the protocol. This protocol-specific reason was mapped to the following SDTM-controlled term: noncompliance with study requirements.

f. Includes subjects in the mITT population who completed 15 years in the study and subject deaths per protocol.

As of this data-cut, the overall median follow-up for ADP-0044-002 Cohort 1 (synovial sarcoma) was 27.8 months (range: 16 – 38 months).

The Applicant's Position:

The ADP-0044-002 study enrolled a patient population who have very limited treatment options. The 44 subjects with SS who received afamitresgene autoleucel at the proposed recommended dose (Cohort 1), as of data cut-off date of 29Mar2023, provide the primary evidence to support the benefit of afamitresgene autoleucel in the intended population.

The FDA's Assessment:

[In cohort 1 of study ADP-0044-002, the first patient enrolled on December 17, 2019, and the last patient enrolled on July 27, 2021.

By FDA analysis, 52 patients with SS were enrolled in ADP-0044-002 Cohort 1 and underwent leukapheresis (ITT population). One patient (Patient (b) (6)) was initially enrolled in Cohort 1 and underwent leukapheresis. After slow progression of pulmonary metastases, this patient ultimately received treatment with volumetric-modulated arc therapy and did not receive afamitresgene autoleucel. The investigator's intent was to reassign this patient to Cohort 2, but

this patient never received treatment. This patient is included in the ITT population by FDA analysis.

Of the 52 patients with SS enrolled in Cohort 1, 45 patients (86.5%) received lymphodepletion, and 44 patients (84.6%) received afamitresgene autoleucel. For the eight patients who did not receive afamitresgene autoleucel, the reasons were: death from disease under study (n=3), loss of eligibility prior to lymphodepletion (n=3), physician decision (n=1), and withdrawal by patient (n=1).

Forty-four patients with SS received afamitresgene autoleucel in Cohort 1 (mITT population) and provide the primary evidence to support efficacy of afamitresgene autoleucel in the proposed indication.

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 out of 52).

One patient (b) (6) received a lower dose than manufactured due to large tumor burden including a para-cardiac lesion and concerns over possible acute inflammation/pseudo-progression potentially resulting in compression of the heart. Additionally, one of this patient's product bags was leaking upon thaw. Therefore, this patient received only one bag of the product (containing 3.055×10^9 MAGE-A4 TCR positive T cells) rather than the full manufactured dose of 9.165×10^9 MAGE-A4 TCR positive T cells.

FDA agrees with mITT patient disposition as outlined in Applicant's Table 14.1

Protocol Violations/Deviations

Data:

[Table 15](#) summarizes important protocol deviations.

Table 15: Applicant – Summary of Important Protocol Deviations

Protocol Deviation	Overall Events	Received Study Treatment
Received wrong treatment	0	0
Developed withdrawal criteria but not withdrawn	1	1
Received excluded concomitant medication	0	0
Pre-screening eligibility	7	0
Eligibility for synovial sarcoma or MRCLS not met	4	0
Eligibility for age not met	3	0
Eligibility prior to enrollment/treatment	11	9
Eligibility for bilirubin clearance not met	2	2
Eligibility for renal function not met	1	1
Eligibility for gene therapy using an integrating vector	1	1
Eligibility for corticosteroids not met	1	1

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Protocol Deviation	Overall Events	Received Study Treatment
Eligibility for MRCLS translocation not met	2	1
Eligibility for HTLV criteria not met	2	2
Eligibility for HLA testing method not met	1	0
Washout period for radiation to target lesion not met	1	1

Source: ADP-0044-002-S1, Appendix 16.2.2.a

Mitigations to address the impact of COVID-19 on the study included allowing assessments, such as safety laboratory collections and scans to be done locally and conducting telemedicine visits to assess AEs and concomitant medications. Visits that were missed or conducted out of window were documented as protocol deviations and assessed to ensure study integrity. Site monitoring was conducted remotely to conduct source document verification and data cleaning. Thirteen subjects had COVID-19–related deviations, which are summarized in [Table 16](#).

Table 16: Applicant – Protocol Deviations due to COVID-19

Subject Number	Protocol Deviations Due to COVID-19
(b) (6)	<p>Central laboratory evaluations and weight not done during Week 12 visit as visit was performed locally due to COVID-19.</p> <p>Central laboratory evaluations not done during Month 08 Visit due to visit being conducted locally due to COVID-19.</p> <p>Central laboratory evaluations not collected during Month 10 Visit; subject completed visits remotely with a local physician due to COVID-19.</p> <p>Central laboratory evaluations not collected during Month 12 Visit as visit was done remotely with a local physician due to COVID-19. EQ-5D-3L Questionnaire also not done during Month 12 Visit.</p>
(b) (6)	<p>Day 29 Visit was performed remotely due to the COVID-19 pandemic. The following procedures were not performed: central laboratory evaluations.</p> <p>Week 6 visit done remotely due to COVID-19. Local/central laboratory evaluations not done.</p> <p>Central laboratory evaluations by remote visit. Subject scheduled local laboratory evaluations at outside laboratory. Due to pandemic, cancelled subject appointment.</p> <p>Due to COVID-19 pandemic, Week 8 Visit was performed remotely; therefore, central laboratory evaluations were not performed.</p> <p>Weight not assessed as visit was conducted remotely due to COVID-19.</p> <p>Due to COVID-19 pandemic, visit was performed via telemedicine. Due to this, central laboratory evaluations were not done.</p> <p>COVID-19: due to remote visit due to COVID-19 pandemic, weight not assessed.</p> <p>COVID-19: due to remote visit due to COVID-19, the following evaluations were not performed: ECOG, weight, EQ-5D-3L, and central laboratory evaluations.</p> <p>COVID-19: the following evaluations were not done due to a remote visit due to COVID-19, ECOG, weight, EQ-5D-3L, central laboratory evaluations.</p> <p>Central laboratory evaluations not collected as it was a telemedicine visit due to COVID-19.</p>
(b) (6)	<p>Tumor biopsy not performed during Baseline Visit. Due to COVID-19, no biopsies were performed at this site.</p>

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Subject Number	Protocol Deviations Due to COVID-19
(b) (6)	ECOG assessment was not collected as main study visit was completed via tele-health between investigator and subject, due to COVID-19 pandemic. "COVID-19" EQ-5D-3L Health Questionnaire not done as visit was completed via tele-health between investigator and subject, due to COVID-19 pandemic.
(b) (6)	Week 8 visit not done as subject contracted COVID-19 and was in quarantine through the duration of the visit window. Subject returned for Week 12 Visit.
(b) (6)	Baseline computed tomography conducted prior to lymphodepleting chemotherapy instead of at Baseline (b) (6) due to COVID testing. The Sponsor notified of discrepancy prior to completion. The Sponsor advised this was acceptable and provided guidance.
(b) (6)	Visit video connection due to potential contact even with COVID-19, expected assessment D29 were completed on (b) (6) (1 week delay): impact on central laboratory evaluations, local laboratory evaluations, and scan evaluation.
(b) (6)	ICF - COVID Addendum v02Jul2020 signed 22Sep2020 consented by SC however SC did not complete segment related to assistance with ICF - appears to have been missed in error. COVID information letter not given to subject at Screening in error.
(b) (6)	Information letter and guidance to investigators regarding additional risk related to COVID-19 were approved by Institutional Review Board (IRB) on 26Sep2020. Information not communicated to subject due to site error.
(b) (6)	T-cell infusion (b) (6), late site signature on ICF (ICF available at site since 07Dec2020). Principal Investigator (PI) was absent due to COVID situation. ICF signed by PI on return to site.
(b) (6)	Information letter and guidance to investigators regarding additional risk related to COVID-19 were approved by IRB on 26Sep2020. Information not communicated to subject due to site error.
(b) (6)	COVID Addendum ICF v2.0 03Jul2020 was not signed prior to apheresis visit on (b) (6).
(b) (6)	The Tumor Assessment scan was out of window by 1 extra day due to the restrictions at the site with COVID and scheduling of subject visits.
(b) (6)	Loss of persistence and Phenotyping Samples. Due to covid, lack of study kits, use of a requisition form and sample labels from another ADP study + answered incorrectly to queries.
(b) (6)	Subject signed COVID-19 consent addendum (Version 1, dated 15May2020, IRB approved 15May2020) on 29Sep2020. Subject dated signature but only included date and month, not year.
(b) (6)	The local and central labs were not drawn during the Month 10 visit due to this being a virtual visit due to COVID restrictions at the site.
(b) (6)	ECOG, Vital Signs, and Weight not conducted due to the visit being conducted remotely.
(b) (6)	Baseline biopsy was not collected.

Source: ADP-0044-002 Appendix 16.2.2, ADP-0044-002-S1 Appendix 16.2.2a.

The Applicant's Position:

The Applicant assessment of all deviations concluded that no deviations occurred that resulted in undue risks to subject safety, and no deviations occurred that would have a major impact on study integrity or require subject exclusion from analysis in the ITT or mITT populations.

The FDA's Assessment:

[The Applicant's table of deviations includes both patients with SS and MRCLS.]

FDA summary of important protocol deviations/violations for patients with SS enrolled on ADP-0044-002 and potential impact on efficacy assessment is outlined below in [Table 17](#).

Of the 44 patients with SS in the mITT population, 9 patients had eligibility deviations/violations (20%). In addition to the listed eligibility deviations, one patient did not have SS diagnosis confirmed by independent pathology review because the patient received their cell infusion after the original data cut-off date and completion of the independent pathology review adjudication report. However, the pathology report confirmed that tumor tested positive for SYT-SSX translocation consistent with SS.

Eight out of the 44 patients (18%) had missing or incomplete imaging assessments. The missing/incomplete imaging assessments impacted DOR for one patient by FDA analysis (See [Table 17](#) and [Section 8.1.2, Efficacy Results – Secondary and other relevant endpoints](#), for details).

In summary, most protocol deviations were minor and were unlikely to substantially affect the conclusion of the results.]

Table 17: FDA – Important Protocol Deviations/Violations, Patients with SS, Study ADP-0044-002

Patient ID	Deviation/Violation	Responder by IRC Re-Review	Potential Impact on Efficacy Assessment
(b) (6)	Received a prior gene therapy with an integrating vector and Applicant was unable to perform persistence screening. Two local tests showed no detectable cells.	No	No
(b) (6)	Did not meet required steroid washout period by one day	No	No
(b) (6)	Did not meet required washout period for cytotoxic chemotherapy prior to leukapheresis by 1 week	Yes	No
(b) (6)	Did not meet eligibility ALT requirement	No	No
(b) (6)	Did not meet eligibility renal function requirement	Yes	No
(b) (6)	Did not meet eligibility bilirubin requirement	Yes	No
(b) (6)	Did not meet eligibility bilirubin requirement	No	No
(b) (6)	Screening assessments were completed 48 days prior to leukapheresis rather than within 28 days	Yes	No
(b) (6)	Non-measurable disease by RECIST v1.1 at baseline per independent review	No	No
(b) (6)	Missed the following study visit/imaging assessments due to non-compliance for personal reasons: Week 12, Week 16, Month 10, Month 12, Month 14, Month 16	Yes	Yes - impact on DOR. Patient will be censored at Month 8
(b) (6)	Missed Month 18 and Month 26 visits/imaging assessments	Yes	No – completed subsequent imaging assessments
(b) (6)	Missed Month 18 and Month 30 visits/imaging assessments	Yes	No – completed subsequent imaging assessments

Patient ID	Deviation/Violation	Responder by IRC Re-Review	Potential Impact on Efficacy Assessment
			assessments
(b) (6)	Missed Week 8 visit/imaging assessment due to COVID-19	Yes	No – completed subsequent imaging assessments
(b) (6)	Missed Day 29/Week 4 visit/imaging assessment	No	No
(b) (6)	Missed Month 18 visit/imaging assessment	Yes	No - completed subsequent imaging assessments
(b) (6)	Missed Week 16 visit/imaging assessment	Yes	No - completed subsequent imaging assessments
(b) (6)	Missing Week 16 CT C/A/P (only MRI facial completed). Missing Month 10 CT A/P	Yes	No - completed subsequent imaging assessments

Source: CSR Table 16-2-2 and Applicant response to FDA information requests

Abbreviations: ALT = alanine aminotransferase, A/P = abdomen/pelvis, C/A/P = chest/abdomen pelvis, COVID-19 = Coronavirus disease 2019, CT = computerized tomography, DOR = duration of response, MRI = magnetic resonance imaging, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

Table of Demographic Characteristics

Data:

Demographics and baseline characteristics are summarized for the mITT population in [Table 18](#).

In the SS sub-group, the median age at consent was 41 years (range: 19-73 years), most subjects were younger than 65 years old (93.2%), and 50% were female. Most subjects with SS were White (88.6%), not Hispanic or Latino (86.4%), and from North America (70.5%).

Demographic characteristics for the 52 subjects in the mITT population were similar to those in the ITT population (ADP-0044-002-S1/-S2).

Table 18: Applicant – Demographic Characteristics (mITT Population)

	Synovial Sarcoma (N=44)	Overall (N=52)
Age at time of consent (years)		
Mean (standard deviation)	41.0 (13.07)	41.4 (12.86)
Median	40.5	41.0
Min, max	19, 73	19, 73
Age categorization, n (%)		
<65 years	41 (93.2)	49 (94.2)
≥65 years	3 (6.8)	3 (5.8)
Sex, n (%)		
Female	22 (50.0)	24 (46.2)
Male	22 (50.0)	28 (53.8)

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	Synovial Sarcoma (N=44)	Overall (N=52)
Height (cm)		
N	42	50
Mean (standard deviation)	171.31 (9.663)	171.16 (9.343)
Median	172.10	172.10
Min, max	147, 187	147, 187
Weight (kg)		
Mean (standard deviation)	79.85 (18.705)	78.83 (17.731)
Median	78.00	76.65
Min, max	45.9, 120.3	45.9, 120.3
Body mass index (kg/m ²)		
N	42	50
Mean (standard deviation)	27.1 (6.27)	26.8 (5.87)
Median	25.8	25.6
Min, max	18, 43	18, 43
Ethnicity, n (%)		
Hispanic or Latino	2 (4.5)	2 (3.8)
Not Hispanic or Latino	38 (86.4)	43 (82.7)
Not reported	4 (9.1)	6 (11.5)
Unknown	0	1 (1.9)
Race, n (%)		
Asian	3 (6.8)	3 (5.8)
Black or African American	2 (4.5)	2 (3.8)
White	39 (88.6)	45 (86.5)
Missing	0	2 (3.8)
Geographical region, n (%)		
Europe	13 (29.5)	15 (28.8)
North America	31 (70.5)	37 (71.2)

Sources: ADP-0044-002 Table SUR-14.1.2.1.1_C1; ADP-0044-002-S1 Table 14.1.2.1.1a. ADaM: ADSL

Note: "Overall" column includes 8 subjects with MRCLS. North America region includes USA and Canada, and Europe region includes France, Spain, and UK.

The Applicant's Position:

Most subjects treated were from the US and the age and gender were representative of the patients with SS. There was limited racial minorities in the study population, and this is a limitation of the dataset. Subjects with SS treated in Study ADP-0044-002 are representative of the intended population.

The FDA's Assessment:

[In the mITT population, 64% (28 out of 44) of patients with SS were from the United States. The median age was 41 years and 82% (36 of 44 subjects) were between the ages of 20 and 49. The majority of patients were white, non-Hispanic or Latino individuals, and 50% of patients were female. Other than the equal percentage of female and male subjects in the study, the

overall demographics of the study population are reasonably representative of the patient population with SS in the United States, which is slightly more male, predominately Caucasian, with a reported mean age of 39 years.

There is limited representation of Hispanic (n=2) ethnicity, and Asian (n=3) or African American (n=2) race in the study.]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

The study included subjects with measurable disease according to RECIST v1.1, with approximately half of the study population (52.9%) having bulky disease (baseline SLD \geq 100mm), and included subjects with ECOG performance status of 0 or 1, and with glomerular filtration rate (GFR) \geq 60 mL/min. Baseline cancer characteristics for the mITT population are summarized in [Table 19](#).

Table 19: Applicant – Baseline Cancer Characteristics (mITT Population)

	Synovial Sarcoma (N=44)	Overall (N=52)
Stage of cancer at last staging, n (%)		
Stage II	2 (4.5)	2 (3.8)
Stage III	1 (2.3)	1 (1.9)
Stage IV	35 (79.5)	41 (78.8)
Unknown	6 (13.6)	8 (15.4)
Time from initial diagnosis to enrollment (months) ^b		
Mean (standard deviation)	52.9 (52.19)	52.6 (51.15)
Median	38.3	36.4
Min, max	6, 250	2, 250
Time from initial diagnosis to T-cell infusion (months) ^c		
Mean (standard deviation)	55.5 (52.86)	55.1 (51.69)
Median	41.2	38.6
Min, max	7, 257	5, 257
Prior lines of systemic therapy (continuous)		
Mean (standard deviation)	3.2 (2.22)	3.2 (2.18)
Median	3.0	3.0
Min, max	1, 12	1, 12
Prior lines of systemic therapy (categorical), n (%)		
1	7 (15.9)	10 (19.2)
2	14 (31.8)	15 (28.8)
3	9 (20.5)	9 (17.3)
4+	14 (31.8)	18 (34.6)
Prior cancer therapy, n (%)		
Any therapy	44 (100.0)	52 (100.0)
Anti-cancer therapy	44 (100.0)	52 (100.0)
Surgery	40 (90.9)	48 (92.3)

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	Synovial Sarcoma (N=44)	Overall (N=52)
Radiotherapy	28 (63.6)	34 (65.4)
Bridging therapy (categorical), n (%)		
Yes	16 (36.4)	20 (38.5)
No	28 (63.6)	32 (61.5)
ECOG score, n (%)		
0	23 (52.3)	27 (51.9)
1	20 (45.5)	24 (46.2)
2 ^d	1 (2.3)	1 (1.9)

Sources: SUR Tables 14.1.2.1.1_C1, 14.1.4.1_C1, Listing SUR-16.2.4.7_C1; ADP-0044-002-S2 Table 14.2.1.1.2.6a, ADP-0044-002-S1 Tables 14.1.2.1.1a and 14.1.4.1a. ADaM: ADSL, ADPR, ADCM

a. All subjects were metastatic at baseline, prior to lymphodepletion/T-cell infusion.

b. Refers to time from initial primary tumor diagnosis. Time from initial primary tumor diagnosis to enrollment in months was calculated as follows: (enrollment date – date of initial diagnosis + 1) × (12/365.25).

c. Time from initial diagnosis to T-cell infusion in months was calculated as follows: (date of T-cell infusion – date of initial diagnosis + 1) × (12/365.25).

d. No subject had an ECOG score of 2. The Baseline ECOG score for Subject (b) (6) was 1, and the data discrepancy in the EDC was due to a transcription error from the hospital's dictation software. This error has been corrected in the source.

In the SS sub-group, median number of prior lines of systemic therapy lines was 3 (range: 1-12 lines), and 34.6% of subjects received ≥4 lines. Most common prior therapies included ifosfamide (97.7%), doxorubicin (93.2%), pazopanib (40.4%), trabectedin (25.0%), dacarbazine (11.4%), and gemcitabine (11.4%). Between leukapheresis and initiation of lymphodepletion, 16 (36.4%) subjects with SS received bridging therapy. The most commonly used bridging therapy was pazopanib.

Cytogenic confirmation of SS and MRCLS was obtained for each subject prior to leukapheresis. An independent review assessment of SS disease pathology was also conducted post-hoc for subjects with SS in Study ADP-0044-002 Cohort 1 (data cut-off date: 11-Oct-2021). The independent pathology reviewers confirmed the investigators' diagnoses for all SS subjects treated in ADP-0044-002 Cohort 1, as of the data-cut (Source: Study ADP-0044-002, Pathology Review and CRS Adjudication Report).

The study enrolled HLA-A*02:01P (95.5% of subjects), HLA-A*02:02P (n=1), HLA-A*02:03P (n=1, subject was also positive for HLA-A*02:01), and HLA-A*02:06P (n=1) allele positive subjects. The HLA alleles indicated for the study were based on HLA-A*02 alleles enrolled in the ADP-0044-001 study (35 subjects with HLA-A*02:01P, 1 subject with HLA-A*02:03P, and 2 subjects with HLA-A*02:06P), as well as preclinical data where clinical evidence was limited for certain alleles. A summary of HLA status and antigen MAGE-A4 expression P-scores and H-scores at Pre-screening for the mITT population is provided in [Table 20](#).

Table 20: Applicant – Summary of HLA Status and Tumor MAGE-A4 Expression at Pre-Screening (mITT Population)

	Synovial Sarcoma (N=44)	Overall (N=52)
HLA status, n (%)		
HLA-A*02:01P	42 (95.5)	50 (96.2)
HLA-A*02:02P	1 (2.3)	1 (1.9)
HLA-A*02:03P ^a	1 (2.3)	1 (1.9)
HLA-A*02:06P	1 (2.3)	1 (1.9)
H-score ^b		
Mean (standard deviation)	238.5 (60.07)	228.2 (61.94)
Median	257.3	232.9
Min, max	132, 300	112, 300
P-score ^c		
Mean (standard deviation)	81 (21.08)	78.2 (21.76)
Median	90.8	84.3
Min, max	34, 100	34, 100

Sources: ADP-0044-002 Table SUR-14.1.2.2.1_C1, Table SUR-14.1.2.2.1.1_C1, ADP-0044-002-S1 Tables 14.1.2.2.1.1a and 14.1.2.2.1a. ADaM ; ADSL, ADIS

^a. The subject positive for HLA-A*02:03P was also positive for HLA-A*02:01P (ADP-0044-002-S1 Listing 16.2.4.6a). The number 1 or 2 after the letter indicating the locus (A, B, or C) refers to Allele 1 or Allele 2.

^b. H-score was derived by 3 × percentage of strongly staining cells + 2 × percentage of moderately staining cells + percentage of weakly staining cells, giving a range of 0–300.

^c. P-score was derived by (% tumor staining intensity at 2+) + (% tumor staining intensity at 3+).

The Applicant's Position:

The study population was representative of advanced SS with most subjects with stage IV disease. All subjects were metastatic at baseline, prior to lymphodepletion/T-cell infusion. Approximately half of the subjects had bulky disease and subjects were heavily pre-treated with a median of 3 prior lines of systemic therapy and all subjects received prior anthracycline and/or ifosfamide. Second-line systemic therapies were consistent with treatment patterns (i.e., no definitive standard of care).

HLA alleles were assessed by centralized testing using a high-resolution HLA test that is 510(k) cleared (BK110038). MAGE-A4 testing was conducted by centralized testing using an IHC clinical trial assay conducted under an IDE.

The baseline disease characteristics of subjects with SS treated in Study ADP-0044-002 were representative of the intended patient population.

The FDA's Assessment:

[Per the Applicant, the “Disease stage” captured in [Table 18](#) refers to the last known stage of disease at the time of last staging (i.e., at any point since and including time of diagnosis). This is therefore not necessarily the disease stage at baseline prior to treatment. By FDA analysis, all patients had metastatic disease at baseline prior to treatment.]

The majority of patients had received multiple prior lines of therapy, as outlined in [Table 21](#). All patients received prior chemotherapy with doxorubicin and/or ifosfamide. One patient (b) (6) did not initially have prior therapy with doxorubicin and ifosfamide documented in the electronic database prior to database lock. Through information requests, this patient was later confirmed to have received prior first line therapy with doxorubicin and ifosfamide.

Therefore, no patient was intolerant of both an anthracycline and ifosfamide allaying the concern that patients with a different prognosis compared to patients who have received prior doxorubicin and/or ifosfamide may have been enrolled.

There were four patients assessed as responders by independent re-review who received only one prior line of therapy. All four patients progressed following treatment with anthracycline and ifosfamide prior to treatment with afamitresgene autoleucel.

Table 21: FDA – Prior Systemic Antineoplastic Therapies Received by Patients (>5%) Included in Primary Efficacy Evaluation

Prior Therapies	Cohort 1, ITT Population, N=52 (%)	Cohort 1, Primary Efficacy Population (mITT), N=44 (%)
Ifosfamide	52 (100%)	44 (100%)
Anthracycline	51 (98%)	43 (98%)
Doxorubicin	50 (96%)	42 (95%)
Epirubicin	3 (6%)	3 (7%)
Pazopanib	24 (46%)	21 (48%)
Trabectedin	12 (23%)	11 (25%)
Dacarbazine	5 (10%)	5 (11%)
Gemcitabine	6 (12%)	5 (11%)
Anti-PD-1/PD-L1	3 (6%)	3 (7%)
Olaratumab	3 (6%)	3 (7%)
Regorafenib	3 (6%)	3 (7%)
Catequentinib	4 (8%)	3 (7%)
Investigational agents	6 (12%)	5 (11%)

Source: ADCM dataset, CSR Table 16-2-4, and Applicant response to FDA information requests

Abbreviations: FDA, Food and Drug Administration; ITT, intent-to-treat; mITT, modified intent-to-treat; N = total number of patients

Bridging therapy was administered to 16 patients in Cohort 1 (36%), as outlined in [Table 22](#).

Table 22: FDA – Bridging Therapies Received by Patients Included in Primary Efficacy Analysis

Type of Bridging Therapy	Cohort 1, N=44 (%)
Pazopanib	11 (25%)
Ifosfamide	3 (7%)

Type of Bridging Therapy	Cohort 1, N=44 (%)
Trabectedin	1 (2%)
Doxorubicin	1 (2%)

Source: ADCM dataset and CSR Table 16-2-4

In addition to the systemic treatments listed in [Table 22](#), one patient (b) (6) received radiation therapy to a deep mediastinal lymph node during the bridging period. The patient met the required 3-month radiation wash-out period prior to lymphodepletion. This radiated mediastinal lymph node was chosen as a target lesion by independent review. However, it was subsequently changed to a non-target lesion by FDA analysis as required by the independent review charter, as the lesion did not unequivocally progress following radiation therapy.]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance: Apheresis, lymphodepletion and afamitresgene autoleucel infusion were done in the controlled environment of a qualified clinical trial site.

Concomitant Medication: Per protocol, other treatment considered necessary for a subject's welfare were allowed at the discretion of the Investigator. All concomitant medications were recorded with dose and frequency, including all prescription or over-the-counter medications and herbal remedies. Prohibited concomitant medications post T-cell infusion (i.e., prior to disease progression): non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anti-cancer therapy. Subjects should also not undergo other anticancer locoregional therapies such as non-palliative radiation. Subjects who receive any active anticancer therapy, except for surgical resection prior to disease progression, will be considered as having met the progressive disease (PD) criterion for efficacy and will follow the LTFU schedule. All subjects in the mITT populations had at least 1 concomitant medication, and main ATC class of concomitant medications used by 5% or more subjects are listed in [Table 23](#).

Palliative radiation for pain relief to non-measurable lesions or non-target lesions present at baseline was permitted per study protocol. Lesion sites requiring radiotherapy after the afamitresgene autoleucel infusion were evaluated as to whether this indicated disease progression and recorded in the eCRF as applicable. Concomitant palliative radiotherapy was received by 8 subjects. Curative radiotherapy was received by 2 subjects (Subject (b) (6) and (b) (6)); sources: ADP-0044-002-S1 Listing 16.2.4.9.4a and Listing SUR-16.2.4.9.4_C1).

Table 23: Applicant – Summary of Concomitant Medications in ≥5% of Subjects Overall by ATC Class (mITT Population; Data cut-off: 29Mar2023)

ATC Class	SS (N=44)	Overall (N=52)
Subjects with At Least One Medication	44 (100)	52 (100)
Antiemetics And Antinauseants	44 (100)	51 (98.1)
Direct Acting Antivirals	42 (95.5)	50 (96.2)
Other Analgesics And Antipyretics	42 (95.5)	50 (96.2)
Antihistamines For Systemic Use	38 (86.4)	45 (86.5)
Immunostimulants	35 (79.5)	42 (80.8)
Sulfonamides And Trimethoprim	32 (72.7)	38 (73.1)
Opioids	31 (70.5)	37 (71.2)
Drugs For Constipation	30 (68.2)	36 (69.2)
Antithrombotic Agents	28 (63.6)	35 (67.3)
Drugs For Peptic Ulcer and Gastro-Oesophageal Reflux Disease (Gord)	29 (65.9)	33 (63.5)
I.V. Solutions	29 (65.9)	34 (65.4)
Antimycotics For Systemic Use	28 (63.6)	34 (65.4)
Anxiolytics	25 (56.8)	28 (53.8)
Corticosteroids For Systemic Use, Plain	24 (54.5)	27 (51.9)
I.V. Solution Additives	23 (52.3)	26 (50.0)
Other Beta-Lactam Antibacterials	21 (47.7)	23 (44.2)
All Other Therapeutic Products	19 (43.2)	21 (40.4)
Immunosuppressants (Tocilizumab)	20 (45.5)	21 (40.4)
Potassium	19 (43.2)	20 (38.5)
Beta-Lactam Antibacterials, Penicillins	16 (36.4)	19 (36.5)
Hypnotics And Sedatives	15 (34.1)	17 (32.7)
Propulsives	16 (36.4)	18 (34.6)
Antigout Preparations	12 (27.3)	15 (28.8)
Other Mineral Supplements	15 (34.1)	16 (30.8)
Quinolone Antibacterials	14 (31.8)	16 (30.8)
Antidepressants	11 (25.0)	14 (26.9)
High-Ceiling Diuretics	13 (29.5)	14 (26.9)
Antiepileptics	11 (25.0)	13 (25.0)
Adrenergics, Inhalants	11 (25.0)	12 (23.1)
Anesthetics, Local	9 (20.5)	13 (25.0)
Antiinflammatory And Antirheumatic Products, Non-Steroids	12 (27.3)	13 (25.0)
Antipsychotics	12 (27.3)	12 (23.1)
Thyroid Preparations	12 (27.3)	12 (23.1)
Viral Vaccines	10 (22.7)	13 (25.0)
Beta Blocking Agents	10 (22.7)	11 (21.2)
Stomatological Preparations	10 (22.7)	11 (21.2)
Antipropulsives	10 (22.7)	10 (19.2)
Antacids	6 (13.6)	8 (15.4)
Cough Suppressants, Excl. Combinations With Expectorants	8 (18.2)	8 (15.4)
Other Antibacterials	8 (18.2)	8 (15.4)
Vitamin B12 And Folic Acid	8 (18.2)	8 (15.4)
Agents Against Leishmaniasis And Trypanosomiasis	5 (11.4)	7 (13.5)

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ATC Class	SS (N=44)	Overall (N=52)
Aminoglycoside Antibacterials	6 (13.6)	7 (13.5)
Selective Calcium Channel Blockers With Mainly Vascular Effects	6 (13.6)	7 (13.5)
Anesthetics, General	6 (13.6)	6 (11.5)
Vitamin A And D, Incl. Combinations Of The Two	6 (13.6)	6 (11.5)
Drugs For Functional Gastrointestinal Disorders	4 (9.1)	5 (9.6)
Hormonal Contraceptives For Systemic Use	5 (11.4)	5 (9.6)
Iron Preparations	4 (9.1)	5 (9.6)
Multivitamins, Plain	3 (6.8)	5 (9.6)
Agents Against Amoebiasis And Other Protozoal Diseases	4 (9.1)	4 (7.7)
Angiotensin II Receptor Blockers (Arbs), Plain	4 (9.1)	4 (7.7)
Antiarrhythmics, Class I And Iii	4 (9.1)	4 (7.7)
Decongestants And Other Nasal Preparations For Topical Use	3 (6.8)	5 (9.6)
Expectorants, Excl. Combinations With Cough Suppressants	4 (9.1)	4 (7.7)
Lipid Modifying Agents, Plain	3 (6.8)	4 (7.7)
Other Drugs For Obstructive Airway Diseases, Inhalants	4 (9.1)	4 (7.7)
Other Ophthalmologicals	4 (9.1)	4 (7.7)
X-Ray Contrast Media, Iodinated	3 (6.8)	4 (7.7)
Antibiotics For Topical Use	4 (9.1)	4 (7.7)
Antifibrinolytics	3 (6.8)	3 (5.8)
Blood And Related Products	3 (6.8)	3 (5.8)
Blood Glucose Lowering Drugs, Excl. Insulins	2 (4.5)	3 (5.8)
Calcium	2 (4.5)	3 (5.8)
Cardiac Stimulants Excl. Cardiac Glycosides	3 (6.8)	3 (5.8)
Macrolides, Lincosamides And Streptogramins	4 (9.1)	4 (7.7)
Muscle Relaxants, Centrally Acting Agents	1 (2.3)	3 (5.8)
Other Alimentary Tract And Metabolism Products	3 (6.8)	3 (5.8)
Other Antidiarrheals	3 (6.8)	3 (5.8)
Other Nutrients	3 (6.8)	3 (5.8)
Psychostimulants, Agents Used For Adhd And Nootropics	2 (4.5)	3 (5.8)

Source: Table SUR-14.1.5.2.1_C1. AdaM: ADSL, ADCM.

Abbreviations: ATC=Anatomical Therapeutic Chemical.

Rescue Medication: No rescue medication was used in any subjects.

The Applicant's Position:

Concomitant medication usage are as expected for this patient population.

The FDA's Assessment:

[The FDA concurs with the summary of concomitant medication use.]

Six patients with SS received on-study radiotherapy. Per the Applicant, one patient (b) (6) received palliative radiation therapy (30 Gy) in a location of a target lesion chosen by independent review (retroperitoneum). This patient was not a responder by independent

review. The remaining five patients who underwent on-study radiotherapy either initiated radiotherapy after their last imaging assessment on study (b) (6) (e.g., radiotherapy after their end of treatment scan) or did not undergo radiotherapy to a target lesion (b) (6) – hip, (b) (6) – tibia, and (b) (6) – brain). None of these patients were responders by independent review.]

Data Quality and Integrity

Data:

Not applicable.

The Applicant's Position:

No issues related to data quality and integrity were identified by the Applicant.

The FDA's Assessment:

[During review of the efficacy data submitted in the BLA, study conduct issues were identified that raised concerns about the quality of the efficacy data. The following are some of the general issues identified:

- 1) Radiographic imaging assessment:
 - a) Presence of inaccuracies in target lesion measurements in the submitted dataset
 - b) Inconsistencies in adherence to RECIST v1.1 (e.g., response assessment using inconsistent imaging modalities when the same imaging modality was available to reviewers)
 - c) Inconsistencies in the implementation of response adjudication following the Independent Review Charter provided with the BLA submission
- 2) Use of several efficacy data cut-off dates not pre-specified in the statistical analysis plan or protocol

The above issues, when evaluated in the context of a single arm study with a small sample size (Cohort 1) and the small number of responders, raised concerns about the reliability of the objective response rate and duration of response results. FDA therefore requested an independent, third-party re-review of response assessment for the 44 patients in Cohort 1 using a different, blinded, IRC imaging vendor.]

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary endpoint of the study was ORR per independent review using RECIST v1.1 in Cohort 1 and was based on the 29Mar2023 data cut-off (ADP-0044-002-S2). Per RECIST v1.1 by independent review, the ORR in the SS group (N=44) was 38.6% (95% CI: 24.36, 54.50) ([Table 24](#)). The waterfall plot for the maximum percentage change in the sum of longest diameter

(SLD) in target lesion using RECIST v1.1 via independent review for SS, is presented in [Figure 15](#). The Spider plot of the change in SLD target lesion from Baseline using RECIST v1.1 via independent review is presented in [Figure 16](#).

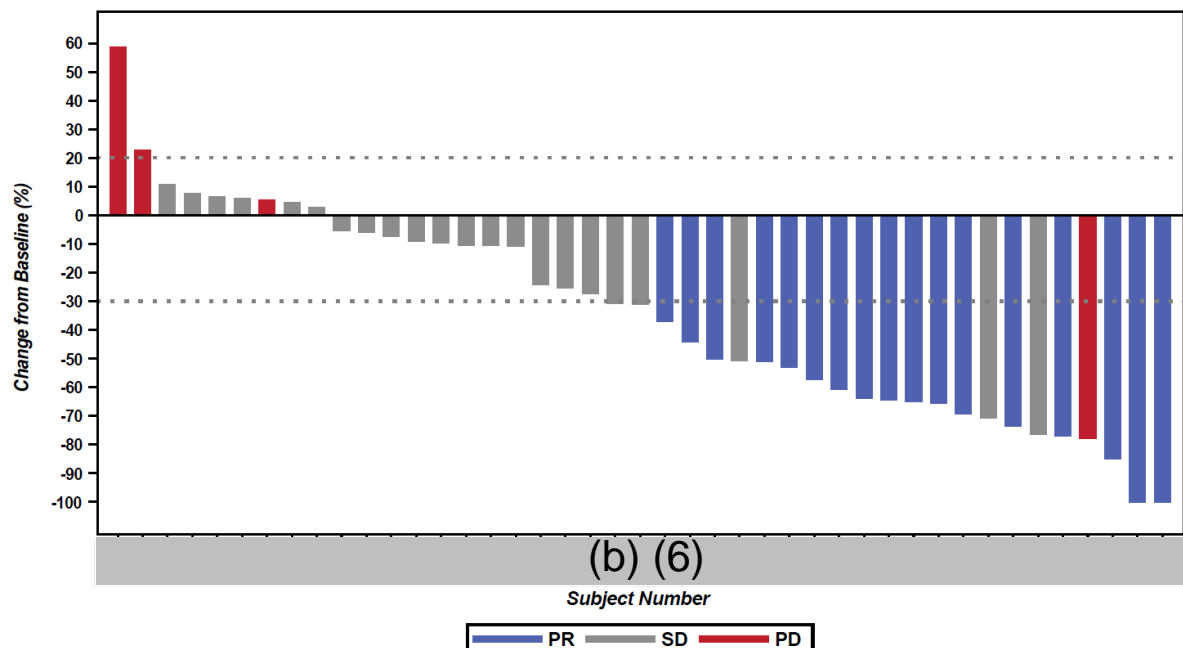
Table 24: Applicant – Summary of BOR and ORR using RECIST v1.1 by Independent Review (mITT Population); Cut-Off Date 29Mar2023 (Updated Efficacy; ADP-0044-002-S2) – Synovial Sarcoma

Parameter Category or Criterion	Synovial Sarcoma (N=44)
Best overall response, n (%)	
Complete response	0
Partial response	17 (38.6)
Stable disease	23 (52.3)
Progressive disease	4 (9.1)
Overall response rate	
Complete response + partial response, n (%)	17 (38.6)
95% CI ^a	(24.36, 54.50)

Source: ADP-0044-002-S2 Table 14.2.1.1.2a. Reference: AdaM: ADSL, ADRS

a. Two-sided 95% CI based on exact Clopper-Pearson (exact binomial) method.

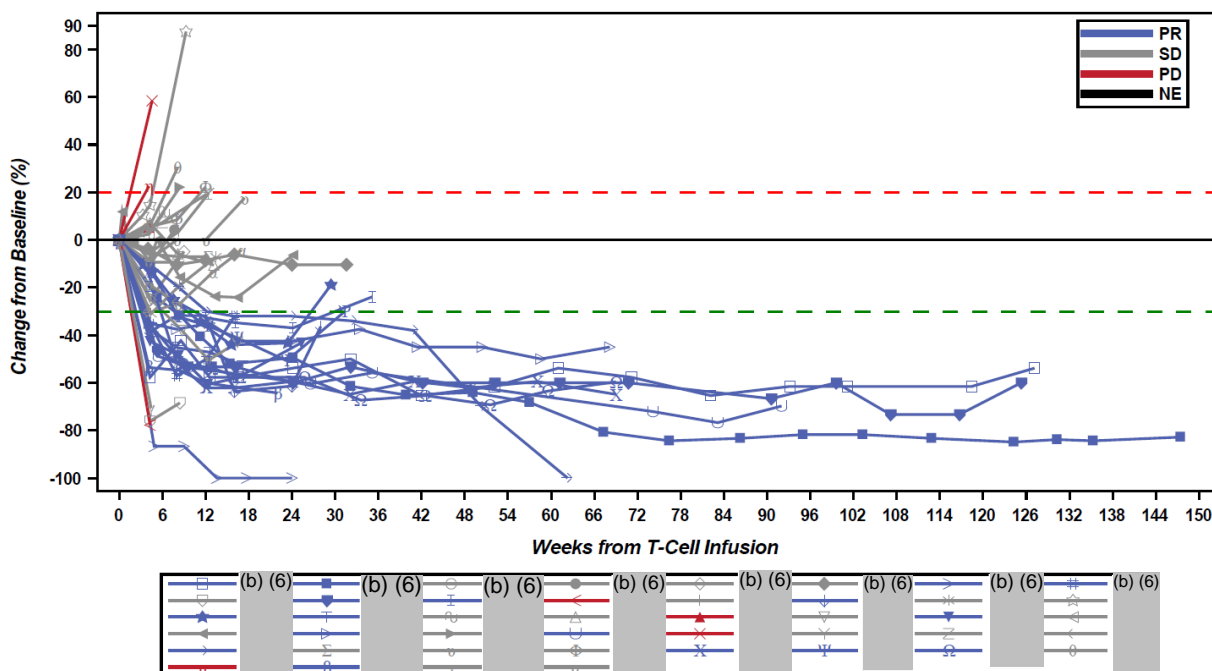
Figure 15: Applicant – Waterfall Plot for Maximum Percentage Change in SLD in Target Lesion From Baseline by Independent Review (mITT Population) – Synovial Sarcoma



Source: ADP-0044-002-S2 Figure 14.2.1.8.4a. Reference: AdaM: ADSL, ADRS, ADLS

Note: Subject (b) (6) in the synovial sarcoma group did not have measurable target lesion per RECIST v1.1 by independent review.

Figure 16: Applicant – Spider Plot of Change in SLD in Target Lesion From Baseline – Overall (mITT Population) – Independent Review Assessment – Synovial Sarcoma



Source: ADP-0044-002-S2 Figure 14.2.1.9.4a. AdaM: ADSL, ADRS, ADLS

Note: Subject (b) (6) in the synovial sarcoma group did not have measurable target lesion per RECIST v1.1 by independent review.

The Applicant's Position:

Study ADP-0044-002 met its primary endpoint, i.e., the lower limit of the 95% exact Clopper Pearson CI was greater than the prespecified null hypothesis rate of 18%. Afamitresgene autoleucel demonstrated a clinically meaningful confirmed ORR as assessed by independent review. Responses were observed across all key subgroups analyzed ([Table 32](#)). Although caution must be taken when comparing ORRs from different trials, the ORR observed in the SS group after a single infusion of afamitresgene autoleucel is an improvement over historical ORRs for available second-line therapies in advanced SS, such as pazopanib and trabectedin ([Table 1](#)).

The FDA's Assessment:

[The primary endpoint of Study ADP-0044-002 was confirmed ORR per RECIST v1.1 by IRC for Cohort 1 mITT population.]

Applicant Table 24, Applicant Figure 15, and Applicant Figure 16 show efficacy results based on the original IRC review of response assessment. FDA does not agree with response assessment by the original IRC. FDA's primary efficacy evaluation was based upon confirmed ORR (CR+PR)

and DOR per RECIST v1.1 by IRC re-review in patients with SS in Cohort 1 mITT population (n=44) using a data cut-off of March 29, 2023.

By FDA analysis based on IRC re-review of response assessment, the ORR in the SS mITT group (n=44) was 43.2% (95% CI: 28.4, 59.0) ([Table 25](#)).

Table 25: FDA – Summary of Best Overall Response and Overall Response Rate (mITT Population) – Independent Re-Review Assessment

Parameter Category or Criterion	Synovial Sarcoma (N=44)
Best overall response, n (%)	-
Complete response	2 (4.5)
Partial response	17 (38.6)
Stable disease	20 (45.5)
Progressive disease	5 (11.4)
Overall response rate	-
Complete response + partial response, n (%)	19 (43.2)
95% CI ^a	(28.4, 59.0)

Source: SDTM re-review datasets, ADP-0044-002-S2 Table 14.2.1.1.2_IR and Applicant response to FDA information requests.
a. Two-sided 95% CI based on exact Clopper-Pearson (exact binomial) method.

Reviewer Comment: The FDA’s primary efficacy evaluation was based upon the IRC re-review of response assessment, rather than the original IRC response assessment. Due to data quality and study conduct issues identified in the original IRC efficacy data submitted, FDA requested an independent, third-party re-review of response assessment for the 44 patients in Cohort 1 using a different, blinded, IRC imaging vendor. See [Section 8.1.2, Data Quality and Integrity](#) for additional details regarding the issues that triggered a re-review of response assessment.

As noted in [Section 8.1.1, Trial Design](#), a limitation of the study design was that it allowed on-study tumor biopsies of target and non-target lesions, which may confound response assessment analysis. There were 29 patients with SS (66% of mITT population) who underwent on-study tumor biopsy either at baseline and/or between Week 3 and Week 8, of which 13 patients were responders by IRC re-review. Of those 13 responders, 11 had biopsies of target lesions chosen by IRC re-review. [Table 26](#) lists the biopsied target lesions for responders by IRC re-review and FDA assessment of the impact on efficacy assessment. By FDA analysis, the on-study biopsies did not impact response assessment for any patients in Cohort 1.

Table 26: FDA – Responders Who Underwent On-Study Biopsy of a Target Lesion by IRC Re-Review

Patient ID	Biopsied Target Lesion (Biopsy Timepoint)	Total Number of Target Lesions	Potential Impact on Efficacy Assessment	Rationale
(b) (6)	T1 – Thigh (Baseline, ~Week 4)	2	No	Biopsied T1 lesion was large (75mm at baseline). Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e. changed to non-target).
(b) (6)	T2 – Lung (Baseline, ~Week 4)	5	No	Biopsied T2 lesion was large (95mm at baseline). Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e. changed to non-target).
(b) (6)	T3 – Lung (Baseline, ~Week 4)	5	No	Biopsied T3 lesion was large (64mm). Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).
(b) (6)	T3 – Gluteal (~Week 4)	3	No	Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).
(b) (6)	T1 – Chest wall (Baseline, ~Week 4)	1	No	Biopsied T1 lesion was large (127mm at baseline).
(b) (6)	T1 – Lung (~Week 4)	2	No	Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).
(b) (6)	T2 – Lung (Baseline, ~Week 4)	2	No	Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).
(b) (6)	T1 – Lung (Baseline)	1	No	Biopsy occurs 4 days before baseline imaging. Baseline imaging report indicates that lesion was unchanged in size from prior imaging before biopsy. Patient has durable and ongoing response as of data cut-off.
(b) (6)	T1 – Lung (Baseline, ~Week 4)	3	No	Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a

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Patient ID	Biopsied Target Lesion (Biopsy Timepoint)	Total Number of Target Lesions	Potential Impact on Efficacy Assessment	Rationale
				target lesion (i.e., changed to non-target).
(b) (6)	T1 – Lung (~Week 4)	2	No	Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).
(b) (6)	T3- Peritoneum (Baseline, ~Week 4)	5	No	Biopsied T3 lesion was large (121mm at baseline). Patient continues to meet criteria for confirmed PR based on RECIST v1.1 if the biopsied target lesion is removed as a target lesion (i.e., changed to non-target).

Source: Applicant responses to FDA information requests

Abbreviations: T1 = Target lesion 1, T2 = Target lesion 2, T3 =Target lesion 3

Of note, Patient (b) (6) received radiation therapy to a deep mediastinal lymph node during the bridging period that was subsequently chosen as a target lesion by IRC re-review. Given the target lesion did not unequivocally progress following radiation therapy, this lesion was considered a non-target lesion by FDA analysis, consistent with the independent review charter and RECIST v1.1 guidelines. The BOR (PR) and DOR for this patient remained unchanged.

Concordance in BOR between the original independent review and the new independent review was 79.6%. Out of the 17 responders in the original independent review, 16 patients remained responders by IRC re-review. There were three responders by IRC re-review that were not responders in the original independent review, two of which were also not responders by investigator assessment. See [Table 27](#) for a patient level comparison of BOR by IRC re-review versus original independent review.]

Table 27: FDA – Patient Level Listing of Best Overall Response by IRC Re-Review Vs. Original IRC Review, Cohort 1

Patient ID	Independent Re-Review	Original Independent Review	Discordant
(b) (6)	CR	PR	Yes
	CR	PR	Yes
	PR	SD	Yes
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	SD	Yes

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Patient ID	Independent Re-Review	Original Independent Review	Discordant
(b) (6)	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	SD	Yes
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	PR	No
	PR	PR	No
	SD	SD	No
	SD	PR	Yes
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	PD	Yes
	SD	SD	No
	SD	SD	No
	SD	SD	No
	SD	SD	No
	PD	PD	No
	PD	PD	No
	PD	PD	No
	PD	SD	Yes
	PD	SD	Yes

Source: ADP-0044-002-S2 Table 16.2.6.3.4 IR.

Abbreviations: CR = complete response, PR = partial response, SD = stable disease

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Concordance in ORR per RECIST v1.1 by investigator assessment with independent review was high (78.85%; ADP-0044-002-S2 Table 14.2a). Of the 44 subjects with SS in the mITT population, 18 subjects responded by investigator assessment, 2 responders (4.5%) had a CR and 16 responders (36.4%) had a PR, with an ORR of 40.9% (95% CI: 26.34, 56.75; [Table 28](#)). Efficacy data (assessed by Independent Review and by Investigator Assessment), are summarized in [Table 28](#).

The median follow-up time at the data cut-off was 27.8 months. The Kaplan–Meier estimated median PFS was 3.8 months (95% CI: 2.760, 6.439) and 4.1 months (95% CI: 2.793, 6.932) by independent review and investigator review, respectively (Source: ADP-0044-002-S2 Table 14.2.1.5.1.2a and Table 14.2.1.5.1.1a). The Kaplan–Meier estimated median OS was 16.9 months (95% CI: 10.91, NE), and the 12-month Kaplan–Meier OS probability was 60% (95% CI: 46.9, 76.3) and 24-month Kaplan–Meier OS probability was 40% (95% CI: 28.5, 59.3). OS data are immature with data for 45.5% of subjects censored at the data cut-off (Source: ADP-0044-002-S2, Table 14.2.1.6.1a). In the 17 subjects who had a RECIST response by independent review, the median OS was not reached, and the 12-month Kaplan–Meier OS probability was 90% (95% CI: 65.0, 99.1) and the 24-month Kaplan–Meier OS probability was 70% (95% CI: 43.1, 86.6) (Source: ADP-0044-002-S2, 14.2.1.6.3a).

Table 28: Applicant – Efficacy data From SS subjects dosed in Study ADP-0044-002 (mITT population) – Data Cut-off: 29Mar2023

Parameter Category or Criterion	Independent Review	Investigator Assessment
	SS (N=44)	
Best overall response, n (%)		
Complete Response	0	2 (4.5)
Partial response	17 (38.6)	16 (36.4)
Stable disease	23 (52.3)	19 (43.2)
Progressive disease	4 (9.1)	7 (15.9)
Overall Response Rate (ORR)		
Complete response + partial response, n (%)	17 (38.6)	18 (40.9)
95% CI ^a	(24.36, 54.50)	(26.34, 56.75)
Time to Confirmed Response (TTR)		
Median TTR in weeks	4.9	5.1
95% CI	(4.286, 8.286)	(4.286, 8.143)
Range (Min, Max)	4.1, 12.1	4.1, 12.6
Duration of Response (DoR)		
Median DoR in months	11.6	14.4

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Parameter Category or Criterion	Independent Review	Investigator Assessment
	SS (N=44)	
95% CI ^b	(4.44, NE)	(4.86, NE)
Range (Min, Max)	(2.7, 32.0)	(1.9, 31.2)

Source: ADP-0044-002-S2Table 14.2.1.1.2a and Table 14.2.1.1.1a (BOR/ORR), Table 14.2.1.2.1a and Table 14.2.1.2a (TTR), Table 14.2.1.3.2.1a and Table 14.2.1.3.1.1a (DOR in months); DOR Table 14.2.1.3.2.1a; Table 14.2.1.3.1.1a AdaM: ADSL, ADRS, ADTTE.

a. Two-sided 95% CI based on exact Clopper-Pearson (exact binomial) method.

b. Confidence Interval for quartiles estimated using the Log-Log method.

The Applicant's Position:

In subjects with SS, time to response was short at 4.9 weeks. ORR and durability were the major efficacy outcomes in the study and secondary endpoint of DoR demonstrated that responses were durable with a median DoR of 11.6 months per independent review and 14.4 months by investigator review.

The ORR and durability of responses observed with afamitresgene autoleucel in advanced SS are clinically meaningful and provide substantial evidence of effectiveness in the context of a rare and life-threatening disease with very limited treatment options.

The FDA's Assessment:

[Concordance in ORR Between Independent Review and Investigator Review]

Concordance in ORR by RECIST v1.1 by investigator assessment and the original independent review for patients with SS was 77%. Concordance in ORR between investigator assessment and the IRC re-review for patients with SS was 70%.

Applicant Analysis of DOR by IRC Re-Review

By Applicant analysis, the median DoR by IRC re-review for SS in the mITT population was 6 months (95% CI: 3.7, NE). The median time to response was 4.9 weeks (95% CI: 4.3, 7.6).

FDA Adjudication of DOR by IRC Re-Review

Based on the IRC re-review data and Applicant response to FDA information requests, FDA has re-adjudicated DOR for one patient. See details in [Table 29](#). This re-adjudication did not change the median DOR of 6 months.

Table 29: FDA – Adjudication of Duration of Response by IRC Re-Review

Patient ID	Description of DOR Adjudication
(b) (6)	No study visits or imaging assessments were performed for 9 months (from study Month 10 through Month 16). Per Applicant response to information request, this was due to non-compliance for personal reasons. Due to the prolonged period of missing disease assessments, FDA considers this patient ‘lost to follow up,’ and the patient was censored at the last adequate disease assessment (Month 8).

Source: Applicant response to information requests.

Abbreviations: CT = computerized tomography, DOR = duration of response, FDA = Food and Drug Administration, IRC = Independent Review Committee, IV = intravenous, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

FDA Analysis of DOR by IRC Re-Review

FDA analysis of DoR by IRC re-review is presented in [Table 30](#). KM estimated DoR was 6.0 months (95% CI: 4.6, NR) per IRC re-review, with a median follow-up time of 21.9 months by reverse KM estimate. Durable response at 6, 12, and 24 months was 45.6%, 39%, and 39%, respectively based on KM estimate. DoR by investigator analysis is also summarized.

By IRC re-review, DOR was censored for 8 of the 19 SS responders (42.1%) as of the data cut-off. Reasons for censoring were alive and PD free (n=5), end of intervention phase before PD (n=2), and missing imaging assessments (n=1). The two patients who were censored due to “end of intervention phase before PD” are summarized below:

Patient (b) (6) Ended the interventional stage at Week 24 visit due to progressive disease by investigator, after which no further scans were performed for the study. By IRC re-review, this patient had an ongoing partial response at the Week 24 visit and therefore was censored. The patient died approximately 4 months later from disease progression.

Patient (b) (6): Ended the interventional stage at Month 16 visit due to progressive disease by investigator, after which no further scans were performed for the study. By IRC re-review, this patient had an ongoing partial response at Month 16 visit and therefore was censored. The patient is alive as of the data cut-off date.

Table 30: FDA –Duration of Response by IRC Re-Review and Investigator, Cohort 1, mITT Population

Parameter Category	Re-review IRC	Investigator
Number of patients achieved CR or PR, n	19	18
Number of events, n (%)	11 (57.9%)	11 (61.1%)
Progression	11 (57.9%)	11 (61.1%)
Death	0	0
Censored, n (%)	8 (42.1%)	7 (38.9%)
Alive and PD free	5 (26.3%)	6 (33.3%)
End of intervention before PD	2 (10.5%)	1 (5.6%)
Multiple imaging assessments missing	1 (5.3%)	0
DOR (months) ^a	-	-
Median	6.0	14.4

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Parameter Category	Re-review IRC	Investigator
95% CI	(4.6, NR)	(6.0, NR)
Range	(1.9, 36.1+)	(1.9, 31.3+)
Follow-up (months) ^b	-	-
Median	21.9	28.2
95% CI	(14.7, NR)	(21.8, NR)
Percentage of patients with response duration (%) ^a	-	-
≥6 months	45.6	64.9
≥12 months	39.0	53.1
≥24 months	39.0	33.2

Source: FDA statistical reviewer's analysis

a. Estimated using the Kaplan-Meier method.

b. Estimated by reverse Kaplan-Meier method.

Abbreviations: CI = confidence interval, CR = complete response, DOR = duration of response, IRC = independent review committee, mITT = modified intent-to-treat, N = number of patients, n (%) = number of patients in a specified category, NR = not reached, PD = progressive disease, PR = partial response

There were three patients who were new responders by IRC re-review who were not responders in the original IRC review, two of which were also not responders by investigator review. These three new responders by IRC re-review did not have durable responses (<14 weeks). Additionally, one patient (b) (6) who had a DOR of 50 weeks by original IRC had a DOR of 20 weeks by IRC re-review. These affected the median DOR for the re-review relative to the median DOR reported by the original IRC.

FDA Analysis of Time to Response

By IRC re-review, the median TTR was 4.9 weeks (95% CI: 4.4 weeks, 8 weeks).

By investigator assessment, the median TTR was 5.1 weeks (95% CI: 4.3 weeks, 11.3 weeks).

FDA Analysis of PFS and OS Endpoints

FDA disagrees with the Applicant's claims based on PFS and OS. ADP-0044-002 is a single-arm study with no comparator group. Time-to-event endpoints such as PFS and OS are not interpretable and, therefore, not included in FDA benefit-risk assessment.]

Dose/Dose Response

Data:

Justification for Study ADP-0044-002 regimen was based on clinical data driven by safety, tolerability, and clinical activity from the ADP-0044-001 phase 1 study. A single regimen was used in the study:

- Lymphodepleting chemotherapy regimen consisting of cyclophosphamide 600 mg/m²/day for 3 days (Days -7 to -5) and fludarabine 30 mg/m²/day for 4 days (Day -7 to Day -4) prior T-cell infusion.

- Afamitresgene autoleucel dose range of 1 – 10 x 10⁹ transduced cells.

In the ADP-0044-002 study, responses were observed at the lowest dose administered (2.68 x10⁹ transduced cells) and the highest dose administered (9.99 x10⁹ transduced cells) in the study. In the exploratory subgroup analysis, there was a similar response rate among SS subjects who received <7 x 10⁹ transduced cells (ORR 44.1%; 95% CI: 20.25, 66.50) and those who received ≥ 7 x10⁹ transduced cells (ORR 36% [95% CI: 17.97, 57.48]). Additionally, no dose-response trends with ORR or DoR were observed over the afamitresgene autoleucel dose range based on E-R analyses.

The Applicant's Position:

Dose-response analysis was not performed specifically for this study as regimen used was based on evidence from the phase 1 dose-escalation study (ADP-0044-001). Refer to [Section 6.3](#) for efficacy dose-response analysis performed on pooled data across studies.

The FDA's Assessment:

[The recommended dose is between 2.68 x 10⁹ to 10 x 10⁹ MAGE-A4 T cell receptor (TCR) positive T cells and no patients were treated outside this range in the primary efficacy population (N=44). See [Section 6.3.1](#) (clin pharm E-R analyses).]

Durability of Response

Data:

See [Efficacy Results – Secondary and other relevant endpoints](#).

The Applicant's Position:

In subjects with SS, responses were durable with a median DoR of 11.6 months by independent review and 14.4 months by investigator review.

The FDA's Assessment:

[The Applicant's position describes DoR based on the original IRC review of response assessment. FDA does not agree with response assessment by the original IRC. See [Section 8.1.2, Data Quality and Integrity](#) for details regarding the issues that triggered a re-review of response assessment.]

By FDA analysis, median DOR by IRC re-review was 6 months (range: 1.9, 36.1+ months).]

Persistence of Effect

Data:

The persistence of effect is indicated by the durability of the response. See [Efficacy Results – Secondary and other relevant endpoints](#).

The Applicant's Position:

In SS subjects, responses were durable with a median DOR of 11.6 months (95% CI: 4.44, NE) by independent review.

The FDA's Assessment:

[The Applicant's position describes DoR based on the original IRC review of response assessment. FDA does not agree with response assessment by the original IRC. See [Durability of response](#) section.]

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

As an exploratory endpoint, European Quality of Life-5 Dimensions 3 Response Levels (EQ-5D-3L) were administered at Baseline and after afamitresgene autoleucel infusion at Weeks 8, 16, and 24, and Month 12. Once disease progression was established, the EQ-5D-3L assessment was no longer required. The EQ-5D-3L comprised 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 levels each (no problems, some problems, or extreme problems). The EQ visual analog scale recorded the subject's self-rated health on a vertical scale with endpoints ranging from "best imaginable health state" to "worst imaginable health state".

A summary of EQ-5D-3L with individual components per visit is provided in [Table 31](#).

Table 31: Applicant – Summary of Health State and Change From Baseline for EQ-5D-3L (mITT Population; Data-cut: 11Oct2021)

Health Score	Synovial Sarcoma (N=43)		Overall (N=51)	
	Result	Change From Baseline	Result	Change From Baseline
Baseline				
n	37		44	
Mean (standard deviation)	61.7 (26.57)		60.4 (26.48)	
Median	65.0		63.0	
Min, max	5, 95		5, 95	
Missing	6		7	

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Health Score	Synovial Sarcoma (N=43)		Overall (N=51)	
	Result	Change From Baseline	Result	Change From Baseline
Week 8				
n	29	25	35	30
Mean (standard deviation)	64.3 (26.75)	4.1 (28.04)	65.8 (25.16)	6.7 (28.82)
Median	71.0	10.0	71.0	10.0
Min, max	7, 100	-72, 63	7, 100	-72, 77
Missing	0	4	0	5
Week 16				
n	16	14	18	15
Mean (standard deviation)	74.1 (21.58)	3.5 (28.88)	75.3 (20.57)	3.1 (27.88)
Median	80.0	7.5	80.0	5.0
Min, max	8, 100	-82, 35	8, 100	-82, 35
Missing	0	2	0	3
Week 24				
n	16	12	18	13
Mean (standard deviation)	69.3 (28.93)	13.1 (28.83)	70.8 (27.52)	11.8 (27.96)
Median	77.5	7.5	80.0	5.0
Min, max	6.5, 100	-20, 82	6.5, 100	-20, 82
Missing	0	4	0	5
Month 12				
n	3	2	3	2
Mean (standard deviation)	78.3 (11.55)	15.0 (28.28)	78.3 (11.55)	15.0 (28.28)
Median	85.0	15.0	85.0	15.0
Min, max	65, 85	-5, 35	65, 85	-5, 35
Missing	0	1	0	1
Last assessment before progression				
n	28	22	34	27
Mean (standard deviation)	70.5 (23.56)	14.0 (25.96)	71.0 (22.06)	14.9 (26.76)
Median	75.0	12.5	75.0	10.0
Min, max	6.5, 100	-22, 82	6.5, 100	-22, 82
Missing	0	21	0	24

Source: ADP-0044-002 CSR, Table 14.3.9.4. AdaM: ADSL, ADQS

Note: Overall column includes 8 subjects with MRCLS.

The Applicant's Position:

Most subjects had no problems or some problems across all 5 dimensions until disease progression; 59% of patients had a “better” health change at one or more time points following infusion.

The FDA's Assessment:

[Applicant [Table 31](#) incorrectly states the number of patients with synovial sarcoma (n=43). The efficacy evaluable population (mITT) included 44 patients with synovial sarcoma, not 43. Applicant [Table 31](#) "Overall" column (n=51) includes subjects with MRCLS. Subjects with MRCLS were not included in FDA benefit-risk analysis.]

FDA disagrees with the Applicant's claims based on patient reported outcomes. ADP-0044-002 is a single-arm study with no comparator group. Therefore, PRO data are not interpretable and are not included in the FDA benefit-risk assessment.]

Additional Analyses Conducted on the Individual Trial

Data:

ORR in ITT population

The ORR by Independent Review in the ITT population was also evaluated. The ORR in the 51 SS subjects who underwent leukapheresis was 33.3% (95% CI: 20.76, 47.92).

Kaplan-Meier Plot of Progression-Free Survival and Overall Survival for Responders versus Non-Responders

Post-hoc Kaplan-Meier estimates for PFS and OS in responders (N=17: PR) versus non-responders (N=35: SD+PD) by independent review was also performed for subjects with SS. In the 17 subjects who had a RECIST response by independent review, the median OS was not reached, and the 12-month Kaplan-Meier OS probability was 90% (95% CI: 63, 99) and the 24-month KM OS probability was 60% (95% CI: 31, 83).

Subgroup Analyses of ORR Based on Independent Review

The following subgroup analyses were performed on Independent review of data for ORR:

- Age (<40 years; ≥40 years)
- Gender (male; female)
- Prior lines of systemic therapy (≤2; ≥3)
- Geographical region (North America; Europe)
- H-score (<200; ≥200)
- Baseline sum of diameter (<100 mm; ≥100 mm)
- Bridging therapy (yes; no)
- Transduced cell dose (<7 × 10⁹; ≥7 × 10⁹)
- Cytokine release syndrome, any grade (yes; no)

Treatment effects appeared to be generally consistent across all relevant subgroups. Any apparent variations in efficacy are limited by the small number of subjects with a response in

each subgroup and should be viewed with caution ([Table 32](#)). Different subject, treatment history, and tumor characteristic factors appeared associated with higher response rates, with gender, baseline tumor burden, MAGE-A4 expression, and bridging therapy having the largest effects.

Table 32: Applicant – Overall Response Rate using RECIST v1.1 by Independent Review – Synovial Sarcoma; Subgroup Analyses

Subgroup	Overall Response Rate (CR + PR); n (%), (95% CI) ^a	
Age	<40 years N=21	≥40 years N=23
	7 (33.3), (14.59, 56.97)	10 (43.5), (23.19, 65.51)
Gender	Male N=22	Female N=22
	6 (27.3), (10.73, 50.22)	11 (50), (28.22, 71.78)
Prior Lines of Systemic Therapy	≤2 Lines N=21	≥3 Lines N=23
	7 (33.3), (14.59, 56.97)	10 (43.5), (23.19, 65.51)
Geographical Region	North America N=31	Europe N=13
	11 (35.5), (19.23, 54.63)	6 (46.2), (19.22, 74.87)
H-Score	<200 N=14	≥200 N=30
	4 (28.6), (8.39, 58.10)	13 (43.3), (25.46, 62.57)
Baseline Sum of Diameter	SLD <100 mm N=22	SLD ≥100 mm N=21
	12 (54.5), (32.21, 75.61)	5 (23.8), (8.22, 47.17)
Bridging Therapy	Yes N=16	No N=28
	4 (25), (7.27, 52.38)	13 (46.4), (27.51, 66.13)
Transduced Cell Dose	<7 × 10 ⁹ N=19	≥7 × 10 ⁹ N=25
	8 (42.1), (20.25, 66.50)	9 (36), (17.97, 57.48)
CRS Any Grade	Yes N=33	No N=11
	11 (33.3), (17.96, 51.83)	6 (54.5), (23.38, 83.25)

Source: ADP-0044-002-S2 Table 14.2.1.1.2.1a to 14.2.1.1.2.9a. AdAM: ADSL, ADRS

a. Two-sided 95% CI based on exact Clopper-Pearson (exact Binomial) method.

The Applicant's Position:

The lower limit of the 95% CI for ORR by independent review in the ITT population was also greater than 18%.

Subjects with SS who had a response had longer PFS compared with non-responders.

Responses were observed across all key subgroup covariates analyzed. Higher response rates were observed in subjects who are female, had higher MAGE-A4 expression, had lower disease burden at baseline, or did not require bridging therapy.

The FDA's Assessment:

[ORR in ITT Population]

The Applicant's position describes ORR in the ITT population based on the original IRC review of response assessment. FDA does not agree with response assessment by the original IRC. See [Section 8.1.2, Data Quality and Integrity](#) for details regarding the issues that triggered a re-review of response assessment.

By FDA analysis, 52 patients with SS were included in the ITT population, not 51 patients. See [Section 8.1.2, Patient Disposition](#), for additional details.

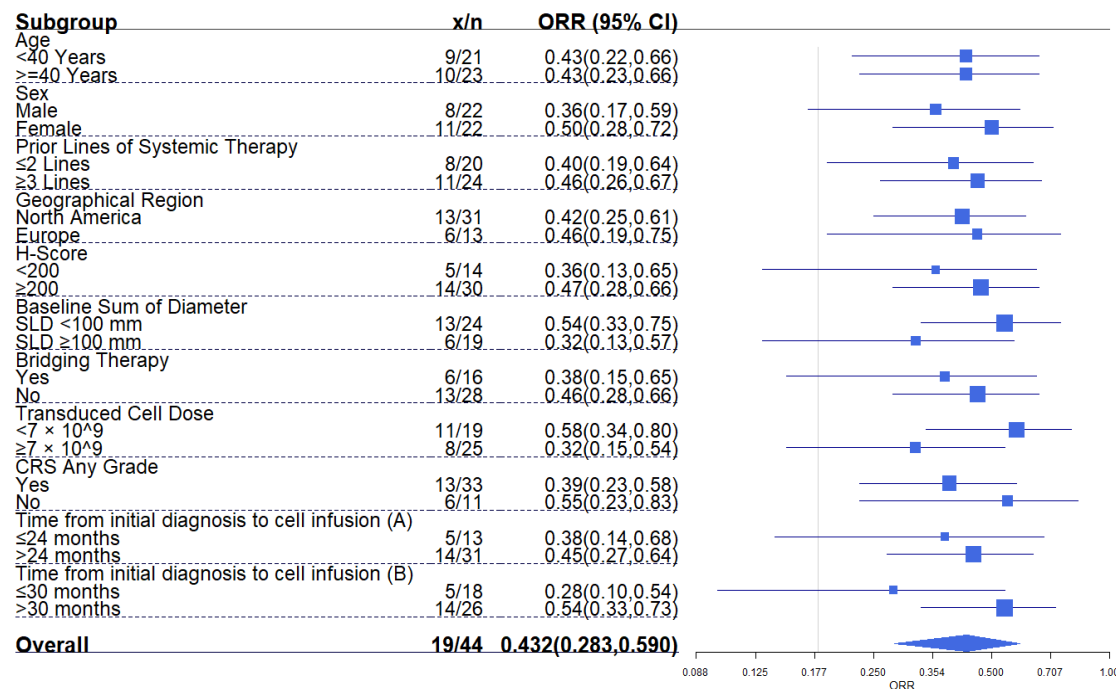
The ORR in the ITT population (n=52 by FDA analysis) was 36.5% (95% CI: 23.6, 51.0).

Subgroup Analysis of ORR Based on IRC Re-Review

Applicant Table 32 shows subgroup analysis of ORR in the mITT population (N=44 patients) by original IRC review. FDA does not agree with the subgroup analysis of ORR based on response assessment by the original IRC. See [Section 8.1.2, Data Quality and Integrity](#) for additional details regarding the issues that triggered a re-review of response assessment. FDA analysis of ORR by subgroups in the mITT population using IRC re-review data is summarized in [Figure 17](#).

By FDA analysis, there were 24 patients who received ≥ 3 prior lines of therapy, rather than 23 patients as displayed in Applicant Table 32.

Figure 17: FDA – ORR by Subgroups



Source: FDA statistical reviewer's analysis

Abbreviations: CI = confidence interval, CRS = cytokine release syndrome, ORR = overall response rate, SLD = sum of longest diameter

Reviewer Comment: Given the small number of patients in these exploratory subgroup analyses of this small, single arm trial, the results of the presented analyses are considered exploratory and hypothesis generating, and thus definitive conclusions cannot be made about these results.]

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

[The primary evidence of effectiveness of afamitresgene autoleucel in the indicated population comes from patients with SS dosed in Cohort 1 of Study ADP-0044-002, a single-arm, open label, multi-cohort, multicenter, multiregional (United States, Europe, and Canada) Phase 2 study. The objective response rate of 43.2% and median duration of response of 6.0 months are considered clinically meaningful in this pre-treated population with limited treatment options. Taking into account the rarity of the disease and the lack of alternative treatment options for advanced unresectable and/or metastatic SS, ORR supported by DOR is considered reasonably likely to predict clinical benefit in the proposed indication.]

8.1.4 Assessment of Efficacy Across Trials

Primary Endpoints

Data:

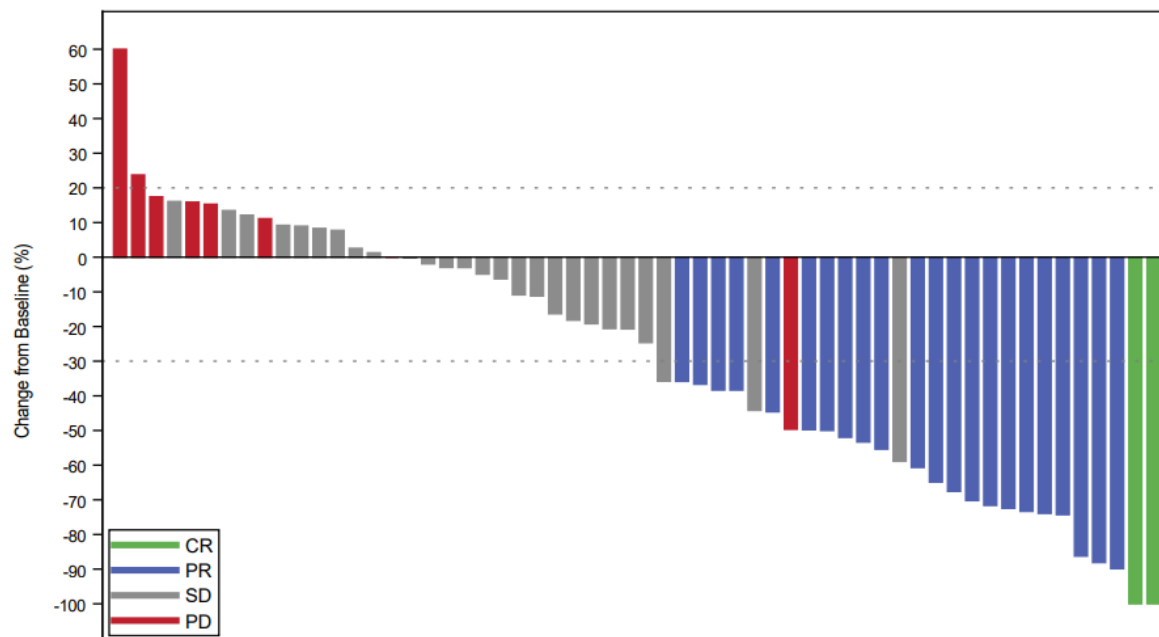
The primary evidence to support the efficacy of afamitresgene autoleucel in subjects with advanced (unresectable/ metastatic) SS is provided by Study ADP-0044-002 (see [Section 8.1.2](#)). As supportive evidence, a pooled analysis with 59 subjects with SS was performed (m2.7.3., Section 3):

- 16 SS subjects from study ADP 0044–001 (01Sep2020)
- 43 SS subjects from study ADP-0044–002, Cohort 1 (data cut-off: 11Oct2021)

All subjects in the pooled analyses received a T-cell dose within the recommended phase 2 dose range and received the same lymphodepleting chemotherapy consisting of cyclophosphamide/fludarabine, except for 4 subjects with SS who received a higher cyclophosphamide containing regimen (in the phase 1 study). Investigator assessments for efficacy were done in both studies, therefore pooled analyses were based on investigator response assessments. The primary efficacy endpoints presented for the pooled population is ORR based on investigator assessed BOR per RECIST v1.1.

Of the 59 treated subjects with SS in the pooled mITT population, 24 subjects responded to treatment per RECIST v1.1 (CR or PR) as assessed by the Investigator review using RECIST v1.1 criteria. Two (3.4%) responders had a CR and 22 (37.3%) had a PR with an ORR of 40.7% (95% CI: 28.07, 54.25). Waterfall plots for the maximum percentage change in the SLD in target lesion from Baseline using RECIST v1.1 via Investigator review for the subjects with SS are presented in [Figure 18](#).

Figure 18: Applicant – Waterfall Plot for Maximum Percentage Change in SLD in Target Lesion From Baseline by Investigator Assessment (mITT Population) – Synovial Sarcoma



Source: Module 5.3.5.3, ISE, Figure 14.2.1.8.1. AdaM: ADSL, ADRS, ADLS

The Applicant's Position:

The ORR per investigator review observed in the pooled analysis (40.7%; 95% CI: 28.07, 54.25) was consistent with the ORR per independent review observed in Study ADP-0044-002 (38.6%; 95% CI: 24.36, 54.50). The ORR obtained with afamitresgene autoleucel in advanced SS is an improvement over historical response rates for pazopanib or trabectedin ([Table 1](#)).

The FDA's Assessment:

[A pooled analysis of patients with SS treated on Studies ADP-0044-002 and ADP-0044-001 is provided by the Applicant as supportive efficacy data. The pooled analysis is based on investigator response assessment, which may be subject to bias and variance in assessment of response. Additionally, lymphodepletion doses varied in the ADP-0044-001 Phase 1 study. Due to these issues, the pooled analysis was of limited value for FDA benefit-risk assessment.]

Secondary and Other Endpoints

Data:

The secondary endpoints for the pooled analyses were: TTR, DoR, PFS, and OS.

For the 24 subjects with SS with a response, were responders per investigator assessment the median TTR was 6.2 weeks (95% CI: 4.43, 8.14), and median DOR was 12 months (95% CI: 1.45,

NE). Approximately 46% of subjects with response had response duration greater than 6 months (m2.5 Clinical Overview, Section 4.2).

The Applicant's Position:

The pooled efficacy data in subjects with SS was consistent with the efficacy observed in Study ADP-0044-002. The efficacy obtained with afamitresgene autoleucel, is an improvement over historical ORRs for approved second-line therapies in advanced SS, such as pazopanib and trabectedin ([Table 1](#)), and responses in SS are also durable. The observed ORR and DoR are clinically meaningful and a measure of direct clinical benefit in the context of the rarity and poor prognosis of this disease.

The FDA's Assessment:

[Due to the limitations described in [Section 8.1.4, Primary Endpoints](#), the pooled analysis was of limited value for benefit-risk assessment. Additionally, time-to-event endpoints such as PFS and OS are not interpretable in single arm trials.]

Subpopulations

Data:

The following subgroup analyses were performed on pooled data for ORR and BOR:

- Age (<40 years; ≥40 years)
- Gender (male; female)
- Prior systemic lines of therapy (≤2; ≥3)
- Geographical region (North America; Europe)
- H-score (<200; ≥200)
- Baseline sum of diameter (<100 mm; ≥100 mm)
- Bridging therapy (yes; no)
- Transduced cell dose (<7 × 10⁹; ≥7 × 10⁹)
- Cytokine release syndrome, any grade (yes; no)

Responses occurred in all subgroups analyzed, but a higher proportion of subjects with SS had a response if they have low tumor burden (SLD <100 mm), less prior lines of systemic therapy (≤2 prior lines), high MAGE-A4 expression (H-score ≥ 200) and have not received bridging therapy before afamitresgene autoleucel infusion ([Table 33](#)).

Table 33: Applicant – ORR using RECIST v1.1 – Synovial Sarcoma; Subgroup Analyses (N=59)

Subgroup	Overall Response Rate (CR + PR); n (%), (95% CI ^a)	
Age	<40 years	≥40 years
	8 (33.3), (15.63, 55.32)	16 (45.7), (28.83, 63.35)
Gender	Male	Female
	11 (35.5), (19.23, 54.63)	13 (46.4), (27.51, 66.13)

Subgroup	Overall Response Rate (CR + PR); n (%), (95% CI) ^a	
Prior Systemic Lines of Therapy	≤2 Lines	≥3 Lines
	16 (55.2), (35.69, 73.55)	8 (26.7), (12.28, 45.89)
Geographical Region	North America	Europe
	20 (42.6), (28.26, 57.82)	4 (33.3), (9.92, 65.11)
H-Score	<200	≥200
	5 (27.8), (9.69, 53.48)	19 (46.3), (30.66, 62.58)
Baseline Sum of Diameter	SLD <100 mm	SLD ≥100 mm
	17 (53.1), (34.74, 70.91)	7 (25.9), (11.11, 46.28)
Bridging Therapy	Yes	No
	7 (29.2), (12.62, 51.09)	17 (48.6), (31.38, 66.01)
Transduced Cell Dose	<7 × 10 ⁹	≥7 × 10 ⁹
	9 (36.0), (17.97, 57.48)	15 (44.1), (27.19, 62.11)
CRS Any Grade	Yes	No
	18 (39.1), (25.09, 54.63)	6 (46.2), (19.22, 74.87)

Source: Module 5.3.5.3, ISE, Table 14.2.1.1.1.1 to 14.2.1.1.1.10. AdAM: ADSL, ADRS

a. Two-sided 95% CI based on exact Clopper-Pearson (exact Binomial) method.

The Applicant's Position:

Responses were observed across key subgroup covariates. Higher response rates were observed in subjects with low tumor burden (SLD <100 mm), less prior lines of systemic therapy (≤2 prior lines), high MAGE-A4 expression (H-score ≥ 200) and that had not received bridging therapy before afamitresgene autoleucel infusion.

The FDA's Assessment:

[Due to the limitations described in [Section 8.1.4, Primary Endpoints](#), the pooled analysis was of limited value for FDA benefit-risk assessment. Additionally, given the small number of patients in these exploratory subgroup analyses, the results of the presented analyses are considered exploratory and hypothesis generating, and thus definitive conclusions cannot be made about these results.]

8.1.5 Integrated Assessment of Effectiveness

The FDA's Assessment:

[Efficacy assessment is based on IRC data from a single trial, ADP-0044-002. The pooled analysis of ADP-0044-002 and ADP-0044-001 is based on investigator response assessment, which may be subject to bias and variance in assessment of response. Additionally, lymphodepletion doses varied in the ADP-0044-001 Phase 1 study. Due to these issues, the pooled analysis was of limited value for FDA benefit-risk assessment.]

8.2 Review of Safety

Data:

The safety and tolerability of afamitresgene autoleucel has been evaluated across the following studies:

- Phase 2 Study ADP-0044-002 Cohort 1 (Data cut-off: 29Mar2023; N= 52, 44 subjects with SS)
- Phase 2 Study ADP-0044-002 across Cohorts 1 & 2 (Data cut-off: 29Mar2023; N=80 subjects with SS; 88 overall)
- Phase 1 Study ADP-0044-001 (Data cut-off: 01Sep2020; N=38, 16 subjects with SS)
- Phase 1 sub-study ADP-0044-001R (Data cut-off: 13Jan2022; N=5).

The Applicant's Position:

The primary evidence to support the safety of afamitresgene autoleucel in the proposed indicated population is provided by subjects with SS treated in Study ADP-0044-002 Cohort 1 (data cut-off date: 29Mar2023). Pooled data across studies was used as supportive safety data.

The FDA's Assessment:

[The FDA concurs with the Applicant the primary safety analysis includes 44 patients from Study ADP-0044-002 Cohort 1.]

8.2.1 Safety Review Approach

Data:

Not applicable.

The Applicant's Position:

The safety profile summarized in the BLA consists of data for 2 clinical studies of afamitresgene autoleucel in monotherapy: ADP-0044-002 phase 2 study (Cohort 1 enrollment and dosing complete; interventional and LTFU phases ongoing; Cohort 2 ongoing), and ADP-0044-001 phase 1 study (enrollment and dosing complete; interventional and LTFU phases ongoing); and 1 sub-study of afamitresgene autoleucel in combination with low dose radiation: ADP-0044-001R (interventional phase complete; LTFU ongoing). A total of 130 subjects who received at least one dose of afamitresgene autoleucel are included in the safety database. The primary evidence of safety is derived from the registration-directed trial, ADP-0044-002, Cohort 1. The primary safety analysis in subjects with SS dosed in this study is representative of the proposed indicated population and is consistent with the overall safety profile.

Integrated Summary of Safety (ISS) – The safety analysis in the ISS/SCS was based on the pooled data from studies ADP-0044-002 (data cut-off: 11Oct2021), ADP-0044-001 (data cut-off: 01Sep2020), and sub-study ADP-0044-001R (data cut-off: 13Jan2022). Overall, 93 subjects (59 s

subjects with SS, and 34 subjects with other tumor indications) were treated with afamitresgene autoleucel and were included in the safety database. All subjects with SS and 86 of 93 subjects (92.5%) in the overall population presented in the pooled analysis received an afamitresgene autoleucel dose within the range proposed for labeling.

Safety Update Report (SUR) – The safety update provides the cumulative safety update of afamitresgene autoleucel through 29Mar2023 (safety data cut-off date for Study ADP-0044-002). The data cut-off dates for Studies ADP 0044-001 and ADP-0044-001R remains the same. Overall, 130 subjects (96 subjects with SS) were included in the safety database at the time of the SUR.

The FDA's Assessment:

[The primary safety analysis was performed in 44 patients with SS treated with afamitresgene autoleucel in Study ADP-0044-002 Cohort.

The supportive safety analysis was performed in 80 patients with SS in Study ADP-0044-002 Cohort 1 and Cohort 2

The overall pooled supportive safety analysis was evaluated in 130 patients with synovial sarcoma, MRCLS, and solid tumors from ADP-0044-002 (Cohorts 1 and 2); ADP-0044-001, which is a Phase 1 study to evaluate safety of afamitresgene autoleucel in HLA-A*02 positive patients with MAGE-A4 positive, inoperable, locally advanced or metastatic tumors; and ADP-0044-001R, a sub-study of ADP-0044-001 of low dose radiation in combination with afamitresgene autoleucel.

The administration of afamitresgene autoleucel is preceded by lymphodepletion chemotherapy consisting of cyclophosphamide and fludarabine; therefore, the safety assessment will evaluate the entire treatment regimen, including lymphodepletion, which consisted of fludarabine 30mg/m² for 4 days (Day-7 to Day-4) and cyclophosphamide 600mg/m² for 3 days (Day -7 to -5).

Additionally, patients may receive other concomitant medications, which may potentially confound the casualty of AEs occurring after afamitresgene autoleucel administration. During the safety review, adverse drug reactions are defined as treatment-emergent AEs (TEAEs), treatment-emergent serious adverse events (TESAEs), and AESIs with onset or worsening after the start of afamitresgene autoleucel infusion, regardless of perceived relationship and causality with the investigational product.

The Applicant reported AEs of organ systems by preferred terms, which may underestimate the incidence of some AEs; therefore, the FDA grouped the preferred terms that represented the same pathophysiologic process in order to minimize such underestimation. The grouping

practice used to analyze the AEs is consistent with the approach used for marketing applications of oncology products.

All grade AEs were counted by maximum toxicity grade (i.e., multiple incidences of the same AE in one patient are counted once at the worst grade for this patient).]

8.2.2 Review of the Safety Database

Overall Exposure

Data:

The safety of afamitresgene autoleucel supporting the application is primarily based on data from SS subjects treated in the Study ADP-0044-002. The BLA Summary of Clinical Safety (SCS) presented the pooled safety analyses for 93 subjects treated with afamitresgene autoleucel in Study ADP 0044-002 (SPEARHEAD-1, Cohort 1, data cut-off date: 11-Oct-2021), Study ADP-0044-001 (data cut-off date: 01-Sep-2020), and Study ADP 0044 001R (data cut-off date: 13-Jan-2022). Of the 93 subjects, 43 subjects with synovial sarcoma (SS) were from Study ADP-0044-002, Cohort 1.

The Safety Update Report (SUR) presents the cumulative safety update of afamitresgene autoleucel through 29-Mar-2023 (safety data cut-off date for Study ADP-0044-002) to support the review of the Biologics License Application (BLA). The data cut-off dates for Studies ADP 0044-001 and ADP-0044-001R remains the same as in the original BLA.

The safety data in this SUR include 130 subjects treated with afamitresgene autoleucel in Studies ADP-0044-002 (Cohorts 1 & 2), ADP-0044-001, and ADP-0044-001R: 96 subjects with SS and 34 subjects with other tumors including subjects with myxoid/round cell liposarcoma (MRCLS). The data are summarized using 4 groups:

- Study ADP-0044-002 SS Cohort 1 (N=44)
- Study ADP-0044-002 SS Cohorts 1 & 2 (N=80)
- Pooled SS (N=96)
- Overall (N=130)

All 130 subjects received at least 1 dose of afamitresgene autoleucel and were included in the modified intent-to-treat (mITT) population.

In Study ADP-0044-002 SS Cohort 1, the median transduced cell dose was 8.004×10^9 (range: $2.675\text{--}9.994 \times 10^9$)). Across ADP-0044-002 Cohort 1 and 2 the median transduced cell dose was 6.193×10^9 (range: $1.010\text{--}9.996 \times 10^9$) for subjects with SS and was 7.222×10^9 cells (range: $1.010\text{--}9.996 \times 10^9$ cells) in the pooled SS group (Table 34).

For the pooled overall group (N=130), the median transduced cell dose was 6.518×10^9 (range: $0.1\text{--}9.996 \times 10^9$ cells; (Table 34)).

Table 34: Applicant – Summary of T-Cell Infusion (mITT Population)

Treatment	Study ADP-0044-002		Pooled SS (N=96)	Pooled Overall (N=130)
	SS Cohort 1 (N=44)	SS Cohorts 1 & 2 (N=80)		
Total transduced cells ($\times 10^9$) ^a				
n	44	80	96	130
Mean (SD)	7.286 (2.5060)	6.647 (2.7624)	6.974 (2.7517)	6.605 (2.9662)
Median	8.004	6.193	7.222	6.518
Minimum, maximum	2.675, 9.994	1.010, 9.996	1.010, 9.996	0.1, 9.996
Transduction efficiency (%)				
n	44	79	95	129
Mean (SD)	57.6 (14.25)	55.8 (14.52)	56.5 (13.78)	56.4 (13.61)
Median	60.5	56.0	56.0	56.0
Minimum, maximum	25, 87	15, 87	15, 87	15, 87
Entire product infused, n (%)				
Yes	44 (100.0)	79 (98.8)	95 (99.0)	128 (98.5)
No	-	1 (1.3)	1 (1.0)	2 (1.5)

Sources : Tables SUR-14.1.7_C1, SUR-14.1.7_C1C2, and SUR-14.1.7.

a. The error in the reported total transduced cell dose of 11.620×10^9 cells in Subject (b) (6) (Cohort 2; Listing SUR-16.2.5.2_C2) was updated to 5.8098×10^9 cells. The summary statistics presented in the table reflect the revised numbers (data on file).

The Applicant's Position:

The safety of afamitresgene autoleucel provided by data from subjects with SS treated in Study ADP-0044-002 (Cohort 1; N=44) is intended to be used for the purpose of labeling. Safety data across afamitresgene autoleucel clinical studies (N=130) is intended to provide supportive safety evidence.

The FDA's Assessment:

[The primary safety analysis was performed in 44 patients with SS treated with afamitresgene autoleucel in Study ADP-0044-002 Cohort.

The supportive safety of afamitresgene autoleucel was evaluated in 80 patients with SS treated in Cohort 1 and 2 in Study ADP-0044-002.

According to the Applicant, the supportive safety which is the pooled safety analyses includes 93 patients of which 43 patients with synovial sarcoma (SS) were from Study ADP-0044-002, Cohort 1. According to FDA's assessment, the primary safety analysis includes not 43 but 44 patients with SS due to a later cutoff date to allow longer follow up. FDA limited the supportive safety analysis to the 80 patients with SS from Study ADP-0044-002 (Cohorts 1 and 2) and excluded patients without SS, which were 13 patients for the total of 93 that the Applicant references.

The overall pooled supportive safety was evaluated in 130 patients with various solid tumors in the following studies:

- ADP-004-002 (Cohort 1 and 2)
- ADP-004-001
- ADP-004-001R]

Relevant characteristics of the safety population:

Data:

Baseline Characteristics for the 44 subjects with SS comprising the primary safety population in Study ADP-0044-002 Cohort 1 are summarized in [Table 35](#). Subjects were White (88.6%), Asian (6.8%), Black or African American (4.5%) and Hispanic or Latino (4.5%). Demographic and baseline characteristics from the pooled analyses is summarized in SUR Tables SUR-14.1.2.1.1 and 14.3.1.3.1.2 and were comparable across studies.

Table 35: Applicant – Demographic and Baseline Characteristics (mITT Population)

	Synovial Sarcoma (N=44)	Overall (N=52)
Age at time of consent (years)		
Mean (standard deviation)	41.0 (13.07)	41.4 (12.86)
Median	40.5	41.0
Min, max	19, 73	19, 73
Age categorization, n (%)		
<65 years	41 (93.2)	49 (94.2)
≥65 years	3 (6.8)	3 (5.8)
Sex, n (%)		
Female	22 (50.0)	24 (46.2)
Male	22 (50.0)	28 (53.8)
Height (cm)		
N	42	50
Mean (standard deviation)	171.31 (9.663)	171.16 (9.343)
Median	172.10	172.10
Min, max	147, 187	147, 187
Weight (kg)		
Mean (standard deviation)	79.85 (18.705)	78.83 (17.731)
Median	78.00	76.65
Min, max	45.9, 120.3	45.9, 120.3
Body mass index (kg/m ²)		
N	42	50
Mean (standard deviation)	27.1 (6.27)	26.8 (5.87)
Median	25.8	25.6
Min, max	18, 43	18, 43
Ethnicity, n (%)		
Hispanic or Latino	2 (4.5)	2 (3.8)
Not Hispanic or Latino	38 (86.4)	43 (82.7)

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	Synovial Sarcoma (N=44)	Overall (N=52)
Not reported	4 (9.1)	6 (11.5)
Unknown	0	1 (1.9)
Race, n (%)		
Asian	3 (6.8)	3 (5.8)
Black or African American	2 (4.5)	2 (3.8)
White	39 (88.6)	45 (86.5)
Missing	0	2 (3.8)
Geographical region, n (%)		
Europe	12 (27.3)	13 (25.0)
North America	31 (70.5)	37 (72.2)
United Kingdom	1 (2.3)	2 (3.8)
Histological grade, n (%)		
G1 – well differentiated (low grade)	0	2 (3.8)
G2 – moderately well differentiated (intermediate grade)	9 (20.5)	9 (17.3)
G3 – poorly differentiated (high grade)	22 (50.0)	26 (50.0)
G4 – undifferentiated (high grade)	4 (9.1)	5 (9.6)
Unknown	9 (20.5)	10 (19.2)

Sources: Module 5.3.5.3 SUR Table 14.1.2.1.1_C1, Tables SUR-14.1.2.1.1_C1. AdaM: ADSL

Note: Overall column includes 8 subjects with MRCLS

The Applicant's Position:

Demographics and baseline disease characteristics were generally as expected for the population with advanced SS.

The FDA's Assessment:

[FDA concurs with the Applicant regarding the demographics and baseline disease characteristics for the primary safety analysis population. There was limited participation of African American, Hispanic/Latino, Indigenous and Native American, Native Hawaiian, and other Pacific Islanders and other persons of color.

The demographic characteristics of patients included for the supportive safety analysis population (N=80) and the pooled overall supportive safety analysis population (N=130) are similar to the demographics of the primary efficacy analysis population. The median age was 40 years old, more men than women were treated, and most identified as White race and not Hispanic or Latino. Analysis performed using Table 36 below summarizes the demographics and baseline characteristics of the safety population. In the supportive safety analysis population, the median age was 40 years (range: 16-73 years), 38 were female, 42 were male, 68 were White, 5 were Asian, 3 were Black or African American, and 1 was American Indian or Alaska Native. Two patients had missing demographic characteristics, and one patient was listed as multiple. Furthermore, the review process also involved the review of a 120-day safety report

submitted by the Applicant on February 22, 2024, with the data cut-off date of March 29, 2023. See Table 36 below.]

Table 36: FDA – Demographic and Baseline Characteristics, Safety Analysis Population (N=80) and Safety Analysis Pooled Population (N=130)

	Synovial Sarcoma (Cohort 1&2)	Safety Analysis Pooled Population
Characteristic	N=80 n (%)	N=130 n (%)
Age at study entry (years)	-	-
n	80	130
Mean (SD)	41.49 (13.62)	46.53 (14.83)
Median	40.50	46
Q1, Q3	31, 50.25	34.25, 59
Min, Max	16, 73	16, 78
Age at study entry category, n (%)	-	-
≥16 and <18 years	1 (1.25)	1 (0.77)
≥18 and <65 years	74 (92.50)	113 (86.92)
≥65	5 (6.25)	16 (12.31)
Sex, n (%)	-	-
Male	42 (52.50)	71 (54.62)
Female	38 (47.50)	59 (45.38)
Height (cm)	-	-
n	74	119
Mean (SD)	170.75 (9.58)	170.84 (9.76)
Median	170.50	170.80
Min, max	145.50, 188	145.50, 190
Weight (kg)	-	-
n	80	130
Mean (SD)	80.05 (19.06)	80.35 (19.68)
Median	77.80	77.40
Min, max	45.90, 132.90	42.90, 148.80
Body mass index (kg/m ²)	-	-
n	74	119
Mean (SD)	27.27 (6.03)	27.08 (6.01)
Median	25.78	25.72
Min, max	17.52, 47.37	15.49, 47.37
Race, n (%)	-	-
White	68 (85)	112 (86.15)
Asian	5 (6.25)	8 (6.15)
Black or African American	3 (3.75)	4 (3.08)
American Indian or Alaska Native	1 (1.25)	1 (0.77)
Multiple	1 (1.25)	1 (0.77)
Missing	2 (2.50)	4 (3.08)

	Synovial Sarcoma (Cohort 1&2)	Safety Analysis Pooled Population
Characteristic	N=80 n (%)	N=130 n (%)
Ethnicity, n (%)	-	-
Not Hispanic or Latino	67 (83.75)	112 (86.15)
Hispanic or Latino	6 (7.50)	8 (6.15)
Not reported	7 (8.75)	9 (6.92)
Unknown	0	1 (0.77)
ECOG performance status, n (%)	-	-
0	40 (50)	58 (44.62)
1	39 (48.75)	71 (54.62)
2	1 (1.25)	1 (0.77)
Geographical region, n (%)	-	-
Europe	18 (22.50)	19 (14.62)
North America	60 (75)	108 (83.08)
UK	2 (2.50)	3 (2.31)

Source: Source: ADSL datasets from 120 Safety Update

Abbreviations: cm = centimeter, ECOG = Eastern Cooperative Oncology Group, kg = kilograms, m = meter, max = maximum, min = minimum, n = number of patients in a specified category, N = number of patients, UK = United Kingdom

Adequacy of the Safety Database:

Data:

See Section on [Overall Exposure](#) and [Relevant characteristics](#) of the safety population.

The Applicant's Position:

The proposed population indicated for afamitresgene autoleucel represents a sub-population of a rare disease, i.e., patients with unresectable/ metastatic SS who are positive for an eligible HLA-A*02 allele and whose tumor expresses MAGE-A4. Consequently, the size of the safety database reflects the rarity of this biomarker selected population. Demographics and baseline disease characteristics of subjects with SS treated across trials were also as expected for the population with advanced disease.

It is the Applicant's position that the safety database adequately supports benefit-risk assessment in the context of this rare disease.

The FDA's Assessment:

[The FDA concurs with the Applicant that the safety database adequately supports benefit-risk assessment in the context of this rare disease.]

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not applicable.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that could preclude a comprehensive clinical safety review.

The FDA's Assessment:

[FDA concurs that there were no issues identified regarding data integrity or submission quality that could preclude a comprehensive clinical safety review.]

However, two safety narratives were not comprehensive, and the interventions were not fully provided; therefore, information requests to the Applicant were submitted. The two examples are further described below:

- Patient (b) (6) ADP-004-002 Cohort 1: This patient experienced two separate episodes of infection that led to delayed cell infusion, requiring two courses of lymphodepletion chemotherapy. This patient had Grade 3 febrile neutropenia starting on Day -1 lasting for 14 days and was admitted to the hospital due to fever, low blood pressure, asthenia, vomiting, neutropenia, and lymphopenia and was diagnosed with septic shock. Details related to the treatment course that led to two courses of lymphodepletion, medications used to treat the infections and how long cell treatment was delayed were not fully captured. In response to a clinical information request, the Applicant clarified that the patient had a PCR antigen testing completed with negative results followed by initiation of lymphodepletion on (b) (6). The patient experienced adverse event of COVID-19 beginning on January 22, 2021, which resolved on February 25, 2021, following administration of acyclovir and sulfamethoxazole/ trimethoprim. The TEAE of COVID-19 delayed the planned T cell infusion following first-time LD chemotherapy. The patient also experienced a TESAE of Grade 3 sepsis starting on January 27, 2021, that was considered related to the LD chemotherapy. The sepsis event resolved on February 5, 2021, following treatment with meropenem, norepinephrine, and oxygen. The patient underwent repeat baseline study procedures and then initiated a second round of LD chemotherapy on (b) (6), followed by T cell infusion on (b) (6).
- Patient (b) (6) ADP-0044-002 Cohort 1: This patient received treatment with afamitresgene autoleucel at dose of 8.23×10^9 transduced cells on (b) (6), and 1 day post cell infusion, a CT scan of thorax was performed; however, it was not clear as to what symptoms the patient experienced prompting the CT scan. In response to a clinical information request, the Applicant clarified that the patient had an increased cough and prolonged chest pain and given the patient's past history of bilateral

pneumothoraxes, bronchopneumopathy and pleural detachment, a CT scan of the chest was performed.]

Categorization of Adverse Event

Data:

Adverse events (AE) were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

A treatment-emergent adverse event (TEAE) in the interventional phase was defined as an adverse event (AE; identified by PT) that begins or is on-going on or after the first day of lymphodepleting chemotherapy has been administered until discontinuation from the interventional phase. Treatment-related TEAEs were those with reasonable causality to lymphodepletion or T-cell infusion marked as “definitely related”, “probably related”, or “possibly related” on the eCRF. TEAEs with an outcome of death are those with a grade of 5 or an outcome of “fatal.” An AE in the long-term follow-up (LTFU) period was defined as an AE that started or increased in severity/ toxicity after discontinuation from the interventional period until discontinuation from the LTFU period.

The following AEs were collected during LTFU period:

- New malignancies.
- New incidence or exacerbation of a pre-existing neurological disorder (excluding all Grade 1 and Grade 2 AEs assessed as unrelated unless the investigator considers clinically significant).
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder (excluding all Grade 1 and Grade 2 AEs assessed as unrelated unless the investigator considers clinically significant).
- All rheumatologic disorders will be reported irrespective of grade; new incidence of a hematologic disorder (excluding cytopenias following cytotoxic chemotherapy before bone marrow recovery, and Grade 1 and 2 laboratory abnormalities, unless the investigator considers clinically significant).
- Opportunistic and/or serious infections (excluding infections secondary to chemotherapy induced cytopenias)
- Unanticipated illness or hospitalization deemed at least possibly related to gene modified cell therapy.

The AE of special interest (AESI) for afamitresgene autoleucel are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and prolonged cytopenia.

CRS

CRS was graded as per the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading [Lee 2019], with inclusion of organ toxicity based on NCI CTCAE v 5.0.

An external independent Event Adjudication Committee performed blinded adjudication of CRS for all subjects treated in Cohort 1 of study ADP-0044-002 (data cut off 11-Oct-2021). The events were assessed based on the ASTCT consensus grading [Lee 2019].

ICANS

ICANS was graded as per ASTCT ICANS consensus grading for adults [Lee 2019]. Additional analysis of any neurologic event was based on TEAE preferred terms reported under the system organ class of Nervous System Disorders and Psychiatric Disorders.

Prolonged Cytopenia

Prolonged Cytopenia was defined as Grade 3 or higher Anemia, or Thrombocytopenia, or Neutropenia. The severity was assessed using CTCAE v 5.0 criteria Grade 3 or higher at Week 4. Visit windowing for Week 4 was based on worst value from Day 24 to Day 41 post T cell infusion inclusive.

Time to resolution of prolonged cytopenia (considered separately for anemia, thrombocytopenia, and neutropenia) was defined as the first time to return to Grade ≤ 2 after Week 4 and was derived as (date of resolution [or censoring] – date of T cell infusion + 1). The date of resolution was identified every 4 weeks. The time to resolution was estimated using the Kaplan-Meier method.

The Applicant's Position:

The recording, coding, and categorization of AEs is considered by the Applicant to be appropriate and consistent with accepted standards as defined in regulations and guidance and according to clinical practice for development of oncology products and genetically modified T-cell immunotherapies.

The FDA's Assessment:

[Since the treatment includes risks related to lymphodepleting chemotherapy prior to treatment with afamitresgene autoleucel, the FDA safety analysis includes assessments starting at the time patients began the entire treatment regimen, which included lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Risks related to the entire treatment regimen were evaluated during this assessment. The Applicant collected all AE and 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.]

Routine Clinical Tests

Data:

In addition to monitoring for AEs, routine safety evaluations included: clinical laboratory profiles (clinical chemistry, hematology, and urinalysis), ECOG performance status, chimeric antigen receptor T cell therapy associated toxicity (CARTOX)-10 assessment, immune effector cell-associated encephalopathy (ICE) neurological assessment, cardiac assessments (electrocardiogram [ECG], echocardiogram/multigated acquisition scan, and telemetry), physical examination, body weight, T cell persistence (vector copies), RCL, and insertional oncogenesis/T cell clonality. Laboratory safety evaluations and the laboratory results were graded according to the NCI CTCAE v.5.0 severity grade and shifts in grade from baseline to the maximum shift (Source: ADP-0044-002 CSR).

The Applicant's Position:

The routine safety evaluations and time points for collection and analysis of safety measures were appropriate for the indications investigated in Study ADP-0044-002.

The FDA's Assessment:

[FDA concurs with the Applicant that AEs were graded using NCI-CTCAE v 5.0. CRS and ICANS were graded using ASTCT consensus grading ([Lee et al. 2019](#)). The safety evaluations were done similarly.]

8.2.4 Safety Results

Deaths

Data:

A summary of deaths in Study ADP-0044-002 is presented in [Table 37](#).]

Table 37: Applicant – Study ADP-0044-002 Deaths (mITT Population)

	Synovial Sarcoma (N=44) n (%)	Overall (N=52) n (%)
Subject status		
Dead	24 (54.4)	31 (59.6)
Alive at last contact; follow-up ongoing	16 (36.4)	17 (32.7)
Alive at last contact; lost to follow-up/study withdrawal	4 (9.1)	4 (7.7)
Primary cause of death		
Disease under study	24 (54.5)	30 (57.7)
Adverse event	0	0
Other: Cancer Related	0	1 (1.9)
Time to death from T-cell infusion		

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	Synovial Sarcoma (N=44) n (%)	Overall (N=52) n (%)
≤30 days	0	0
>30 days	24 (54.5)	31 (59.6)

Source: ADP-0044-002 Table SUR-14.3.2.9_C1. AdM: ADSL.

Note: N was the number of subjects in each group; n was the number of subjects in each group with non-missing observations for specific variable. Overall column includes 8 subjects with MRCLS.

The Applicant's Position:

No deaths occurred within 30 days of afamitresgene autoleucel infusion (mITT population; data cut-off: 29Mar2023), and no subjects died due to a TEAE in study ADP-0044-002 Cohort 1. Twenty four (24) subjects with SS died between 51 to 875 days after afamitresgene autoleucel infusion, with primary cause of death of disease under study.

The FDA's Assessment:

[For the primary safety analysis, FDA concurs with the Applicant. A total of 24 patients in Cohort 1 died. All deaths were due to disease under study and occurred >30 days after afamitresgene autoleucel administration.

For the supportive safety analysis population (ADP-0044-002 [N=80]), as of the data cut-off date of March 29, 2023, a total of 37 patients died: 24 patients in Cohort 1 and 13 patients in Cohort 2. All deaths were due to disease under study and occurred >30 days after afamitresgene autoleucel administration, except for one patient who died of COVID-19 after treatment (Patient (b) (6); ADP-004-002 Cohort 2, SS; see narrative below).

Additionally, an SAE occurred after the March 29, 2023, data cut-off in a patient with Grade 5 septic shock on Day 9. (Patient (b) (6); ADP-004-002 Cohort 2; SS; See Narrative below).

Narratives of deaths not due to disease under study are below:

Patient (b) (6) (ADP-004-002 Cohort 2; SS): Death due to COVID-19 related pneumonia.

This 29-year-old male patient was enrolled in this study for the treatment of synovial sarcoma diagnosed on an unknown date in December 2020. The patient's relevant medical history included bilateral lung metastasis with multiple pulmonary nodules, right mediastinal mass with possible right atrial invasion, indigestion, tumor pain, pain, cardiac thrombus, and nausea.

At baseline, the patient had an ECOG performance status of 1. The patient received LD chemotherapy with IV fludarabine at a dose of 56.5 mg per day for 4 days, and cyclophosphamide at a dose of 1,130 mg per day for 3 days beginning on (b) (6)

On (b) (6), the patient received treatment with afamitresgene autoleucel at a dose of 2.5668×10^9 transduced cells.

On (b) (6), Study Day 30 post afamitresgene autoleucel administration, a CT scan was performed and revealed moderate sized left pneumothorax. On the same day, a chest tube was placed with suction and oxygen support via nasal cannula, and the patient was hospitalized for tube management with daily chest X-rays. On (b) (6), Study Day 33 post afamitresgene autoleucel administration, a chest X-ray showed resolution of pneumothorax, and the patient was discharged from the hospital in stable condition. The patient discontinued from the study on (b) (6) (161 days on study) and died of COVID-19 on (b) (6) (Day 175 post afamitresgene autoleucel administration). No autopsy was performed.

Patient (b) (6) (ADP-004-002 Cohort 2; SS): Death due to septic shock occurring 9 days after afamitresgene autoleucel.

A 66-year-old male patient was enrolled in this study for treatment of synovial sarcoma diagnosed on (b) (6). His medical history included transient ischemic injury, junctional tachycardia, and atrial fibrillation. At the time of study entry, the patient had ongoing medical conditions of dyslipidemia, dyspnea, left thoracic pain pneumocystosis, and pleural effusion (since April 20, 2023).

In early April 2023 (unknown day), the patient was hospitalized due to dyspnea and oxygen dependence, which was following discontinuation of corticosteroid therapy.

On (b) (6), the patient was hospitalized for lymphodepletion and T cell therapy administration. During hospitalization, placement of a right chest tube was performed, given a large pleural effusion.

Beginning on (b) (6), the patient received lymphodepletion chemotherapy with fludarabine, 54.09 mg per day for 4 days, and cyclophosphamide, 1,080 mg per day for 3 days. On (b) (6), the patient received a dose of G-CSF. On (b) (6), the patient received treatment with afamitresgene autoleucel at a dose of 9.9×10^9 transduced cells. On the same day, the patient started experiencing Grade 1 CRS with body temperature of 38°C.

On (b) (6), Day 2 post T cell infusion, the patient presented with body temperature of 39°C, with hyperthermia, tachycardia, and worsening dyspnea requiring oxygen therapy (4L/min). He was treated with paracetamol and piperacillin 4 mg twice daily and received one dose of tocilizumab (520 mg).

On (b) (6), Day 3 post T cell infusion, the patient started experiencing the SAE of CRS. The patient was hypotensive, which appeared persistent despite volume expansion of 1,000 mL of crystalloids. He was negative for signs of ICANS (ICE score 10/10). He was polypneic with respiratory rate between 25 and 30 cpm and with slight inspiratory indrawing. Reduced vesicular murmur at both bases with diffuse crackles at both bases was noticed. His blood pressure was at 106/64 mmHg, and heart rate at 120 to 130 regular bpm. He received another single dose of tocilizumab (520 mg). He continued presenting respiratory deterioration with an

increase in oxygen requirements of up to 12 L/min, tachycardia at 160 bpm, and two small amounts of hemorrhagic sputum (less than 100 cc) were noticed. Bronchial fibroscopy was performed and showed a very inflamed bronchial mucosa, with some purulent sputum and the presence of very modest quantities of blood in the distal bronchi of the right lung. The patient had extensive capillary leak syndrome, which was requiring massive vascular filling (around 8 L in the first 24 hours), with doses of noradrenaline up to 1 µg/kg/min. All infectious samples (blood cultures, tracheal aspirations, Cyto-Bacteriological Examination of Urine) were negative.

On (b) (6), Day 4 post T cell infusion, the patient started experiencing Grade 4 CRS and was treated with dexamethasone, 10 mg, every 6 hours until (b) (6); tocilizumab, 512 mg, every 8 hours until (b) (6); and IV amikacin, 1,600 mg.

On (b) (6), Day 7 post T cell infusion, the etiological treatment allowed a gradual improvement in the circulatory state, with a gradual decrease in noradrenaline requirements and definitive weaning, as well as respiratory state. On the same day, given the clear hemodynamic improvement and this state of severe vasoplegia, treatment with tocilizumab was stopped on the advice of fellow hematologists, and corticosteroid therapy was gradually reduced. On (b) (6), Day 9 post T cell infusion, the patient was extubated but presented with fever and chills, again associated with hemodynamic deterioration, with a state of severe vasoplegic shock that was attributed to a peripherally inserted central catheter (PICC) line infection, given the inflamed appearance of the insertion port and septic discharge during ablation. Blood cultures taken came back positive for gram-negative bacilli. The patient's laboratory results were as follows: leukocytes at 3.20 giga/L (4.00-10.00), red blood cells (RBCs) at 2.83 tera/L (4.50-6.00), hemoglobin at 85 g/L (130-170), hematocrit at 25.3% (40.0-54.0), RBC distribution width at 17.20% (11-16), platelets at 70 giga/L (150-400), mean platelet volume at 13.7 fL (7.0-13.0), and fibrinogen at 0.87 g/L (2.13-4.22).

The patient developed multiple organ system failure with circulatory failure, requiring more than 8 L of volume expansion and 10 µg/kg/min of noradrenaline, and respiratory failure, with Acute respiratory distress syndrome requiring curarization and ventral decubitus. He was dependent on vasopressin due to hemodynamic failure and orotracheal intubation due to respiratory failure.

The PICC line was removed, and antibiotic therapy was extended with piperacillin/tazobactam, vancomycin, and amikacin; however, maximum organ support was not sufficient to stabilize the patient.

On (b) (6), Day 9 post T cell infusion, the patient died due to the SAE of gram-negative bacilli septic shock. The investigator assessed the event of gram-negative bacilli septic shock as not related afamitresgene autoleucel but possibly related to cyclophosphamide and fludarabine. No autopsy was performed.

In the overall pooled supportive safety population (N=130), 65 patients died; 59 deaths were due to disease under study. Causes of the six remaining deaths are listed below:

- Patient (b) (6) (ADP-004-001; esophageal cancer, acute kidney injury); Died on Day 16

Patient (b) (6) with metastatic adenocarcinoma of the gastroesophageal junction with metastatic disease to the abdomen and malignant ascites had an ECOG performance status score of 4 at the end of treatment visit (Day 16); both patients had an ECOG performance status score of 1 at baseline and had a Grade 3 creatinine post baseline that peaked to 455.26 $\mu\text{mol/L}$ (normal range: 59.228–103.428 $\mu\text{mol/L}$; on Day 8. The patient had a fatal TESA (acute kidney injury) 16 days after T cell infusion that was considered not related to either lymphodepletion chemotherapy or T cell infusion but related to the disease under study.

Since this patient was screened as study eligible prior to lymphodepletion chemotherapy and cell treatment, an information request was sent to clarify the rationale used to conclude that the patient died of disease under study 16 days after T cell infusion. The Applicant indicated that the primary driver of the patient's grade 5 acute renal failure was felt to be pre-renal in nature in the setting of chronic renal failure, malignant ascites requiring paracentesis, and hypotension, which supports the rationale that the patient died as a result of complications of the disease under study.

Due to the temporal nature of the event to the timing of lymphodepletion and T cell infusion, FDA concluded exacerbation of a pre-existing medical history of chronic kidney disease and was related to afamitresgene autoleucel, fludarabine, and cyclophosphamide.

- Patient (b) (6) (ADP-0044-001; SS, unknown reason); Died on Day 300
- Patient (b) (6) (ADP-0044-001; ovarian cancer, cerebrovascular accident; Died on Day 16)

This 71-year-old female patient was enrolled in this study for the treatment of serous ovarian cancer diagnosed on June 4, 2014. The patient received lymphodepletion chemotherapy with fludarabine 20 mg/m²/day for 4 days and intravenous cyclophosphamide 1,800 mg/m²/day for 2 days, beginning on (b) (6) respectively.

On (b) (6) (prior to T cell infusion and 4 days post initiating LD chemotherapy), the patient's alkaline phosphatase, ALT, and AST showed increases in values from baseline to alkaline phosphatase 151 U/L, ALT 260 U/L, AST 245 U/L, and total bilirubin 0.7 mg/dL. On the same day, a limited abdominal ultrasound of the right upper quadrant was performed, which showed prominent pancreas with well-defined hypoechoic mass-like structure anterior to the pancreatic head, likely corresponding to large peripancreatic

lymphadenopathy, with numerous additional peripancreatic lymphadenopathy anterior to the pancreatic body.

On (b) (6), the patient received treatment with afamitresgene autoleucel at the dose of 7.85×10^9 T cells.

An abdominal ultrasound showed irregular wall thickening, an intraluminal mass. There was also dilated common bile duct. There were trace perihepatic ascites and findings of bilateral pleural effusions. On (b) (6), the patient started on rifaximin, potassium chloride, magnesium sulfate, and tocilizumab.

On (b) (6) (8 days post T cell infusion), the patient had mental status changes with a CARTOX score of 6. A brain MRI was performed and showed mild nonspecific white matter changes consistent with encephalopathy and no edema. Lumbar puncture test showed unremarkable results. She was treated with dexamethasone and intravenous tocilizumab 520 mg, her mental status initially improved (CARTOX score of 9). On the same day, the patient deteriorated to CARTOX-2. She was transferred to the ICU for observation.

On (b) (6) (13 days post T cell infusion), the patient was still non-verbal and non-interactive. A CT scan of the head was again performed and showed acute bilateral anterior cerebral artery (ACA)/middle cerebral artery (MCA) watershed infarcts, complete infarction of bilateral thalami, bilateral anterior midbrain including tegmentum, pons, and ventral medulla, with hemorrhage seen in the central pons. Furthermore, there were acute superior cerebellar artery (SCA)/posterior inferior cerebellar artery (PICA) watershed infarcts in the bilateral cerebellar hemispheres. There was superior herniation of the cerebellum with narrowing of the bilateral quadrigeminal and ambient plate cisterns. No significant supratentorial hydrocephalus was seen. The CARTOX score remained 0 until May 26, 2019 (14 days post T cell infusion), and the patient was transitioned to end-of-life care.

- Patient (b) (6) (ADP-0044-001; SS, aplastic anemia); Died on Day 55

This 77-year-old female patient was enrolled in this study for the treatment of synovial sarcoma diagnosed on (b) (6). Baseline laboratory results were platelets 357 K/cumm (150-400 Kcumm), Hgb 10.7g/dL (11.9-15.5 g/dL), and WBC was 5.5 K/cumm (3.8-9.9 K/cumm).

The patient received lymphodepletion chemotherapy with fludarabine 20 mg/m²/day for 4 days beginning on (b) (6), cyclophosphamide 2,980 mg/m² on (b) (6) 2,988 mg/m² (b) (6). Of note, this patient was on the highest lymphodepletion chemotherapy regimen: cyclophosphamide (1,800 mg/m²/day) for 2 days in combination with fludarabine (30 mg/m²/day) for 4 days. On (b) (6) (prior to T cell infusion and 3 days post initiation of LD chemotherapy), the patient presented with Grade 4 cytopenias

(unknown values). On the same day, the patient was diagnosed with aplastic anemia Grade 3 (bone marrow biopsy results were not provided).

On (b) (6), the patient received treatment with afamitresgene autoleucel at the dose of 8.37×10^9 T cells.

Three days post T cell infusion, the patient was transferred to the ICU for worsening dyspnea, tachypnea, CRS and Grade 4 arrhythmia. Chest X-ray showed left pleural effusion which was negative for malignancy. The patient received several platelet transfusions, G-CSF and one unit of PRBC. On (b) (6) (16 days post T cell infusion), the patient's laboratory data were WBC count 0.2 K/cumm, Hgb 10.1 g/dL, platelets 9 K/cumm, and RBC count 3.35 M/cumm (reference range 3.90-5.20 M/cumm).

On (b) (6) (34 days post T cell infusion), the patient was started with oral eltrombopag for aplastic anemia.

On (b) (6) (39 days post T cell infusion), the patient tested positive for *Streptococcus mitis* and *Rothia mucilaginosa*. She was started on foscarnet and norepinephrine bitartrate. She became hypotensive with a blood pressure of 80/40 mmHg, which did not improve despite IV fluid administration. Due to suspicion of CRS (in addition to the previous diagnosis and treatment on (b) (6)), the patient was given a single dose of intravenous tocilizumab 530 mg as well as a single dose of intravenous siltuximab 740 mg. The patient was also started on intravenous micafungin for the infection. On the same day, the patient's relevant laboratory data showed creatinine 1.63 mg/dL (reference range 0.6-1.10 mg/dL), WBC count 0.0 K/cumm, Hgb 8.8 g/dL, platelets 1 K/cumm, and RBC count 3.07 M/cumm. The patient decided to pursue at home hospice and on (b) (6) (55 days post T cell infusion), the patient passed away due to aplastic anemia.

- Patient (b) (6) (ADP-004-002, Cohort 1; MRCLS, other cancer related); Died on Day 553
- Patient (b) (6) (ADP-0044-002, Cohort 2; SS, COVID-19); Date of death unknown

Two deaths occurred prior to 30 days post afamitresgene autoleucel infusion in the overall pooled supportive safety population (N=130):

- [Patient](#) (b) (6) (esophageal cancer) in Study ADP-0044-001 died on Day 16 due to acute kidney injury.
- [Patient](#) (b) (6) (ovarian cancer) in Study ADP-004-001 died on Day 16 due to cerebrovascular accident.]

Serious Adverse Events

Data:

Treatment emergent serious adverse events (TESAEs) in study ADP-0044-002 are summarized by SOC and PT in [Table 38](#).

Table 38: Applicant – Study ADP-0044-002 – Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (mITT Population)

System Organ Class Preferred Term	Synovial Sarcoma (N=44) n (%)	Overall (N=52) n (%)
Subject with any treatment-emergent SAEs	23 (52.3)	26 (50.0)
Respiratory, thoracic, and mediastinal disorders	7 (15.9)	7 (13.5)
Pleural effusion	3 (6.8)	3 (5.8)
Pulmonary embolism	2 (4.5)	2 (3.8)
Dyspnea	1 (2.3)	1 (1.9)
Hemoptysis	1 (2.3)	1 (1.9)
Pneumothorax	1 (2.3)	1 (1.9)
Infections and infestations	6 (13.6)	6 (11.5)
Empyema	2 (4.5)	2 (3.8)
COVID-19 pneumonia	1 (2.3)	1 (1.9)
Pneumonia	1 (2.3)	1 (1.9)
Staphylococcal abscess	1 (2.3)	1 (1.9)
General disorders and administration site conditions	3 (6.8)	4 (7.7)
Pyrexia	1 (2.3)	2 (3.8)
Influenza-like illness	1 (2.3)	1 (1.9)
Respiratory complication associated with device	1 (2.3)	1 (1.9)
Immune system disorders	4 (9.1)	5 (9.6)
CRS	4 (9.1)	5 (9.6)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3 (6.8)	4 (7.7)
Tumor pain	1 (2.3)	2 (3.8)
Lymphoproliferative disorder	1 (2.3)	1 (1.9)
Tumor necrosis	1 (2.3)	1 (1.9)
Vascular disorders	4 (9.1)	4 (7.7)
Deep vein thrombosis	2 (4.5)	2 (3.8)
Superior vena cava occlusion	1 (2.3)	1 (1.9)
Hemorrhage	1 (2.3)	1 (1.9)
Blood and lymphatic system disorders	2 (4.5)	2 (3.8)
Anemia	1 (2.3)	1 (1.9)
Neutropenia	1 (2.3)	1 (1.9)
Pancytopenia	1 (2.3)	1 (1.9)
Gastrointestinal disorders	2 (4.5)	2 (3.8)
Abdominal pain	2 (4.5)	2 (3.8)
Nausea	1 (2.3)	1 (1.9)
Investigations	1 (2.3)	2 (3.9)
Platelet count decreased	1 (2.3)	1 (1.9)
SARS-CoV-2 test positive	0	1 (1.9)
Musculoskeletal and connective tissue disorders	1 (2.3)	2 (3.8)
Back pain	1 (2.3)	2 (3.8)
Musculoskeletal pain	0	1 (1.9)
Nervous system disorders	1 (2.3)	2 (3.8)
Spinal cord compression	1 (2.3)	2 (3.8)
Cerebrovascular accident	1 (2.3)	1 (1.9)

System Organ Class Preferred Term	Synovial Sarcoma (N=44) n (%)	Overall (N=52) n (%)
Cardiac disorders	1 (2.3)	1 (1.9)
Atrial fibrillation	1 (2.3)	1 (1.9)
Metabolism and nutrition disorders	1 (2.3)	1 (1.9)
Malnutrition	1 (2.3)	1 (1.9)
Psychiatric disorders	1 (2.3)	1 (1.9)
Anxiety	1 (2.3)	1 (1.9)
Renal and urinary disorders	1 (2.3)	1 (1.9)
Acute kidney injury	1 (2.3)	1 (1.9)

Source: ADP-0044-002 Table SUR-14.3.2.7.1_C1. AdAM: ADSL, ADAE

Notes: For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term. AEs were coded using MedDRA v23.0. Overall column includes 8 subjects with MRCLS.

The Applicant's Position:

In subjects with SS treated in ADP-0044-002, 52.3% experienced a TESA. The most frequently occurring TESAs were CRS (4 subjects) and pleural effusion (3 subjects), pulmonary embolism, empyema, deep vein thrombosis, abdominal pain (2 subjects each); all other TESAs occurred in 1 subject each. TESAs considered related to the T-cell infusion occurred in 9 subjects with SS, and the most common TESA related to the T-cell infusion was CRS (4 subjects).

The FDA's Assessment:

[In the primary safety population (N=44; SS), TESA occurred in 52% of patients with SS. The most common serious adverse reactions (occurring in ≥5%) included infection (14%), CRS (9%) and pleural effusion (7%).]

In the supportive safety population (N=80; SS), 31 (38.8%) patients experienced a TESA, 16 (20.0%) were considered related to cell infusion. The most frequently reported TESAs were respiratory, thoracic, and mediastinal disorders, occurring in 10 (12.5%) patients; infections and infestations, occurring in 8 (10%) patients; CRS, occurring in 6 (7.5%) patients; blood and lymphatic system disorders, occurring in 4 (5%) patients; vascular disorders, occurring in 4 (5%) patients; investigations occurring, in 4 (5%) patients; vascular disorders, occurring in 4 (5%) patients; neoplasms benign, malignant, and unspecified, occurring in 3 (3.8%) patients; and gastrointestinal disorders, occurring in 3 (3.8%) patients.

In the overall pooled supportive safety population (N=130), 64 (49.2%) patients experienced a TESA. The most frequently reported TESAs were infections and infestations, occurring in 17 (13.1%) patients; CRS, occurring in 16 (12.3%) patients; blood and lymphatic system disorders, occurring in 9 (6.9%) patients; general disorders and administration site conditions, occurring in 9 (6.9%); blood and lymphatic, occurring in 9 (6.9%) patients; investigations, occurring in 8 (6.2%) patients; nervous systems disorders, occurring in 7 (5.4%) patients; cardiac disorders,

occurring in 6 (4.6%) patients; vascular disorders, occurring in 5 (3.8%) patients; and neoplasms benign, malignant, and unspecified, occurring in 5 (3.8%) patients.

Table 39: FDA – Serious Adverse Events by System Organ Class and Preferred Term, 120-Day Safety Update, Pooled Population

System Organ Class/ Preferred Term	Synovial Sarcoma (N=80) n (%)	Pooled Population (N=130) n (%)
Any treatment-emergent SAE	31 (38.8)	64 (49.2)
Blood and lymphatic system disorders	4 (5.0)	9 (6.9)
Anemia	3 (3.8)	3 (2.3)
Aplastic anemia	0	1 (0.8)
Febrile neutropenia	0	1 (0.8)
Neutropenia	1 (1.3)	1 (0.8)
Pancytopenia	1 (1.3)	5 (3.8)
Cardiac disorders	1 (1.3)	6 (4.6)
Aortic valve incompetence	0	1 (0.8)
Arrhythmia	0	1 (0.8)
Atrial fibrillation	1 (1.3)	3 (2.3)
Cardiac failure congestive	0	1 (0.8)
Myocarditis	0	1 (0.8)
Endocrine disorders	0	1 (0.8)
Adrenal insufficiency	0	1 (0.8)
Gastrointestinal disorders	3 (3.8)	5 (3.8)
Abdominal pain	2 (2.5)	2 (1.5)
Abdominal pain lower	0	1 (0.8)
Nausea	1 (1.3)	1 (0.8)
Pancreatitis	1 (1.3)	1 (0.8)
Small intestinal obstruction	0	1 (0.8)
General disorders and administration site conditions	3 (3.8)	9 (6.9)
Influenza -like illness	1 (1.3)	1 (0.8)
Pyrexia	1 (1.3)	7 (5.4)
Respiratory complication associated with device	1 (1.3)	1 (0.8)
Immune system disorders	6 (7.5)	16 (12.3)
Cytokine release syndrome	6 (7.5)	16 (12.3)
Infections and infestations	8 (10.0)	17 (13.1)
Anal abscess	0	1 (0.8)
Cellulitis	0	1 (0.8)
COVID-19	1 (1.3)	1 (0.8)
COVID-19 pneumonia	1 (1.3)	1 (0.8)
Empyema	2 (2.5)	2 (1.5)
Endocarditis	0	1 (0.8)
Endocarditis staphylococcal	0	1 (0.8)
Pneumonia	2 (2.5)	4 (3.1)
Pneumonia aspiration	0	1 (0.8)
Rash pustular	0	1 (0.8)
Sepsis	1 (1.3)	3 (2.3)

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System Organ Class/ Preferred Term	Synovial Sarcoma (N=80) n (%)	Pooled Population (N=130) n (%)
Staphylococcal abscess	1 (1.3)	1 (0.8)
Injury, poisoning and procedural complications	0	1 (0.8)
Toxicity to various agents	0	1 (0.8)
Investigations	4 (5.0)	8 (6.2)
Alanine aminotransferase increased	1 (1.3)	2 (1.5)
Aspartate aminotransferase increased	0	1 (0.8)
Blood alkaline phosphatase increased	0	1 (0.8)
Blood bilirubin increased	1 (1.3)	1 (0.8)
Neutrophil count decreased	0	1 (0.8)
Platelet count decreased	3 (3.8)	5 (3.8)
SARS-CoV-2 test positive	0	1 (0.8)
White blood cell count decreased	1 (1.3)	1 (0.8)
Metabolism and nutrition disorders	1 (1.3)	3 (2.3)
Hyperglycemia	0	1 (0.8)
Hyponatremia	0	1 (0.8)
Malnutrition	1 (1.3)	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (1.3)	4 (3.1)
Arthralgia	0	1 (0.8)
Back pain	1 (1.3)	2 (1.5)
Muscular weakness	0	1 (0.8)
Musculoskeletal pain	0	1 (0.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (3.8)	5 (3.8)
Lymphoproliferative disorder	1 (1.3)	1 (0.8)
Myelodysplastic syndrome		1 (0.8)
Tumor necrosis	1 (1.3)	1 (0.8)
Tumor pain	1 (1.3)	2 (1.5)
Nervous system disorders	1 (1.3)	7 (5.4)
Cerebrovascular accident	1 (1.3)	2 (1.5)
Encephalopathy	0	1 (0.8)
Neurotoxicity	0	2 (1.5)
Sciatica	0	1 (0.8)
Seizure	0	1 (0.8)
Spinal cord compression	1 (1.3)	2 (1.5)
Syncope	0	1 (0.8)
Psychiatric disorders	1 (1.3)	2 (1.5)
Anxiety	1 (1.3)	1 (0.8)
Mental status changes	0	1 (0.8)
Renal and urinary disorders	1 (1.3)	2 (1.5)
Acute kidney injury	1 (1.3)	2 (1.5)
Reproductive system and breast disorders	1 (1.3)	1 (0.8)
Cervical dysplasia	1 (1.3)	1 (0.8)

System Organ Class/ Preferred Term	Synovial Sarcoma (N=80) n (%)	Pooled Population (N=130) n (%)
Respiratory, thoracic and mediastinal disorders	10 (12.5)	14 (10.8)
Dyspnea	1 (1.3)	1 (0.8)
Hemoptysis	1 (1.3)	1 (0.8)
Laryngeal hemorrhage	0	1 (0.8)
Pleural effusion	4 (5.0)	6 (4.6)
Pneumothorax	2 (2.5)	3 (2.3)
Pulmonary embolism	2 (2.5)	2 (1.5)
Pulmonary hemorrhage	1 (1.3)	1 (0.8)
Skin and subcutaneous tissue disorders	0	1 (0.8)
Rash	0	1 (0.8)
Vascular disorders	4 (5.0)	5 (3.8)
Deep vein thrombosis	2 (2.5)	2 (1.5)
Hemorrhage	1 (1.3)	1 (0.8)
Hypotension	0	1 (0.8)
Superior vena cava occlusion	1 (1.3)	1 (0.8)

Source: AdAM: ADSL, ADAE

Abbreviations: COVID-19 = Coronavirus Disease 2019, n = number of patients in a specified category, N = number of patients, SAE = serious adverse event, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Reviewer Comment: Some terms may be listed separately based on their System Organ Class and the Preferred Term in the ADAE data set.]

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Not applicable.

The Applicant's Position:

No subjects discontinued Study ADP-0044-002 (Cohort 1) due to an adverse event.

The FDA's Assessment:

[FDA concurs with the Applicant that no patients discontinued Study ADP-0044-002 (Cohort 1) due to an AE.]

Data:

Not applicable.

The Applicant's Position:

Not applicable, afamitresgene autoleucel is administered as a single dose.

The FDA's Assessment:

[Although there were no dose interruption or reductions, three patients experienced delays in afamitresgene autoleucel administration; see narratives below:

- Patient (b) (6) (ADP-004-002 Cohort 1) Treatment with afamitresgene autoleucel was delayed by 1 day due to a Grade 3 event of abdominal pain which was considered probably related to fludarabine and cyclophosphamide by investigator and which was considered resolved.
- Patient (b) (6) (ADP-004-002 Cohort 2) experienced two separate episodes of infection that led to two separate rounds of LD chemotherapy and delayed afamitresgene autoleucel administration
- Patient (b) (6) (ADP-004-001) The patient's afamitresgene autoleucel administration infusion was delayed by two days to (b) (6), due to pleural effusion, fever, and arrhythmia.]

Significant Adverse Events

Data:

CRS and prolonged cytopenia are important identified risks. Neurotoxicity including ICANS, and infections are important potential risks associated with afamitresgene autoleucel.

Cytokine release syndrome (CRS)

In subjects with SS, all but one of the 33 CRS events (75.0%) were Grade 1 or Grade 2, and no subject had more than one CRS event (in the 8 subjects with MRCLS, all CRS events were Grade 1). One subject with SS had Grade 3 CRS that required combination vasopressin and inotrope support for management of hypotension. In ADP-0044-002, tocilizumab administration was recommended for Grade 2 CRS and was permitted for Grade 1 CRS if symptoms persisted for ≥ 24 hours or if the subject was of older age or had co-morbidities (e.g., high tumor burden). Overall, 18 subjects were administered at least 1 dose of tocilizumab to manage CRS events and 2 subjects were administered corticosteroids. In subjects with SS, the median time to onset of CRS was 2 days (range: 1– 5 days), and median time to CRS resolution of 3 days (range: 1–14 days) ([Table 40](#)).

Table 40: Applicant – Summary of Cytokine Release Syndrome (mITT Population)

	ADP-0044-002 Cohort 1 SS (N=44)
Subjects with any grade CRS, n (%) ^a	33 (75.0)
By worst grade, n (%)	
Grade 1	23 (53.5)
Grade 2	9 (20.5)
Grade 3	1 (2.3)

	ADP-0044-002 Cohort 1 SS (N=44)
Grade 4	0
Grade 5	0
Time to first CRS (days)	
Mean (SD)	2.7(1.13)
Median (minimum, maximum)	2.0 (1, 5)
Time to resolution of CRS (days) ^b	
Mean (SD)	3.8 (2.53)
Median (minimum, maximum)	3.0 (1, 14)
Subjects requiring tocilizumab, n (%) ^c	18 (40.9)

Sources: Tables SUR-14.3.8_C1, SUR-14.3.8.1_C1, SUR-14.3.8.2_C1, SUR-14.3.8.3_C1, and Listings SUR-16.2.4.4.1_C1.

a. If a subject had multiple CRS events, then the event with the worst grade was selected for the summary.

b. Time to resolution of CRS (days): For a subject with only 1 CRS event: Stop date of CRS – start date of CRS + 1. If a subject had multiple CRS, then non-event date in between was subtracted.

c. Subject (b) (6) (SS) received tocilizumab but was not included in the count as the reason for administration was “other: CRS symptoms” (CSR Study ADP-0044-002, Listing 16.2.4.4).

The most common CRS-related symptoms in SS subjects were fever (97.0%), tachycardia (51.5%), hypotension (30.3%), nausea/vomiting (21.2%), and headache (15.2%) ([Table 41](#)).

Table 41: Applicant – Summary of CRS Symptoms (>5%) in Subjects With CRS (mITT Population)

	ADP-0044-002 Cohort 1 SS (N=33) n (%)
Subjects with at least 1 symptom	32 (100)
Fever	32 (97.0)
Tachycardia	17 (51.5)
Hypotension	10 (30.3)
Nausea/vomiting	7 (21.2)
Headache	5 (15.2)
Hypoxia	3 (9.1)
Diarrhea	3 (9.1)
Arrhythmia	2 (6.1)
Rash	2 (6.1)
Increased transaminase	2 (6.1)

Sources: Table SUR-14.3.8.5_C1, AdAM: ADSL ADAE

Note: Percentages relative to the number of subjects with CRS.

An independent adjudication of CRS events was conducted for subjects in Study ADP-0044-002 Cohort 1, data cut-off 11-Oct-2021 (N=43). Regarding adjudication of CRS events, overall concordance between independent adjudicators and investigator assessment was high (82.35%). There was no discordance between independent and investigator determined Grade 3 CRS (in 1 subject), and there were no CRS events determined as Grade 4 (Source: Study ADP-0044-002, Pathology Review and CRS Adjudication Report).

Table 42: Applicant – Concordance of CRS by Independent Adjudicator and by Investigator

	Independent Adjudication CRS				
Investigator CRS	Grade 1	Grade 2	Grade 3	No CRS	Total
Synovial Sarcoma N=43, n (%)					
Grade 1	19 (44.19)	4 (9.30)	0	0	23 (53.49)
Grade 2	2 (4.65)	6 (13.95)	0	0	8 (18.60)
Grade 3	0	0	1 (2.33)	0	1 (2.33)
No CRS	0	1 (2.33)	0	10 (23.26)	11 (25.58)
Total	21 (48.84)	11 (25.58)	1 (2.33)	10 (23.26)	43 (100.0)
Concordant					36 (83.72)
Discordant					7 (16.28)

Source: Study ADP-0044-002, Pathology Review and CRS Adjudication Report, Table 14.3.8.2b. AdaM: ADCRS

Prolonged Cytopenia

In study ADP-0044-002, prolonged cytopenia (Grade ≥ 3 anemia, thrombocytopenia, or neutropenia at Week 4) occurred in 20.5% subjects with SS, with 11.4% experiencing neutropenia, 9.1% anemia, and 4.5% thrombocytopenia (Table 43). However, only a total of 4 subjects with SS (9.0%) had \geq Grade 3 prolonged cytopenia lasting continuously without resolution to \leq Grade 2 for more than 4 weeks post afamitresgene autoleucel infusion. Prolonged cytopenia resolved in 75% of subjects with anemia (3 of 4 subjects) and in all subjects with neutropenia (2 of 2 subjects) or thrombocytopenia (5 of 5 subjects). One subject (Subject (b) (6)) was censored as of the data cut-off date and subsequently died (Listing SUR-16.1.1.1). The median time to resolution of prolonged cytopenia from T-cell infusion was 7.3 (range: 6.1 to 8.4) weeks for anemia, 6.3 (range: 6.1 to 6.4) weeks for thrombocytopenia, and 9.3 (range: 6.4 to 12.3) weeks for neutropenia.

There were no fatalities related to prolonged cytopenia, all events clinically improved, and no affected subject required long-term blood product transfusions, or growth factors, for stabilization of hematological parameters.

Table 43: Applicant – Summary of Prolonged Cytopenia (MITT Population)

Criteria	ADP-0044-002 Cohort 1 SS (N=44) n (%)
Week 4	9 (20.5)
Anemia: Hemoglobin <80 g/L	4 (9.1)
Thrombocytopenia: Platelet $<50 \times 10^9/L$	2 (4.5)
Neutropenia: ANC $<1.0 \times 10^9/L$	5 (11.4)

Sources: Tables SUR-14.3.2.8.3.1_C11. AdaM: ADSL, ADLB

Note: Prolonged cytopenia was defined as Grade 3 or higher anemia, thrombocytopenia, or neutropenia. The severity was assessed using CTCAE Version 5.0 criteria. Week 4 was derived based on the worst value from Days 24 to 41 post T-cell infusion, inclusive.

Table 44: Applicant – Hematological Laboratory Values for SS Subjects With Prolonged Cytopenia in Study ADP-0044-002 (mITT Population)

Subject ID	Week of Prolonged Cytopenia	Hemoglobin (g/L)	Neutrophils (10 ⁹ /L)	Platelets (10 ⁹ /L)
(b) (6)	Week 4	76	1.67	57
	Week 4	75, 70	1.5, 2.6	167, 186
	Week 8	61	4.8	174
	Week 8	77	6.3	170
	Week 4	101	0.77	90
	Week 12	79	0.8	46
	Week 4	79	8	268
	Week 4	107, 113	0.3, 0.3	93, 131
	Week 8	122	0.6	138
	Week 8	127, 130	0.8, 1	144, 132
	Week 4	92	0.8	33
	Week 4	119	0.84	108
	Week 8	120, 136	0.87, 0.94	100, 138
	Week 4	78	1.05	47
	Week 8	91	1.64	86, 106
	Week 4	130, 141	0.73, 1.58	137, 171
	Week 8	152	1.72	170

Source: Listings SUR-16.2.7.11_C1. AdaM: ADSL, ADLB

a. Subject (b) (6) received filgrastim on Days 16, 32, 43, and 58 for low neutrophil count (Listing 16.2.4.4).

Note: Values meeting the criteria are indicated in bold font.

Note: Prolonged cytopenia was defined as Grade 3 or higher anemia, thrombocytopenia, neutropenia, or WBC decreased (leukopenia). The severity was assessed using CTCAE v5.0 criteria. Week 4 was derived based on the worst value from Day 24 to Day 41 post-T-cell infusion, inclusive. Week 8 was derived based on the worst value from Day 42 to Day 69 post-T-cell infusion, inclusive. Week 12 was derived based on the worst value from Day 70 to Day 98 post-T-cell infusion, inclusive. Values meeting the criteria are indicated in bold font.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Regarding ICANS, the overall incidence and severity were low, with only 1 reported case (Grade 1) in a subject with SS who had concomitant Grade 2 CRS and did not have brain metastasis at baseline imaging. ICANS (ICE score 9) resolved the following day (Day 3) (Listing SUR-16.2.7.3.1_C1); CRS resolved after tocilizumab and dexamethasone administration (dexamethasone was initiated after ICANS had resolved) (Listings SUR-16.2.7.2_C1, SUR-16.2.4.4_C1).

Overall neurological AEs (AEs from nervous system SOC or psychiatric disorder SOC; including ICANS) were reported in 27 subjects (61.4%). The most common neurologic AEs (in 2 subjects, any grade) are presented in [Table 45](#). Grade ≥3 neurological AEs were reported in 3 subjects: headache, occurring 54 days after T-cell infusion (Subject (b) (6)); syncope prior to T-cell infusion (Subject (b) (6)); and spinal cord compression 121 days after T-cell infusion (in Subject (b) (6)). None of the Grade ≥3 neurological AEs were considered related to T-cell infusion, and all 3 subjects recovered (source: m2.7.4 Section 2.3.3.2).

Table 45: Applicant – ADP-0044-002 Neurologic Adverse Events – Any grade; occurring in 2 or more subjects (mITT Population)

Preferred Term	ADP-0044-002 (N=44)
Headache	8 (18.2)
Dizziness	5 (11.4)
Presyncope	3 (6.8)
Anxiety	2 (4.5)
Depression	2 (4.5)
Insomnia	2 (4.5)
Peripheral Sensory Neuropathy	2 (4.5)
Tremor	2 (4.5)
Sciatica	2 (4.5)

Sources: SUR Appendix A and Table SUR-14.3.8.6_C1. AdAM: ADSL, ADAE.

Note: Neurological AEs included all PTs within the SOC of Nervous System Disorders and Psychiatric Disorder

Febrile Neutropenia and Infections

In Study ADP-0044-002, febrile neutropenia occurred in 11.4% of subjects with SS (9.6% in the overall group), and 9.1% were Grade ≥ 3 (7.7% in the overall group). Onset of febrile neutropenia ranged from 1 day prior to infusion to 4 days post afamitresgene autoleucel infusion and duration of resolution ranged from 2 to 6 days; all cases resolved with growth factor support and/or empiric antimicrobial therapy.

Thirty-five (35; 79.5%) subjects with SS (29 in the overall group) received immunostimulants (e.g., filgrastim, filgrastim-aaf1, filgrastim sndz, TBO-filgrastim, or G-CS), and 30 or the 35 received immunostimulants on or after T-cell infusion for low ANC, neutropenia (including for febrile neutropenia), or other hematologic abnormality.

Infections occurred in 31.8% of subjects with SS (25.5% in the overall group). One subject had Epstein Barr virus (EBV, Grade 1) reactivation that was considered related to T-cell infusion and resolved 12 days after onset. Grade ≥ 3 infections occurred in 13.6% of subjects with SS (9.8% in the overall group), i.e., empyema (4.5%), pneumonia (2.3%), COVID-19 pneumonia (2.3%), COVID-19 (2.3%), candida infection (2.3%), and staphylococcal abscess (2.3%). Overall, no discernible pattern associated with neutropenia was observed, and no infection events were fatal (Source: SUR, Section 3.3.3.4.3).

The Applicant's Position:

CRS and prolonged cytopenia are important identified risks, and neurotoxicity including ICANS, and infections were important potential risks associated with afamitresgene autoleucel, with the main safety concern being CRS.

CRS although frequent, was mostly low grade (Grade 1 and Grade 2 per ASTCT grading [Lee 2019]) confirmed by an external independent adjudication), occurred early and events were short in duration. Of the subjects who received tocilizumab for management of CRS (18/33

subjects who experienced CRS), 13 received 1 dose, while 5 subject received 2 or more doses. Only 2 subject required corticosteroid use for CRS, and all cases resolved. The early administration of tocilizumab (e.g., Grade 1 lasting more than 24 hours) implemented in ADP-0044-002 was effective in the management of CRS.

Cytopenias, including prolonged cytopenias are known risks of lymphodepletion chemotherapy and have also been reported with T-cell therapies. Prolonged cytopenia (Grade ≥ 3 cytopenia at Week 4 post-infusion) occurred in 20.5 % subjects with SS, however, only 4 of these had \geq Grade 3 cytopenia lasting continuously without resolution to \geq Grade 2 for more than 4 weeks post-infusion. All events clinically improved. The incidence of clinical sequelae, including systemic infections was also low. In addition, administration of growth factor or blood product transfusion support was sufficient to manage the events.

The incidence of ICANS was low, with 1 subject experiencing a Grade 1 event. The clinical pattern of neurologic AEs did not suggest a neurological syndrome caused by T cell infusion since there was no consistent clinical pattern or neurologic symptomatic focus.

Febrile neutropenia occurred after lymphodepletion and afamitresgene autoleucel infusion and was managed successfully with growth factor support and empiric antimicrobial therapy as applicable per standard institutional practice. The infections profile was consistent with patients undergoing myelosuppressive chemotherapy.

The risks of afamitresgene are toxicities that oncologist and cell therapy specialists are well trained to manage, are reversible with intervention, and are acceptable for a population with a serious and life-threatening condition.

The FDA's Assessment:

[Cytokine Release Syndrome: Treatment Emergent of Any Grade]

Treatment emergent CRS of any grade was observed in 33 patients in the primary safety population (N=44, SS). The median time to first CRS event was 2 days, and median time to resolution was 3 days. CRS was managed with tocilizumab. Management for CRS (including Grade 1) in the primary efficacy analysis population (Study ADP-0044-002 Cohort 1; n=44) was tocilizumab (55%). Thirteen patients received one dose and five patients received more than one dose. Of the five patients who received more than one dose of tocilizumab, two patients received dexamethasone in addition to tocilizumab.

Treatment emergent CRS of any grade was observed in 59 (73.8%) patients in the supportive safety population (N=80, SS). A total of 40 (50%) patients experienced Grade 1 events, 18 (22.5%) patients experienced Grade 2 events, and 1 (1.3%) patient experienced a Grade 3 event. The most common symptoms observed were fever, tachycardia, hypotension, nausea and vomiting, headache, hypoxia, diarrhea, arrhythmia, rash, and increased transaminase (see [Table 47](#)).

In the overall pooled supportive safety population (N=130), a total of 87(66.9%) patients experienced CRS events. There were 55 (42.3%) patients that experienced Grade 1 CRS events, and 29 (22.3%) patients had Grade 2 CRS events.

After the March 29, 2023, data cut-off, one patient experienced a Grade 4 CRS event (Patient (b) (6)). There were no Grade 5 CRS events. See above narratives of deaths not due to disease under study for details related to this event.

All patients were managed similarly. A total of 32 (40%) patients received tocilizumab in the N=80 SS supportive safety population and 49 (37.7%) in the overall pooled supportive safety population N=130. Additional treatment of CRS included oxygen, intravenous fluids, paracetamol, non-steroidal anti-inflammatory drugs, corticosteroids, antibiotics, magnesium sulfate, furosemide, and ipratropium.

Table 46: FDA – Cytokine Release Syndrome

CRS Summary	ADP-0044-002 Cohort 1 and 2 SS (N=80)	Pooled Overall (N=130)
Patients with any grade CRS, n (%)	59 (73.8)	87 (66.9)
By worst grade, n (%)		
Grade 1	40 (50.0)	55 (42.3)
Grade 2	18 (22.5)	29 (22.3)
Grade 3	1 (1.3)	2 (1.5)
Grade 4	0	1 (0.8)
Grade 5	0	0
Time to first CRS (days)		
Mean (SD)	2.7 (1.0)	3.2 (2.9)
Median (minimum, maximum)	2.0 (1.0, 5.0)	2.0 (1.0, 23.0)
Time to resolution of CRS (days)		
Mean (SD)	3.6 (2.2)	4.3 (3.7)
Median (minimum, maximum)	3.0 (1.0, 14.0)	3.0 (1.0, 26.0)
Patients requiring tocilizumab, n (%)	32 (40.0)	49 (37.7)

Source: AdaM: ADSL, ADAE, ADTTE, ADCM

Abbreviations: CRS = cytokine release syndrome, max = maximum, min = minimum, n = number of patients with specified characteristic, N = total number of patients, SD = standard deviation, SS = synovial sarcoma

Table 47: FDA – CRS Symptoms

CRS Symptom	ADP-0044-002 Cohorts 1 and 2 SS (N=80) n (%)	Pooled Overall (N=130)
Patients with at least 1 symptom	59 (73.8)	63 (48.5)
Fever	58 (72.5)	62 (47.7)
Tachycardia	34 (42.5)	36 (27.7)
Hypotension	19 (23.8)	19 (14.6)
Nausea/vomiting	17 (21.3)	18 (13.8)
Headache	13 (16.3)	14 (10.8)
Hypoxia	5 (6.3)	5 (3.8)
Diarrhea	4 (5.0)	4 (3.1)

CRS Symptom	ADP-0044-002 Cohorts 1 and 2 SS (N=80) n (%)	Pooled Overall (N=130)
Arrhythmia	2 (2.5)	2 (1.5)
Rash	3 (3.8)	3 (2.3)
Increased transaminase	6 (7.5)	6 (4.6)

Source: AdAM: ADSL, ADAE, SDTM: CE

Abbreviations: CRS = cytokine release syndrome, n = number of patients with specified characteristic, N = total number of patients, SS = synovial sarcoma

Immune Effector Cell-Associated Neurotoxicity Syndrome

Overall, two patients experienced ICANS, which was accompanied by CRS. Both events were low grade and resolved after tocilizumab and dexamethasone were administered.

In the primary safety population N=44, in ADP-0044-002 Cohort 1, patient (b) (6) experienced Grade 1 ICANS with concurrent Grade 2 CRS on Day 2. The patient had an ICE score of 9, which resolved on Day 3.

In the supportive safety population (ADP-0044-002 Cohort 2), Patient (b) (6) experienced Grade 1 ICANS on Day 2 with an ICE score of 8 and 9, which resolved without treatment. The patient also experienced Grade 1 CRS, which resolved after 3 days with tocilizumab and dexamethasone, and Grade 2 anxiety, which resolved after 7 days with lorazepam and olanzapine.

Neurotoxicity

In the primary safety population, ADP-004-002 Cohort 1 N=44, neurotoxicity of any grade (>10%) was headache, which was 18% and dizziness which was 11%; Grade 3 headache was 2%.

In the supportive safety population, ADP-004-002 Cohort 1 & 2 N=80 SS, the most common TEAE were headache (28%), dizziness (13.8%), insomnia (10%) and anxiety (7.5%). There were 4 patients with Grade ≥3; Patient (b) (6) Cohort 1, experienced headache 54 days post T cell infusion, syncope in Patient (b) (6) Cohort 1, prior to T cell infusion, spinal cord compression in Patient (b) (6) Cohort 1, 121 days after T cell infusion and Patient (b) (6) Cohort 2, experienced anxiety, agitation, and suicidal ideation on Day -1 prior to T cell infusion.

Effects on Ability to Drive and Use Machines

Reviewer Comment: Due to the potential for neurologic events, including dizziness and presyncope, patients receiving afamitresgene autoleucel are at risk for altered or decreased coordination in the 4 weeks following infusion.

Prolonged Severe Cytopenia

The incidence of cytopenia was assessed based on a grouped term analysis of the following preferred terms: include, anemia, neutropenia, neutrophil count decreased, platelet count decreased, and pancytopenia. Prolonged cytopenia was defined in the study as Grade 3 or higher neutropenia, anemia, or thrombocytopenia (decreased platelet) persisting for ≥ 4 weeks from receiving T cell therapy.

According to the protocol version 5.0, neutropenia was managed with prophylactic use of G-CSF according to American Society of Clinical Oncology guidelines on Day 3 until resolution of neutropenia.

Bone marrow recovery following lymphodepletion was defined in the study as ANC $\geq 1,000/\mu\text{L}$ for two consecutive measurements approximately 7 days apart, and platelet count $\geq 20,000/\mu\text{L}$ without transfusion support for 1 week.

In the primary safety population (N=44; SS), prolonged severe cytopenia is described. Patients with Grade ≥ 3 cytopenia not resolved by Week 4 included anemia (9%), neutropenia (11%), and thrombocytopenia (5%). The median time to resolution was 7.3 weeks (range: 6.1 to 8.4 weeks) for anemia, 9.3 weeks (range: 6.4 to 12.3 weeks) for neutropenia and 6.3 weeks (range: 6.1 to 6.4 weeks) for thrombocytopenia.

Infections

Febrile Neutropenia and Infections

Febrile neutropenia is characterized as an ANC $< 1,000/\text{mm}^3$ and a single temperature of $> 38.3^\circ\text{C}$ (101°F) or sustained temperature of $\geq 38^\circ\text{C}$ (100.4°F) for more than 1 hour (CTCAE v5.0).

Febrile neutropenia and infections in the primary safety analysis population (N=44, SS) is described. Five (11.4%) patients experienced febrile neutropenia and infections (all grades) occurred in 32% of patients and Grade 3 or higher infections occurred in 14% of patients.

In the supportive safety population (N=80, SS), 9 (11.3%) patients experienced febrile neutropenia and 7 (8.8%) patients experienced Grade 3 and greater infections and infestations.

Grade 3 sepsis was identified in one patient in the N=80, SS group (Cohort 2). Patient (b) (6) experienced two separate episodes of infection that lead to delayed T cell infusion, and the patient required two LD chemotherapy regimens.

In the overall pooled supportive safety population (N=130), 23 (17.7%) patients experienced febrile neutropenia and 15 (11.5%) patients experienced Grade 3 and greater infections and infestations.

Table 48: FDA – Patients With Febrile Neutropenia (N = 44 SS, N=80 SS, N=130 Overall Pooled)

TEAE Preferred Term	SS Cohort 1 (N=44) n (%)	SS Cohorts 1 and 2 (N=80) n (%)	Pooled Overall (N=130) n (%)
All grade febrile neutropenia	5 (11.4)	9 (11.3)	23 (17.7)
Related to T cell infusion	3 (6.8)	6 (7.5)	14 (10.8)
Grade ≥3 febrile neutropenia	4 (9.1)	7 (8.8)	21 (16.2)
Related to T cell infusion	2 (4.5)	4 (5.0)	12 (9.2)

Source: AdAM: ADSL, ADAE

Abbreviations: n = number of patients with specified characteristic, N = total number of patients, SS = synovial sarcoma, TEAE = treatment-emergent adverse event

Viral reactivation occurred in patient (b) (6) following treatment with afamitresgene autoleucel who developed Epstein-Barr-positive lymphoproliferative disease and is further described below.

Secondary Malignancies

Study ADP-0044-002 Cohort 1

Patient (b) (6) with synovial sarcoma developed biopsy-proven, Epstein-Barr-positive lymphoproliferative disease. On Study Day 154 post T cell infusion, a planned CT scan revealed interval increase in size of adrenal mass when compared to previous scan. On Study Day 178 post T cell infusion, a fine needle biopsy and core biopsy of the adrenal gland was obtained, and the histology results showed a polymorphic B-cell lymphoproliferative infiltrate associated with EBV and in keeping with diffuse B-cell lymphoma. At screening, the patient was CMV IgG positive and EBV IgG positive (IgM negative). The lymphoproliferative disease was successfully treated with 4 doses of rituximab.

Study ADP-0044-001 (Dose Group 1)

Patient (b) (6) with ovarian cancer experienced a Grade 4 SAE of myelodysplastic syndrome on Day 99. This patient received LD chemotherapy with fludarabine 30 mg/m²/day for 3 days and cyclophosphamide 600 mg/m²/day for 3 days, followed by T cell infusion (0.1 × 10⁹). Bone marrow biopsy results at Week 14 post T cell infusion showed therapy-related (multiple chemotherapies prior to study entry) myelodysplastic syndrome/myeloproliferative neoplasm with hypereosinophilia, positive for P53 overexpression, 3% blasts, and negative for metastatic carcinoma. The SAE of myelodysplastic syndrome was considered not related to T cell infusion or LD chemotherapy but related to the patient's previous multiple chemotherapies, including poly ADP-ribose polymerase (PARP) inhibitors.

No T cell-related secondary malignancies have been reported.

Hypersensitivity Reactions

Reports of hypersensitivity infusion reaction was not identified; however, after an information request, the Applicant indicated that patient (b) (6) had a Grade 1 infusion reaction 20 minutes from the start of the T cell infusion. See narrative below:

Study ADP-004-002 Cohort 2

Patient (b) (6) developed Grade 1 infusion reaction on (b) (6) (Day 1). The adverse event began 20 minutes from the start of infusion and symptoms included rigors, cough, and tachycardia. The patient was treated with diphenhydramine, supplemental oxygen, and pethidine and the event resolved that same day on (b) (6). The investigator causality was related to afamitresgene autoleucel.]

Treatment Emergent Adverse Events and Adverse Reactions

Data:

[Table 49](#) provides a summary of overall TEAEs in Study ADP-0044-002 (Cohort 1, 29Mar2023 data cut-off). The most common TEAE were hematological adverse events (AEs) i.e., lymphopenia/ lymphocyte count decreased, neutropenia/neutrophil count decreased, and leukopenia/WBC decreased, which are also known AEs of LD chemotherapy (fludarabine/ cyclophosphamide). All Grade 3 or 4 hematologic laboratory TEAEs were cytopenia. The most common non-laboratorial AEs (occurring in $\geq 20\%$) were CRS (74.4%), nausea (65.1%), vomiting (34.9%), fatigue (32.6%), pyrexia (30.2%), constipation (30.2%), dyspnea (25.6%), abdominal pain (25.6%), non-cardiac chest pain (23.3%), decreased appetite (20.9%), back pain (20.9%), hypotension (20.9%). Non-laboratorial TEAEs and Grade ≥ 3 laboratorial abnormalities that occurred in at least $\geq 10\%$ of subjects with SS are summarized in [Table 50](#) and [Table 51](#), respectively.

Table 49: Applicant – Study ADP-0044-002 – Overall Summary of Adverse Events (mITT Population; Data Cut: 29Mar2023)

Category	Synovial Sarcoma (N=44) n (%)
Subjects with any AE	44 (100.0)
Subjects with any TEAE	44 (100.0)
Subjects with any related TEAE	44 (100.0)
Related to cyclophosphamide	44 (100.0)
Related to fludarabine	44 (100.0)
Related to T-cell infusion	40(90.9)
Subjects with any TEAE \geq Grade 3	44 (100.0)
Subjects with any \geq Grade 3 related TEAE	44 (100.0)
Related to cyclophosphamide	44 (100.0)
Related to fludarabine	44 (100.0)

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Category	Synovial Sarcoma (N=44) n (%)
Related to T-cell infusion	20 (45.5)
Subjects with any TESAE	23 (52.3)
Subjects with any treatment-related TESAE	13 (29.5)
Subjects with any TESAE related to T-cell infusion	11 (25.0)
Subjects with any TEAE with fatal outcome	0

Sources: Tables SUR-14.3.1.1_C1, SUR-14.3.2.6.1_C1. AdAM: ADSL, ADAE

Table 50: Applicant – Non-laboratorial TEAEs (≥10%) in ADP-0044-002 by SOC (mITT Population; Data Cut: 29Mar2023)

SOC Grouped Term	ADP-0044-002 SS Cohort 1 (N=44)	
	All Grades n (%)	Grade ≥ 3 n (%)
Investigations		
Weight decreased	5 (11.4)	1 (2.3)
Gastrointestinal disorders		
Nausea	29 (65.9)	1 (2.3)
Vomiting	16 (36.4)	0 (0)
Constipation	14 (31.8)	0 (0)
Abdominal pain	11 (25.0)	2 (4.5)
Diarrhea	9 (20.5)	0 (0)
General disorders and administration site conditions		
Fatigue	15 (34.1)	0 (0)
Pyrexia	14 (31.8)	2 (4.5)
Non-cardiac chest pain	10 (22.7)	1 (2.3)
Chills	7 (15.9)	0 (0)
Edema	9 (20.5)	0 (0)
Asthenia	7 (15.9)	1 (2.3)
Chest pain	6 (13.6)	0 (0)
Immune system disorders		
Cytokine Release Syndrome	33 (75.0)	1 (2.3)
Nervous system disorders		
Headache	8 (18.2)	1 (2.3)
Dizziness	5 (11.4)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	10 (22.7)	1 (2.3)
Musculoskeletal and connective tissue disorders		
Back pain	9 (20.5)	2 (4.5)
Pain in extremity	6 (13.6)	0 (0)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	11 (25.0)	2 (4.5)
Cough	8 (18.2)	0 (0)
Vascular disorders		
Hypotension	9 (20.5)	0 (0)

SOC Grouped Term	ADP-0044-002 SS Cohort 1 (N=44)	
	All Grades n (%)	Grade ≥ 3 n (%)
Hypertension	7 (15.9)	1 (2.3)
Cardiac disorders		
Sinus Tachycardia/ Tachycardia	9 (20.5)	0 (0)
Skin and subcutaneous tissue disorders		
Alopecia	6 (13.6)	0 (0)

Source: Table SUR-14.3.1.4.1_C1. And Table SUR-14.3.1.3.1.1_C1).. AdaM: ADSL, ADAE

Notes: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.

Table 51: Applicant – Laboratorial TEAEs (≥10%) in ADP-0044-002 by Grouped Term (mITT Population; Data Cut: 29Mar2023)Grouped Term	ADP-0044-002 SS Cohort 1 (N=44)	
	All Grades n (%)	Grade 3 or 4 n (%)
Lymphopenia/lymphocyte count decreased ^a	43 (97.7)	43 (97.7)
Neutropenia/neutrophil count decreased ^b	40 (90.9)	39 (88.6)
Leukopenia/WBC decreased ^c	38 (86.4)	37 (84.1)
Anemia/RBC decreased ^d	18 (40.9)	13 (29.5)
Thrombocytopenia/platelet count decreased ^e	15 (34.1)	8 (18.2)

Sources: Table SUR-14.3.1.3.1.1_C1. AdaM: ADSL, ADAE

Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Medical Dictionary for Regulatory Activities (MedDRA) v 23.0. Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.

a. Includes CD4 lymphocytes decreased, lymphopenia, lymphocyte count decreased, absolute CD4 lymphocyte count decreased, and absolute CD8 lymphocyte count decreased

b. Includes neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, and transfusion-related alloimmune neutropenia

c. Includes leukopenia, white blood cell (WBC) decreased, and radiation leukopenia

d. Includes anemia and red blood cell (RBC) count decreased

e. Includes thrombocytopenia and platelet count decreased

The FDA's Assessment:

[In the primary safety population (Study ADP-0044-002 (Cohort 1; n=44).The most common adverse reactions (occurring in ≥20%) were cytokine release syndrome (CRS; 75%), nausea (70%), vomiting (36%), fatigue (34%), infections (32%) pyrexia (32%), constipation (32%), dyspnea (27%), abdominal pain (25%), non-cardiac chest pain (23%), decreased appetite (23%), tachycardia/sinus tachycardia (21%), back pain (21%), hypotension (21%), diarrhea (21%), and edema (21%). Grade 3 or higher adverse reactions included pyrexia (5%), abdominal pain (5%), back pain (5%), dyspnea (5%), CRS (2%), headache (2%), hypertension (2%), weight decreased (2%), nausea (2%), asthenia (2%), non-cardiac chest pain (2%), and decreased appetite (2%). Other adverse events of special interest (AESI) included immune effector cell-associated neurotoxicity syndrome (ICANS) of Grade 1 in one patient.

In the supportive safety population, N=80 SS, the most common TEAE ≥10% for all Grades include lymphocyte count decrease 81.3%, white count decreased 73.8%, CRS 73.8%, neutrophil count decreased 66.3%, nausea 66.3%, anemia 46.3%, fatigue 45%, skin and tissue disorders 38.8%, hypophosphatemia 32.5%, headache 28.7%, constipation 28.7%, vomiting 27.5%, pyrexia 26.3%, diarrhea 21.3%, hypotension 20% and back pain 20%. Grades 3 and greater TEAE for the N=80 and all Grades including Grade 3 and greater for the overall pooled supportive safety population, N=130 population are described below in Table 52.

Table 52. FDA – TEAEs (≥10%) by SOC and PT, March 29, 2023, Data Cut-Off, Study ADP-0044-002, Cohorts 1 and 2, Overall Pooled

System Organ Class Preferred Term	Synovial Sarcoma Cohort 1 N = 44 All Grades n (%)	Synovial Sarcoma N=80 All Grades n (%)	Pooled Population N=130 All Grades n (%)
Any AE	44 (100.0)	80 (100.0)	130 (100.0)
Blood and lymphatic system disorders	26 (59.1)	51 (63.7)	88 (67.7)
Anemia	18 (40.9)	37 (46.3)	71 (54.6)
Febrile neutropenia	5 (11.4)	9 (11.3)	23 (17.7)
Leukopenia	9 (20.5)	13 (16.3)	15 (11.5)
Lymphopenia	13 (29.5)	17 (21.3)	20 (15.4)
Neutropenia	14 (31.8)	22 (27.5)	24 (18.5)
Thrombocytopenia	6 (13.6)	9 (11.3)	11 (8.5)
Cardiac disorders	13 (29.5)	20 (25.0)	47 (36.2)
Sinus tachycardia	3 (6.8)	6 (7.5)	15 (11.5)
Tachycardia	6 (13.6)	10 (12.5)	18 (13.8)
Gastrointestinal disorders	38 (86.4)	68 (85.0)	113 (86.9)
Abdominal pain	11 (25.0)	15 (18.8)	29 (22.3)
Constipation	14 (31.8)	23 (28.7)	37 (28.5)
Diarrhea	9 (20.5)	17 (21.3)	32 (24.6)
Nausea	29 (65.9)	53 (66.3)	83 (63.8)
Vomiting	16 (36.4)	22 (27.5)	43 (33.1)
General disorders and administration site conditions	36 (81.8)	66 (82.5)	105 (80.8)
Asthenia	7 (15.9)	9 (11.3)	9 (6.9)
Chest pain	6 (13.6)	6 (7.5)	7 (5.4)
Chills	7 (15.9)	14 (17.5)	23 (17.7)
Fatigue	15 (34.1)	36 (45.0)	65 (50.0)
Non-cardiac chest pain	10 (22.7)	13 (16.3)	17 (13.1)
Edema peripheral	7 (15.9)	9 (11.3)	17 (13.1)
Pyrexia	14 (31.8)	21 (26.3)	48 (36.9)
Immune system disorders	33 (75.0)	59 (73.8)	88 (67.7)
Cytokine release syndrome	33 (75.0)	59 (73.8)	87 (66.9)
Infections and infestations	14 (31.8)	24 (30.0)	46 (35.4)
Injury, poisoning and procedural complications	4 (9.1)	5 (6.3)	14 (10.8)

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System Organ Class Preferred Term	Synovial Sarcoma Cohort 1 N = 44 All Grades n (%)	Synovial Sarcoma N=80 All Grades n (%)	Pooled Population N=130 All Grades n (%)
Investigations	41 (93.2)	75 (93.8)	124 (95.4)
Alanine aminotransferase increased	5 (11.4)	10 (12.5)	20 (15.4)
Aspartate aminotransferase increased	4 (9.1)	9 (11.3)	18 (13.8)
Lymphocyte count decreased	34 (77.3)	65 (81.3)	112 (86.2)
Neutrophil count decreased	26 (59.1)	53 (66.3)	96 (73.8)
Platelet count decreased	10 (22.7)	25 (31.3)	48 (36.9)
Weight decreased	5 (11.4)	6 (7.5)	11 (8.5)
White blood cell count decreased	30 (68.2)	59 (73.8)	101 (77.7)
Metabolism and nutrition disorders	24 (54.5)	48 (60.0)	88 (67.7)
Decreased appetite	10 (22.7)	17 (21.3)	37 (28.5)
Hypocalcemia	2 (4.5)	8 (10.0)	13 (10.0)
Hypokalemia	10 (22.7)	19 (23.8)	25 (19.2)
Hyponatremia	1 (2.3)	8 (10.0)	22 (16.9)
Hypophosphatemia	12 (27.3)	26 (32.5)	43 (33.1)
Musculoskeletal and connective tissue disorders	20 (45.5)	37 (46.3)	65 (50.0)
Arthralgia	3 (6.8)	8 (10.0)	18 (13.8)
Back pain	9 (20.5)	16 (20.0)	24 (18.5)
Pain in extremity	6 (13.6)	8 (10.0)	14 (10.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (11.4)	9 (11.3)	19 (14.6)
Tumor pain	3 (6.8)	6 (7.5)	15 (11.5)
Nervous system disorders	26 (59.1)	49 (61.3)	81 (62.3)
Dizziness	5 (11.4)	11 (13.8)	23 (17.7)
Headache	8 (18.2)	23 (28.7)	36 (27.7)
Psychiatric disorders	8 (18.2)	18 (22.5)	30 (23.1)
Insomnia	2 (4.5)	8 (10.0)	14 (10.8)
Renal and urinary disorders	6 (13.6)	13 (16.3)	27 (20.8)
Respiratory, thoracic and mediastinal disorders	27 (61.4)	49 (61.3)	79 (60.8)
Cough	8 (18.2)	12 (15.0)	20 (15.4)
Dyspnea	11 (25.0)	16 (20.0)	35 (26.9)
Skin and subcutaneous tissue disorders	13 (29.5)	31 (38.8)	59 (45.4)
Alopecia	6 (13.6)	10 (12.5)	18 (13.8)
Vascular disorders	19 (43.2)	28 (35.0)	47 (36.2)
Hypertension	7 (15.9)	8 (10.0)	11 (8.5)
Hypotension	9 (20.5)	16 (20.0)	31 (23.8)

Source: AdA: ADSL, ADAE

Abbreviations: AE = adverse event, n = number of patients with specified characteristic, N = total number of patients, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event

The safety in the primary efficacy analysis population (Study ADP-0044-002 (Cohort 1; n=44) is described.

Reviewer Comment: This table include TEAEs that were reported in the ADAE. Some may not be included in the adverse reaction table of the USPI. Laboratory abnormalities in the USPI will be reported based on the ADLB dataset.]

AEs in Long-Term Follow-up

In Study ADP-0044-002, 4 subjects with SS (9.1%) experienced 5AEs during the LTFU Phase: lung disorder, herpes zoster, COVID-19 pneumonia, anemia and atypical pneumonia. All AEs except for herpes zoster were also Grade ≥ 3 SAEs (Source SUR, Table 33 and Table 34).

The FDA's Assessment:

[FDA concurs with Applicant.]

Laboratory Findings

Data:

Hematology

In the SS subjects treated in Study ADP-0044-002 Cohort 1 (29March2023 data cut-off), shifts from CTCAE Grade 0, 1, or 2 at Baseline to CTCAE Grade 3 or 4 post-Baseline were observed for lymphocytes (Grade 4: 88.6%), neutrophils (Grade 3: 25.0%, Grade 4: 65.9%), leukocytes (Grade 3: 11.4%, Grade 4: 75.0%), platelets (Grade 3: 13.6%, Grade 4: 6.8%), and hemoglobin (Grade 3: 34.1%). In addition, for lymphocytes, 5 subjects (11.4%) had shifts from Grade 3 at Baseline to Grade 4 at post-baseline (Source: SUR, Section 4.1).

Chemistry

In the SS subjects treated in Study ADP-0044-002 Cohort 1 (29March2023 data cut-off), shifts from CTCAE Grade 0, 1, or 2 at Baseline to post-Baseline CTCAE Grade 3 or 4 post-baseline occurred for were observed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (Grade 3: 4.5% each), calcium (Grade 3: 2.3%), glucose (Grade 3: 2.3%), magnesium (Grade 3: 4.5%), phosphate (Grade 3: 22.7%, Grade 4: 2.3%), potassium (Grade 3: 4.5%, Grade 4: 2.3%), and sodium (Grade 4: 2.3%; source: SUR, section 4.2).

Hepatobiliary Laboratory Abnormalities In SS subjects treated in Study ADP-0044-002 Cohort 1 (29March2023 data cut-off), 5 subjects had ALT $\geq 3 \times$ ULN and 3 subjects had bilirubin $\geq 2 \times$ ULN (Source: SUR, Table 37). No subject had concurrent ALT and/or AST $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (or bilirubin $\geq 1.5 \times$ ULN). Thus, there were no cases of liver toxicity that met Hy's law.

Renal Laboratory Parameters

In SS subjects treated in Study ADP-0044-002 Cohort 1 (29March2023 data cut-off), 1 subject had a shift in creatinine from NCI-CTCAE Grade 1 at Baseline to NCI-CTCAE Grade 3 post-baseline. This subject had a baseline (Day -13) creatinine value of 112.268 $\mu\text{mol/L}$ (Grade 1; normal range: 0-106.08 $\mu\text{mol/L}$), and after T-cell infusion, the subject's creatinine value

remained within normal limits, except for transient increases to Grade 1 on Day 85 (115.804 µmol/L) and Day 212 (end of treatment; 108.732 µmol/L). The subject discontinued from the interventional phase due to progressive disease. During unscheduled visits, the subject's creatinine increased to Grade 3, with values at 392.496 µmol/L on Day 253, 484.432 µmol/L on Day 254, and 558.688 µmol/L on Day 255 (Listing SUR-16.2.8.1.2_C1). There were no AEs associated with the increase in creatinine values (Listing SUR-16.2.7.1_C1).

The Applicant's Position:

Overall, no clinical meaningful hematology, chemistry or liver and renal chemistry were observed during the first 30 days after afamitresgene autoleucel infusion and during the interventional phase of the study.

The FDA's Assessment:

[The laboratory findings in the primary safety analysis population (ADP-0044-002, Cohort 1; SS; n=44) are described here. Grade 3 or 4 laboratory abnormalities (≥20%) were lymphocyte count decreased, neutrophil count decreased, white cell blood count decreased, and red blood cell decreased.

Table 53: FDA – Most Common (≥10%) Laboratory Parameter Abnormalities, ADP-0044-002, Cohort 1

Laboratory Abnormalities	All Grades N=44 n (%)	Grade 3 or 4 N=44 n (%)
Lymphocyte count decreased	43 (97.7)	43 (97.7)
Neutrophil count decreased	40 (90.9)	39 (88.6)
White blood cell count decreased	38 (86.4)	37 (84.1)
Red blood cell count decreased	18 (40.9)	13 (29.5)
Platelet count decreased	15 (34.1)	8 (18.2)
Alanine aminotransferase increased	5 (11.4)	0 (0)

Source: adsl.xpt, adae.xpt.

Grading based on NCI CTCAE version 5.0.

Abnormalities are laboratory values that were considered an adverse event.

Abbreviations: n = number of patients with specified characteristic, N = total number of patients

Reviewer Comment: This table includes laboratory abnormalities that were reported in the ADAE dataset as adverse events. These will not be included in the adverse reaction table of the USPI. Laboratory abnormalities in the USPI will be reported based on the ADLB dataset _TEAE laboratory findings for the supportive safety population (N=80) and overall pooled supportive safety population (N=130) are described in the tables below and were considered expected.]

Table 54. FDA – Most Common ≥10% Laboratory Parameter Abnormalities Study ADP-0044-002

Laboratory Abnormalities	Cohort 1 (N=44) All Grades n (%)	Cohorts 1 & 2 (N=80) All Grades n (%)
Activated partial thromboplastin time prolonged	1 (2.3)	4 (5.0)
Aspartate aminotransferase increased	4 (9.1)	9 (11.2)
Bilirubin conjugated increased	1 (2.3)	1 (1.2)
Blood alkaline phosphatase increased	1 (2.3)	5 (6.2)
Blood creatinine increased	1 (2.3)	4 (5.0)
Blood phosphorus decreased	1 (2.3)	2 (2.5)
Blood potassium decreased	1 (2.3)	1 (1.2)
Hemoglobin decreased*	19 (43.2)	38 (47.5)
International normalized ratio increased	1 (2.3)	2 (2.5)
Lymphocyte count increased	1 (2.3)	1 (1.2)
Lymphocyte decreased*	43 (97.7)	77 (96.2)
Neutrophil decreased*	40 (90.9)	75 (93.8)
Platelet decreased*	15 (34.1)	33 (41.2)
White blood cell decreased*	38 (86.4)	71 (88.8)
Blood magnesium decreased	0 (0.0)	1 (1.2)

Source: R. Source datasets: adsl.xpt, adae.xpt. ADSL filters: MITTFL = Y, PTUMTYP = SYNOVIAL SARCOMA. ADAE filters: TRTEMFL = Y. Column grouping variable: Custom.

* Hemoglobin Decreased includes the terms (Anemia, Hemoglobin decreased); Lymphocyte Decreased includes the terms (Lymphocyte count decreased, Lymphopenia); Neutrophil Decreased includes the terms (Neutrophil count decreased, Neutropenia); Platelet Decreased includes the terms (Platelet count decreased, Thrombocytopenia). *
White Blood Cell Decreased includes the terms (White blood cell count decreased, Leukopenia);
Abbreviations: n = number of patients with specified characteristic, N = total number of patients

Table 55: FDA – Most Common (≥10%) Laboratory Abnormalities (Pooled)

Laboratory Parameter	All Grades (N=130) n (%)
Activated partial thromboplastin time prolonged	4 (3.1)
Aspartate aminotransferase increased	18 (13.8)
Bilirubin conjugated increased	1 (0.8)
Blood alkaline phosphatase increased	9 (6.9)
Blood creatinine increased	10 (7.7)
Blood phosphorus decreased	1 (0.8)
Blood potassium decreased	2 (1.5)
Hemoglobin decreased*	1 (0.8)
International normalized ratio increased	72 (55.4)
Lymphocyte count increased	2 (1.5)
Lymphocyte decreased*	1 (0.8)
Neutrophil decreased*	126 (96.9)
Platelet decreased*	120 (92.3)
White blood cell decreased*	58 (44.6)
Blood magnesium decreased	115 (88.5)

Source: R. Source datasets: adsl.xpt, adae.xpt. ADSL filters: MITTFL = Y. ADAE filters: TRTEMFL = Y. Column grouping variable: Custom.

* Hemoglobin Decreased includes the terms (Anemia, Hemoglobin decreased); Lymphocyte Decreased includes the terms (Lymphocyte count decreased, Lymphopenia); Neutrophil Decreased includes the terms (Neutrophil count decreased, Neutropenia); Platelet Decreased includes the terms (Platelet count decreased, Thrombocytopenia). * White Blood Cell Decreased includes the terms (White blood cell count decreased, Leukopenia).

Abbreviations: n = number of patients with specified characteristic, N = total number of patients

Vital Signs

Data:

In the Interventional Phase of Study ADP-0044-002 (29Mar2023 data cut-off date), there were no significant changes over time in vital signs (Listing SUR-16.2.8.2_C1), except for the changes associated with CRS events, such as fever and hypotension, there were no significant changes in diastolic blood pressure, systolic blood pressure, pulse rate, respiratory rate, and temperature.

The Applicant's Position:

No clinically meaningful changes in mean and median vital signs were observed, except for changes associated with CRS events, which were self-limited and returned to baseline when CRS resolved.

The FDA's Assessment:

[FDA concurs with Applicant.]

Electrocardiograms (ECGs)

Data:

In the Interventional Phase of Study ADP-0044-002 (29Mar2023 data cut-off date), there were no significant changes over time in any ECG-related indices (Listing SUR-16.2.8.4_C1).

The Applicant's Position:

There was no evidence that afamitresgene autoleucel affects ECG parameters. No subjects had clinically significant ECG changes during the interventional phase of the study.

The FDA's Assessment:

[FDA concurs with Applicant.]

QT

Data:

In the Interventional Phase of Study ADP-0044-002 (29Mar2023 data cut-off date), there were no clinically meaningful ECG findings indicative of QT abnormalities/ prolongation.

The Applicant's Position:

There was no evidence that afamitresgene autoleucel affects ECG parameters. No subjects had clinically significant ECG changes during the interventional phase of the study.

The FDA's Assessment:

[FDA concurs with Applicant.]

Immunogenicity

Data:

Not applicable.

The Applicant's Position:

The incidence rate of treatment-emergent or treatment-booster antibodies against approved CAR T-cell therapies ranges from 0% to 47% (US prescribing information for Kymriah, Yescarta, Tecartus, Breyanzi, and Abemca). For all the approved CAR T-cell therapies, there was no evidence that the incidence of anti-product antibodies had a marked impact on the cellular kinetics, safety, or efficacy of the product.

Unlike CAR T-cell therapies, afamitresgene autoleucel does not express a chimeric receptor on cell surfaces; the engineered cell surface receptor in afamitresgene autoleucel is an enhanced affinity human TCR structurally identical to naturally occurring human TCRs, and therefore

would not be expected to be immunogenic. In addition, as afamitresgene autoleucel is intended for a single infusion, there is no risk of anti-drug antibody-mediated sensitization and anaphylactic reactions with subsequent doses. Given the low expected immunogenicity risk, the immunogenicity of afamitresgene autoleucel has not been evaluated in clinical studies.

The FDA's Assessment:

[No immunogenicity studies have been performed on afamitresgene autoleucel.]

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Secondary Malignancies

Data:

The risk of insertional mutagenesis resulting in secondary malignancies is a concern with genetically modified T-cell therapies.

As of the data cut supporting this submission, there were no reports of T-cell related secondary malignancies in any subject administered afamitresgene autoleucel, including during LTFU phase of clinical studies. One subject with SS in ADP-0044-002 developed biopsy-proven EBV-positive lymphoproliferative disease. On Study Day 154 post T-cell infusion, a planned CT scan revealed interval increase in size of adrenal mass when compared to previous scan. On Study Day 178 post T-cell infusion, a fine needle biopsy and core biopsy of the adrenal gland was obtained, and the histology results showed a polymorphic B-cell lymphoproliferative infiltrate associated with EBV and in keeping with diffuse B-cell lymphoma. At screening, the patient was CMV IgG positive and EBV IgG positive (IgM negative). The lymphoproliferative disease was successfully treated with 4 doses of rituximab. One subject with ovarian cancer enrolled in Study ADP-0044-001 experienced a Grade 4 TESA of myelodysplastic syndrome on Day 99 considered not related to T-cell infusion or LD chemotherapy but related to the subject's multiple previous chemotherapies.

The Applicant's Position:

Although no evidence of secondary malignancies due to afamitresgene autoleucel has been obtained to date, the potential long-term risk of secondary malignancies due insertional mutagenesis in the genetically modified product remains a concern. Adaptimmune plans to conduct a post-approval long-term safety study to further characterize this potential risk.

The FDA's Assessment:

[Two secondary malignancies were reported. One patient with SS on ADP-0044-002 developed EBV-associated polymorphic B-cell lymphoproliferative disease that is considered possibly related to the lymphodepletion regimen. Another patient with ovarian cancer on study ADP-0044-001 developed myelodysplastic syndrome, likely related to prior therapies such as PARP

inhibitor. Monitoring for secondary malignancies will occur in 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.]

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

See [Section 8.1.2 – Secondary or Exploratory COA \(PRO\) Endpoints](#). No additional clinical outcome assessments were performed to inform safety/ tolerability.

The Applicant’s Position:

See [Section 8.1.2 – Secondary or Exploratory COA \(PRO\) Endpoints](#).

The FDA’s Assessment:

[FDA concurs with the Applicant.]

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses were carried out using integrated safety data from Studies and ADP-0044-002 (data cut-off: 29Mar2023), ADP-0044-001 (data cut-off: 01Sep2020) and ADP-0044-001R sub-study (data cut-off: 13-Jan-2022) who received the recommended phase 2 dose range. The integrated database included 96 subjects with SS and 130 subjects overall.

The intrinsic factors evaluated include the following:

- Age group (<40 years, ≥40 years; <65 years, ≥65 years)
- Gender (male, female)

The extrinsic factors evaluated include the following:

- Prior systemic lines of therapy (≤2 lines, ≥3 lines)
- Bridging therapy (yes, no)
- Baseline sum of diameter (SLD <100 mm, SLD ≥100 mm)
- Geographical region (North America, Europe)
- ECOG score (0, 1)
- H-score (<200, ≥200)
- Transduced cell dose (<7B, ≥7B)

The AE profile summarized for each subgroup included the following:

- AESIs: CRS and prolonged cytopenia. Due to the very low incidence of neurological AEs and ICANS, these events were not included.
- TESAEs
- T-cell infusion related TEAEs and TESAEs

The Applicant's Position:

Across studies, subgroup analyses of subjects by age group, gender, prior systemic lines of therapy, bridging therapy, baseline sum of diameter, geographical region, ECOG score, H score, and transduced cell dose indicated no meaningful difference between subgroups, with the exception of a higher incidence of CRS, a known class effect associated with T-cell therapy. The CRS incidence in subjects with SS was about 20% higher in subjects who had bridging therapy at Baseline, in subjects with H-score ≥ 200 , and in subjects who received ≥ 7 billion transduced T-cell dose.

The FDA's Assessment:

[FDA considers these analyses to be exploratory in a small single-arm study.]

8.2.8 Specific Safety Studies/Clinical Trials

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[FDA concurs with the Applicant.]

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[No carcinogenicity or genotoxicity studies have been conducted with afamitresgene autoleucel. In vitro studies with afamitresgene autoleucel manufactured from healthy donors and patients with SS showed no preferential integration near genes associated with oncogenic transformation. No studies have been conducted to evaluate the effects of afamitresgene autoleucel on fertility.]

A genomic insertion site analysis was performed on afamitresgene autoleucel products from (b) (4) individual patients. There was no evidence for preferential integration near genes of concern. Furthermore, transduced T cells recovered from peripheral blood from treated patients at least 10 months post-infusion showed a high level of polyclonality and complete absence of clonal dominance.]

Human Reproduction and Pregnancy

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[The impact on human reproduction and pregnancy has not been studied in afamitresgene autoleucel studies. FDA concurs that this is acceptable due to the seriousness of the disease and high unmet medical need for patients with unresectable or metastatic SS 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.]

Pediatrics and Assessment of Effects on Growth

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[FDA concurs with the Applicant.]

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[FDA concurs with the Applicant.]

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable.

The Applicant's Position:

Not applicable. Afamitresgene autoleucel has not been marketed in any country to date.

The FDA's Assessment:

[FDA concurs with the Applicant's assessment.]

Expectations on Safety in the Postmarket Setting

Data:

Not applicable.

The Applicant's Position:

Potential safety concerns beyond the risks observed in clinical trials are not expected. It is Adaptimmune's position that the safe use of afamitresgene autoleucel can be appropriately managed in the postmarketing setting with product labeling, as well as routine pharmacovigilance to monitor for unexpected adverse events.

The long-term safety-profile, including long-term risk of secondary malignancy due to insertional mutagenesis is planned to be further evaluated as part of a post-approval prospective long-term safety study based on data from a registry.

The FDA's Assessment:

[A postmarketing, prospective, observational study is planned to assess and characterize the risk of secondary malignancies and long-term safety following treatment with afamitresgene autoleucel.]

This study will enroll patients with unresectable mSS treated at approximately 18 infusion centers. The enrolled patients will be followed for 15 years after product administration. The primary objective is to evaluate the development of subsequent primary neoplasms related to insertional mutagenesis or replication competent lentivirus. Secondary objectives include assessment of overall survival, cause of death, T cell related neoplasms, CRS, ICANS, prolonged cytopenia and significant infections, and pregnancy outcomes in patients or partners who receive afamitresgene autoleucel.]

8.2.11 Integrated Assessment of Safety

Data:

The safety of afamitresgene autoleucel was provided primarily by Study ADP-0044-002 (Cohort 1). As supportive evidence, the safety database includes 130 subjects treated with afamitresgene autoleucel in studies ADP-0044-002 (Cohort 1 and 2), ADP-0044-001 and ADP-0044-001R: 96 subjects with SS and 34 subjects with other tumors including subjects with MRCLS. The data were summarized using 4 groups: study ADP-0044-002 SS (Cohorts 1 and 2; N=80), Pooled SS (N=96), and Overall (N=130).

In Study ADP-0044-002 SS (Cohorts 1 and 2), the most common non-laboratorial TEAEs ($\geq 20\%$ of subjects) were CRS (73.8%); nausea (66.3%); fatigue (45.0%); headache and constipation (28.8% each); vomiting (27.5%); pyrexia (26.3%); decreased appetite and diarrhea (21.3% each); and dyspnea, back pain, hypotension, tachycardia/sinus tachycardia, and rash (20.0% each; source: SUR Table 11 and Table SUR-14.3.1.3.1.1_C1C2). The incidence of non-laboratorial TEAEs in the pooled SS and pooled overall groups was generally similar to Study ADP-0044-002 SS ([Table 56](#)). The most commonly observed laboratorial TEAEs were lymphopenia/lymphocyte count decreased (96.3%), neutropenia/neutrophil count decreased (93.8%), and leukopenia/WBC decreased (88.8%), which are also known AEs of LD chemotherapy (fludarabine/cyclophosphamide)([Table 57](#)).

Table 56: Applicant – Non-Laboratorial TEAEs Occurring in ≥10% of Subjects in Other Groups by SOC or PT (MITT Population)

System Organ Class Preferred Term	Study ADP-0044-002 SS Cohorts 1 & 2 (N=80) n (%)		Pooled SS (N=96) n (%)		Pooled Overall (N=130) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TEAE	80 (100.0)	80 (100.0)	96 (100.0)	96 (100.0)	130 (100.0)	130 (100.0)
Gastrointestinal disorders	68 (85.0)	5 (6.3)	82 (85.4)	5 (5.2)	113 (86.9)	8 (6.2)
Nausea	53 (66.3)	2 (2.5)	63 (65.6)	2 (2.1)	83 (63.8)	2 (1.5)
Constipation	23 (28.8)	0	26 (27.1)	0	37 (28.5)	0
Vomiting	22 (27.5)	1 (1.3)	29 (30.2)	1 (1.0)	43 (33.1)	2 (1.5)
Diarrhea	17 (21.3)	0	25 (26.0)	0	32 (24.6)	0
Abdominal pain	15 (18.8)	2 (2.5)	18 (18.8)	2 (2.1)	29 (22.3)	3 (2.3)
General disorders and administration site conditions	66 (82.5)	7 (8.8)	80 (83.3)	8 (8.3)	105 (80.8)	9 (6.9)
Fatigue	36 (45.0)	0	47 (49.0)	0	65 (50.0)	1 (0.8)
Pyrexia	21 (26.3)	2 (2.5)	31 (32.3)	2 (2.1)	48 (36.9)	2 (1.5)
Chills	14 (17.5)	0	17 (17.7)	0	23 (17.7)	0
Non-cardiac chest pain	13 (16.3)	2 (2.5)	15 (15.6)	2 (2.1)	17 (13.1)	2 (1.5)
Asthenia	9 (11.3)	2 (2.5)	9 (9.4)	2 (2.1)	9 (6.9)	2 (1.5)
Edema peripheral	9 (11.3)	0	10 (10.4)	0	17 (13.1)	1 (0.8)
Immune system disorders	59 (73.8)	1 (1.3)	74 (77.1)	3 (3.1)	88 (67.7)	3 (2.3)
Cytokine release syndrome	59 (73.8)	1 (1.3)	73 (76.0)	3 (3.1)	87 (66.9)	3 (2.3)
Nervous system disorders	49 (61.3)	3 (3.8)	59 (61.5)	4 (4.2)	81 (62.3)	10 (7.7)
Headache	23 (28.8)	1 (1.3)	28 (29.2)	1 (1.0)	36 (27.7)	1 (0.8)
Dizziness	11 (13.8)	0	16 (16.7)	0	23 (17.7)	0
Metabolism and nutrition disorders	48 (60.0)	10 (12.5)	60 (62.5)	19 (19.8)	88 (67.7)	35 (26.9)
Decreased appetite	17 (21.3)	1 (1.3)	22 (22.9)	2 (2.1)	37 (28.5)	3 (2.3)
Respiratory, thoracic and mediastinal disorders	49 (61.3)	8 (10.0)	58 (60.4)	10 (10.4)	79 (60.8)	16 (12.3)
Dyspnea	16 (20.0)	2 (2.5)	21 (21.9)	2 (2.1)	35 (26.9)	3 (2.3)
Cough	12 (15.0)	0	16 (16.7)	0	20 (15.4)	0
Musculoskeletal and connective tissue disorders	37 (46.3)	3 (3.8)	46 (47.9)	3 (3.1)	65 (50.0)	6 (4.6)
Back pain	16 (20.0)	3 (3.8)	17 (17.7)	3 (3.1)	24 (18.5)	5 (3.8)
Arthralgia	8 (10.0)	0	13 (13.5)	0	18 (13.8)	1 (0.8)
Pain in extremity	8 (10.0)	0	10 (10.4)	0	14 (10.8)	1 (0.8)
Vascular disorders	28 (35.0)	4 (5.0)	35 (36.5)	5 (5.2)	47 (36.2)	9 (6.9)
Hypotension	16 (20.0)	1 (1.3)	21 (21.9)	2 (2.1)	31 (23.8)	5 (3.8)
Hypertension	8 (10.0)	1 (1.3)	9 (9.4)	1 (1.0)	11 (8.5)	2 (1.5)
Skin and subcutaneous tissue disorders	31 (38.8)	1 (1.3)	39 (40.6)	3 (3.1)	59 (45.4)	6 (4.6)
Alopecia	10 (12.5)	0	12 (12.5)	0	18 (13.8)	0
Cardiac disorders	20 (25.0)	0	31 (32.3)	2 (2.1)	47 (36.2)	7 (5.4)
Tachycardia	10 (12.5)	0	13 (13.5)	0	18 (13.8)	0

System Organ Class Preferred Term	Study ADP-0044-002 SS Cohorts 1 & 2 (N=80) n (%)		Pooled SS (N=96) n (%)		Pooled Overall (N=130) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Sinus tachycardia	6 (7.5)	0	10 (10.4)	0	15 (11.5)	0
Psychiatric disorders	18 (22.5)	1 (1.3)	22 (22.9)	1 (1.0)	30 (23.1)	2 (1.5)
Insomnia	8 (10.0)	0	11 (11.5)	0	14 (10.8)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	9 (11.3)	2 (2.5)	13 (13.5)	2 (2.1)	19 (14.6)	4 (3.1)
Tumor pain	6 (7.5)	1 (1.3)	10 (10.4)	1 (1.0)	15 (11.5)	2 (1.5)

Sources: Tables SUR-14.3.1.4.1_C1C2 and SUR-14.3.1.4.1. AdaM: ADSL, ADAE

Table 57: Applicant – Laboratorial TEAEs by Synonym/Grouped Term in Other Groups (mITT Population)

Synonym/Grouped Term	Study ADP-0044-002 SS Cohorts 1 & 2 (N=80) n (%)		Pooled SS (N=96) n (%)		Pooled Overall (N=130) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Lymphopenia/lymphocyte count decreased ^a	77 (96.3)	77 (96.3)	93 (96.9)	93 (96.9)	126 (96.9)	126 (96.9)
Neutropenia/neutrophil count decreased ^b	75 (93.8)	72 (90.0)	89 (92.7)	85 (88.5)	120 (92.3)	115 (88.5)
Leukopenia/WBC decreased ^c	71 (88.8)	68 (85.0)	85 (88.5)	82 (85.4)	115 (88.5)	111 (85.4)
Anemia/RBC decreased ^d	37 (46.3)	23 (28.8)	47 (49.0)	31 (32.3)	72 (55.4)	54 (41.5)
Thrombocytopenia/platelet count decreased ^e	33 (41.3)	17 (21.3)	43 (44.8)	24 (25.0)	58 (44.6)	38 (29.2)

Sources : Tables SUR-14.3.1.3.1.1_C1C2 and SUR-14.3.1.3.1.1. AdaM : ADSL, ADAE

a. Included the following preferred terms: CD4 lymphocytes decreased, lymphopenia, lymphocyte count decreased, absolute CD4 lymphocyte count decreased, and absolute CD8 lymphocyte count decreased

b. Included the following preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, and transfusion-related alloimmune neutropenia

c. Included the following preferred terms: leukopenia, white blood cell decreased, and radiation leukopenia

d. Included the following preferred terms: anemia and red blood cell count decreased

e. Included the following preferred terms: thrombocytopenia and platelet count decreased

Note: For each synonym term/grouped term, subjects were included only once even if they experienced multiple events in that grouped preferred term.

Overall, 65 subjects (50.0%) died, including 45 subjects with SS, and most deaths (N=59 deaths) were due to disease under study. One subject with SS in study ADP-0044-001, heavily pre-treated with chemotherapy, died of aplastic anemia (Subject (b) (6)). This patient received higher cyclophosphamide dose containing LD regimen (1800 mg/m²/day on Days -3 and -2) and was heavily pre-treated with prior chemotherapy regimens. After this event, the cyclophosphamide dose in the study was reduced back to 600 mg/m²/day for 3 days and this

revised LD regimen was used successfully in ADP-0044-002. Three additional fatal TESAEs included cerebrovascular accident (subject (b) (6) with ovarian cancer), acute kidney injury (subject (b) (6) with esophageal cancer), COVID-19 (subject (b) (6) with SS), other cancer related reason (subject (b) (6); MRCLS). One subject had reason reported as unknown (subject 12625 with SS)

Brief narratives of the three subjects who died of an AE considered related to T-cell infusion are provided below (full narratives available in the SUR, section 11.1):

- Subject (b) (6): a 77-year-old female subject enrolled in study ADP-0044-001 with SS, heavily pre-treated with chemotherapy. The subject received lymphodepletion chemotherapy with fludarabine 20 mg/m²/day for 4 days beginning on (b) (6) and cyclophosphamide 2980 mg/m² on (b) (6) and 2988 mg/m² on (b) (6). Besides synovial sarcoma metastatic disease progression, the subject's relevant medical history included anemia. On (b) (6), the subject received treatment with afamitresgene autoleucel (8.37×10^9 transduced cells). The subject died of aplastic anemia on Day 55 post T-cell infusion in Study ADP-0044-001. Grade 3 cytopenia developed in this subject from Day -5 (lymphodepletion chemotherapy Day 3) and worsened post T-cell infusion. Bone marrow biopsy on Day 38 post T-cell infusion did not detect myelodysplastic syndrome, cytomegalovirus infection, enrichment of T-cells, or MAGE-A4 antigen. The investigator assessed the event of aplastic anemia as probably related to afamitresgene autoleucel, fludarabine, and cyclophosphamide.
- Subject (b) (6): 71-year-old female subject was enrolled in Study ADP-0044-001 with serous ovarian cancer. The relevant medical history included hypertension, retinal artery occlusion, and hypercholesterolaemia. Eight days post T-cell infusion, the subject had mental status changes with a CARTOX score of 6. Thirteen days post T-cell infusion, a CT scan of the head showed acute bilateral anterior cerebral artery (ACA)/middle cerebral artery (MCA) watershed infarcts, complete infarction of bilateral thalami, bilateral anterior midbrain including tegmentum, pons, and ventral medulla, with hemorrhage seen in the central pons. Furthermore, there were acute superior cerebellar artery (SCA)/posterior inferior cerebellar artery (PICA) watershed infarcts in the bilateral cerebellar hemispheres. The patient died of an ischemic cerebrovascular accident on Day 14 post afamitresgene autoleucel infusion after a Grade 3 neurotoxicity. The investigator assessed the event of cerebrovascular accident as possibly related to T-cell infusion.
- Subject (b) (6): 76-year-old male subject was enrolled in Study ADP-0044-001 with stage IV esophageal cancer. The subject had a medical history of chronic kidney disease. Prior to T-cell infusion and 5 days post LD chemotherapy the subject was at the study clinic and was found to be hypotensive with creatinine level of 2.46 mg/dL (reference range 0.67-1.17 mg/dL) (baseline value of 1.86 mg/dL). The subject was diagnosed with acute

kidney injury superimposed on chronic kidney disease. The subject died on Day 16 post afamitresgene autoleucel infusion. The Investigator assessed acute kidney injury as CTCAE Grade 5 (death), not related to afamitresgene autoleucel, fludarabine, and cyclophosphamide. Consistent with that reported for study ADP-0044-002 Cohort 1, in the pooled analysis of subjects with SS across cohorts (29Mar2023 data cut-off), 73.8% had CRS, mostly Grade 1 or 2 (58 of 59 subjects; [Table 58](#)). CRS was considered serious in 6 of the 59 subjects with SS. The median time to first CRS was 2 days (range: 1–9 days), and the median time to resolution was 3.5 days (range: 1–26 days). The median time to onset of CRS was 2.0 days (range: 1–5 days), and the median time to resolution of CRS was 3.0 days (range: 1–14 days). Tocilizumab was administered to 32 of 59 subjects (54.2%). Three of the 59 subjects (5.1%) who experienced a TEAE of CRS, required additional administration of dexamethasone to manage CRS (Listings SUR-16.2.4.4.1_C2, SUR-16.2.7.2_C2, and SUR-16.2.8.6_C2). The incidence of CRS in the pooled SS and pooled overall groups was generally similar to Study ADP-0044-002 ([Table 58](#)). Post safety-update data cut-off, 1 subject in ADP-0044-002 Cohort 2 developed Grade 4 CRS at day 4 post T-cell infusion which resolved on Day 8 post T-cell infusion (following treatment with multiple doses of tocilizumab and dexamethasone, and supportive care).

The most common CRS symptoms ($\geq 20\%$ of subjects) were fever (98.3%), tachycardia (57.6%), hypotension (32.2%), nausea/vomiting (28.8%), and headache (22.0%). The cumulative incidence of the most common CRS symptoms are summarized in [Table 59](#).

Table 58: Applicant – Summary of Cytokine Release Syndrome (mITT Population)

	ADP-0044-002 SS Cohorts 1 & 2 (N=80) n (%)	Pooled SS (N=96) n (%)	Pooled Overall (N=130) n (%)
Subjects with CRS, n (%)	59 (73.8)	73 (76.0)	87 (66.9)
By worst grade, n (%) ^a			
Grade 1	40 (50.0)	45 (46.9)	55 (42.3)
Grade 2	18 (22.5)	25 (26.0)	29 (22.3)
Grade 3	1 (1.3)	2 (2.1)	2 (1.5)
Grade 4	0	1 (1.0)	1 (0.8)
Time to first CRS (days) ^b			
n	59	73	87
Mean (SD)	2.7 (0.99)	2.7 (1.25)	3.2 (2.85)
Median (minimum, maximum)	2.0 (1, 5)	2.0 (1, 9)	2.0 (1, 23)
Time to resolution of CRS (days) ^c			
n	59	73	87
Mean (SD)	3.6 (2.20)	4.3 (3.82)	4.3 (3.71)
Median (minimum, maximum)	3.0 (1, 14)	3.0 (1, 26)	3.0 (1, 26)
Subjects requiring tocilizumab, n (%) ^d	32 (40.0)	41 (42.7)	49 (37.7)

Sources: Tables SUR-14.3.8_C1, SUR-14.3.8_C1C2, SUR-14.3.8, SUR-14.3.8.1_C1, SUR-14.3.8.1_C1C2, SUR14.3.8.1, SUR-

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14.3.8.2_C1, SUR-14.3.8.2_C1C2, SUR-14.3.8.2, SUR-14.3.8.3_C1, SUR-14.3.8.3_C1C2, and SUR-14.3.8.3 and Listings SUR-16.2.4.4.1_C1 and SUR-16.2.4.4.1_C2. ADAM: ADSL, ADCM, ADAE, ADTTE

a. If a subject had multiple CRS events, then the event with the worst grade was selected for the summary.

b. Time to first CRS (days): First CRS date – T-cell infusion date + 1.

c. Time to resolution of CRS (days): For a subject with only 1 CRS event, stop date of CRS – start date of CRS + 1. If a subject had multiple CRS, then non-event date in between was subtracted.

d. Two subjects (Subjects (b) (6)) received tocilizumab but were not included in the count as the reasons for administration were reported as “other: CRS symptoms” and “other: suspicion of CRS,” respectively (Study ADP-0044-002 CSR, Section 9.3.3.1).

Table 59: Applicant – Summary of CRS Symptoms (≥5% in Any Group) in Subjects With CRS (mITT Population)

	Study ADP-0044-002		Pooled SS (N=96) n (%)	Pooled Overall (N=130) n (%)
	SS Cohort 1 (N=44) n (%)	SS Cohorts 1 & 2 (N=80) n (%)		
Subjects with at least 1 symptom ^a	33 (100)	59 (100)	73 (100)	87 (100)
Fever	32 (97.0)	58 (98.3)	72 (98.6)	85 (97.7)
Tachycardia	17 (51.5)	34 (57.6)	34 (46.6)	36 (41.4)
Hypotension	10 (30.3)	19 (32.2)	25 (34.2)	29 (33.3)
Nausea/vomiting	7 (21.2)	17 (28.8)	23 (31.5)	27 (31.0)
Headache	5 (15.2)	13 (22.0)	16 (21.9)	18 (20.7)
Diarrhea	3 (9.1)	4 (6.8)	6 (8.2)	6 (6.9)
Hypoxia	3 (9.1)	5 (8.5)	7 (9.6)	10 (11.5)
Arrhythmia	2 (6.1)	2 (3.4)	2 (2.7)	2 (2.3)
Increased transaminase	2 (6.1)	6 (10.2)	8 (11.0)	8 (9.2)
Rash	2 (6.1)	3 (5.1)	5 (6.8)	8 (9.2)
Increased bilirubin	0	3 (5.1)	5 (6.8)	5 (5.7)

Sources: Tables SUR-14.3.8.5_C1, SUR-14.3.8.5_C1C2, and SUR-14.3.8.5.ADAM:ADSL, ADAE. SDTM: CE

a. Percentages were calculated by considering the number of subjects with CRS as denominator.

In Study ADP-0044-002 SS Cohorts 1 & 2, 13 subjects (16.3%) met the criteria for prolonged cytopenia at Week 4 (9 subjects from Cohort 1 and 4 subjects from Cohort 2). Across studies, incidence of prolonged cytopenia was 21.9% in the SS pooled group, and 23.1% in the overall group. The incidence of prolonged cytopenia was slightly higher in the pooled data compared to ADP-0044-002 due to the higher incidence of prolonged cytopenia in the phase 1 ADP-0044-001 study. In phase 1, a high-dose LD chemotherapy regimen was used in 5 of 16 subjects with SS. Three of these subjects who received the high-dose LD chemotherapy regimen had a prolonged cytopenia, 2 of these subjects had prolonged cytopenia at week 4, 8, and 12 and 1 subject had cytopenia-related fatality of aplastic anemia; this event might have been caused by the high-dose LD chemotherapy regimen.

Overall, the incidence of clinical sequelae, including systemic infections, was low in subjects with SS who received afamitresgene autoleucel at the recommended LD chemotherapy regimen of cyclophosphamide (600mg/m²/day) for 3 days and fludarabine (30mg/m²/day) for 4 days.

In study ADP-0044-002 SS Cohorts 1 & 2, prolonged cytopenia resolved in 66.7% (4 of 6 subjects) with anemia, 60.0% (3 of 5 subjects) with thrombocytopenia, and 85.7% (6 of 7 subjects) with neutropenia. Three subjects were censored as of the data cut-off date (source: Listing SUR-16.1.1.1). The median time to resolution of prolonged cytopenia from T-cell infusion was 6.4 weeks (range: 5.3 to 8.4) for anemia, 6.3 weeks (range: 5.3 to 7.0) for thrombocytopenia, and 9.3 weeks (range: 6.1 to 12.3) for neutropenia. In the overall group, the median (95% CI) time to resolution of anemia and neutropenia were similar to the pooled SS group (source: SUR Table 27).

Only two cases of ICANS (both Grade 1) were reported in subjects with SS (1 in Cohort 1 and 1 in Cohort 2 of study ADP-0044-002). The incidence of neurological AEs in the pooled SS and pooled overall groups was similar to Study ADP-0044-002 SS Cohorts 1 & 2 (source: Tables SUR-14.3.1.4.1 and SUR-14.3.2.2.1).

In Study ADP-0044-002 SS Cohorts 1 & 2, infections of any grade occurred in 24 subjects (30.0%) and were Grade ≥ 3 in 7 subjects (8.8%). The incidence of infection events in the pooled SS and pooled overall groups was generally similar to Study ADP-0044-002 SS Cohorts 1 & 2 (source: SUR Table 31). Post safety update data cut-off, a TESAE of gram-negative bacilli septic shock leading to death was reported in 1 additional subject in ADP-0044-002.

Events of febrile neutropenia were considered related to T-cell infusion in 6 subjects. All 11 subjects with SS who had a TEAE of febrile neutropenia received G-CSF (filgrastim). In subjects with SS across ADP-0044-002 cohorts, 65 subjects (81.3%) received immunostimulants (35 subjects in Cohort 1 and 30 subjects in Cohort 2), with 53 of the 65 subjects receiving immunostimulants on or after T-cell infusion for an AE (low ANC, neutropenia, or other hematologic abnormalities). Of these 53 subjects, 24 subjects received filgrastim or G-CSF for the treatment of neutropenia-associated AEs, 4 subjects received filgrastim both as neutropenia prophylaxis and for treatment of neutropenia-associated AEs, 19 subjects received filgrastim or G-CSF as neutropenia prophylaxis or chemotherapy support, and 6 subjects received filgrastim for prophylaxis or treatment of other hematologic-associated AEs (WBC count and lymphocyte count; source: SUR, section 3.3.3.4.2).

One patient in Cohort 2 developed an infusion reaction on the day of infusion that resolved the same day. Hypersensitivity reactions, are a known risk of DMSO (an excipient of the final drug product).

The risk of insertional mutagenesis resulting in secondary malignancies is a theoretical concern with genetically modified T-cell therapies. As of the data cut-offs, there were no reports of T-cell related secondary malignancies in any subject including in the ongoing LTFU phase. One subject with ovarian cancer enrolled in Study ADP-0044-001 experienced a Grade 4 TESAE of myelodysplastic syndrome on Day 99 considered not related to T-cell infusion or LD chemotherapy but related to the subject's multiple previous chemotherapies. One subject with

SS in ADP-0044-002 developed biopsy-proven EBV-positive lymphoproliferative disease, which was successfully treated with rituximab.

Subgroup analyses by age group, gender, prior systemic lines of therapy, bridging therapy, baseline sum of diameter, geographical region, ECOG score, MAGE-A4 H-score, and afamitresgene autoleucel dose indicated no meaningful difference in afamitresgene autoleucel safety-profile in SS between the subgroups, except for a higher incidence of CRS, a known class effect associated with T-cell therapy. The CRS incidence in subjects with SS was about 20% higher in subjects who had bridging therapy at Baseline, in subjects with H-score ≥ 200 , and in subjects who received ≥ 7 billion transduced T-cell dose.

The safety profile observed in the overall safety database of all subjects exposed to afamitresgene autoleucel (N=130) was consistent with the data in the indicated patient population with advanced SS.

The Applicant's Position:

Overall, afamitresgene autoleucel treatment was well tolerated in clinical studies and toxicities were managed with appropriate monitoring and intervention. The AESIs include CRS, prolonged cytopenias, and neurotoxicity (including ICANS). CRS events in subjects with SS were mainly low grade, had onset within a few days of T-cell infusion, were of short duration, and completely resolved with tocilizumab administration where clinically indicated. The strategy of early administration of tocilizumab (e.g., Grade 1 lasting more than 24 hours) implemented in the ADP-0044-002 study was effective in the management of CRS. Cytopenias, including prolonged cytopenias, are well known risks of lymphodepleting chemotherapy, and hematological AEs were common and generally manageable with applicable supportive care such as growth factor support. The overall incidence of ICANS and other T-cell infusion related neurological AEs was low and reversible to baseline neurological function.

The risks of afamitresgene autoleucel are toxicities that oncologists and cell therapy specialists are well trained to manage, are reversible with intervention, and are acceptable for a population with a serious and life-threatening condition.

The FDA's Assessment:

[The safety profile includes cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which can be life-threatening or fatal. CRS events occurred in a large majority of patients, which were captured early after cell infusion between Day 1 and 3 when events were between Grade 1 and 2 and were proactively treated with tocilizumab, corticosteroids, and antibiotics before the toxicity worsened to a higher grade. Therefore, vigilant monitoring and early treatment intervention of CRS symptoms within the first hours up to 5 days after cell infusion may decrease severe CRS toxicities.]

Some patients developed prolonged severe cytopenia, which could result in a fatal outcome; therefore, monitoring and intervention or growth factor support may be required.

Severe infections have occurred, which resulted in a fatal outcome and patients should be evaluated for infection and managed with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. These risks may be managed with appropriate monitoring and treatment strategies. These adverse events represent toxicities that are acceptable from a benefit-risk perspective in the intended population.]

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

[No statistical issues have been identified in this BLA submission.]

8.4 Conclusions and Recommendations

The FDA's Assessment:

[Study ADP-0044-002 Cohort 1 provides substantial evidence of the effectiveness of afamitresgene autoleucel for the treatment of adult patients 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. Study ADP-0044-002 Cohort 1 demonstrated an ORR of 43.2% (95% CI: 28.4, 59.0) with durability of response. Of the 19 patients who achieved an objective response, the median DOR was 6.0 months (95% CI: 4.6, NR).

In the primary safety analysis of 44 patients, all deaths were due to disease under study and occurred greater than 30 days after afamitresgene autoleucel administration.

The most common adverse reactions (occurring in $\geq 20\%$) were cytokine release syndrome (CRS; 75%), nausea (70%), vomiting (36%), fatigue (34%), infections (32%), pyrexia (32%), constipation (32%), dyspnea (27%), abdominal pain (25%), non-cardiac chest pain (23%), decreased appetite (23%), tachycardia/sinus tachycardia (21%), back pain (21%), hypotension (21%), diarrhea (21%), and edema (21%). Grade 3 or higher adverse reactions included pyrexia (5%), abdominal pain (5%), back pain (5%), dyspnea (5%), CRS (2%), headache (2%), hypertension (2%), weight decreased (2%), nausea (2%), asthenia (2%), non-cardiac chest pain (2%), and decreased appetite (2%). Other adverse events of special interest (AESI) included immune effector cell-associated neurotoxicity syndrome (ICANS) of Grade 1 in one patient.

Recommendations on Regulatory Actions

The review team recommends granting accelerated approval for afamitresgene autoleucel 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. The review team considers this treatment effect to be clinically meaningful and reasonably likely to predict clinical benefit in a patient population with limited treatment options. The overall risks of afamitresgene autoleucel are adequately mitigated through product labeling. The review team recommends granting accelerated approval of afamitresgene autoleucel 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.

Continued 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.

Due to FDA's concerns that the same data quality and study conduct issues identified in ADP-0044-002 Cohort 1 may be present in additional cohorts of the same patient population, the following measures are planned for Cohort 2, which has completed enrollment, and for Cohort 3, which is expected to complete enrollment by July 2024: a new imaging vendor, review and agreement of the imaging review charter prior to implementation, exclusion of previously irradiated tumors as target lesions unless there has been demonstrated progression in the lesion following radiotherapy, and supplemental information to support the FDA review as required (e.g., annotated images). Additional measures will be implemented to address potential patient heterogeneity and on-study biopsies of target lesions impacting response assessment. To avoid the use of several efficacy data cut-off dates that are not pre-specified in the statistical analysis plan or protocol, the confirmatory evidence package will be supported by clinical efficacy and safety data from a single data cut-off and the study completion, which is expected in approximately July 2025.

Monitoring for secondary malignancies and long-term safety will occur in a postmarketing, prospective, observational study with 15 years of follow-up after afamitresgene autoleucel administration.]

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

[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. Pediatrics

The Applicant's Position:

Afamitresgene autoleucel has received FDA agreement on the initial Pediatric Study Plan (iPSP) on 04 Mar 2021.

Adaptimmune requested a partial waiver for afamitresgene autoleucel in the following pediatric subsets: neonates (0 to <1 month) and infants (1 month to < 2 years); and requested a deferral on pediatric assessments for all age groups (children aged 2-17 years old). 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).

The FDA's Assessment:

[The FDA concurs with the Applicant.

The Applicant is required to 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 SS, 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, HLA-A*02:02, HLA-A*02:03, or HLA-A*02:06 allele.]

11. Labeling Recommendations

Data:

Not applicable – initial application.

The Applicant's Position:

Not applicable – initial application.

The FDA's Assessment:

[Several revisions were made to the Applicant's proposed US Prescribing Information, including:

1. Section 2 Dosage and Administration section for clarity
2. Section 14 Clinical Studies to report the IRC re-review results]

Table 60: Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1. Indications and Usage	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	TECELRA is a melanoma-associated antigen A4- (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.
2. Dosage and Administration		Revised section for clarity.
14.	Efficacy data from ADP-0044-002 Cohort 1 original IRC was included	From ADP-0044-002 Cohort 1 efficacy data from the original IRC was excluded and efficacy data from IRC re-review was included.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

[The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of afamitresgene autoleucel for the indicated population. The review team made this determination given the consistency of the safety profile with approved cellular therapies, and the extensive experience of the medical oncology community in managing immune-mediated adverse reactions, including those associated with cellular therapies like afamitresgene autoleucel. Recommendations for the safe and effective use of afamitresgene autoleucel, including monitoring for immune-related adverse events, are provided in the US prescribing information as well as in the patient medication guide.]

13. Postmarketing Requirements and Commitment

The FDA's Assessment:

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
<input type="checkbox"/>	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/>	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/>	Other considerations (e.g.: PK/PD), if applicable:	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

14. Clinical Review and Clinical Team Leaders

X

Primary Clinical Reviewer (Efficacy)

X

Primary Clinical Reviewer (Safety)

X

Clinical MORE Team Leader

15. Oncology Branch 2 Chief

X

16. Division Director - Clinical (DCEO)

X

17. Director, Oncology Center of Excellence (or Designate)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application.

X

18. Director, Office of Clinical Evaluation

X

19. Appendices

19.1 References

The Applicant's References:

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19.2 Financial Disclosure

The Applicant's Position:

ADP-0044-002 and ADP-0044-001 (including ADP-0044-001R sub-study) were considered covered studies. The Applicant assessed clinical investigators from all covered studies for any financial interests/arrangements as defined in 21CFR Part 54.

No investigator participating in covered studies had any disclosable financial interests/arrangements.

The FDA's Assessment:

[FDA concurs with the Applicant.]

Covered Clinical Study (ADP-0044-002):*

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 490		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>Not applicable.</u></p> <p>Significant payments of other sorts: <u>Not applicable.</u></p> <p>Proprietary interest in the product tested held by investigator: <u>Not applicable.</u></p> <p>Significant equity interest held by investigator in study: <u>Not applicable.</u></p> <p>Sponsor of covered study: <u>Not applicable.</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (ADP-0044-001 [including ADP-0044-001R sub-study]):*

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
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Total number of investigators identified: <u>332</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>Not applicable.</u></p> <p>Significant payments of other sorts: <u>Not applicable.</u></p> <p>Proprietary interest in the product tested held by investigator: <u>Not applicable.</u></p> <p>Significant equity interest held by investigator in study: <u>Not applicable.</u></p> <p>Sponsor of covered study: <u>Not applicable.</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3 Nonclinical Pharmacology/Toxicology

Data:

Not applicable – all information contained on [Section 5](#).

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[FDA concurs with the Applicant.]

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

[Refer to FDA Pharmacology/Toxicology and Clinical Pharmacology review memos for this BLA.]

19.4.1.2 PPK Assessment Summary

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[Refer to FDA Pharmacology/Toxicology and Clinical Pharmacology review memos for this BLA.]

19.4.2 Exposure-Response Analysis

19.4.2.1 ER (efficacy) Executive Summary

The FDA's Assessment:

[Refer to FDA Pharmacology/Toxicology and Clinical Pharmacology review memos for this BLA.]

19.4.2.2 ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Evaluate the relationship between exposure and efficacy endpoints using the NCA persistence and cytokine parameter values, including an assessment of the impact of other covariates on efficacy
Study Included		Patients with advanced SS from studies ADP-0044-002 and ADP-0044-001
Endpoint		Binary endpoints: ORR (PR/CR = yes; PD/SD = no), Disease control (SD/PR/CR = yes; PD = no) Time-to-event endpoints: PFS, DOR, TTR
No. of Patients (total, and with individual PK)		59 subjects with SS
Population Characteristics (Table 38)	General	Age median: 42 years (range: 19-76) Weight median: 82 kg (range: 43-149) 31 (52.5%) male, 28 (47.5%) female 52 (88.1%) White, 2 (3.4%) Black or African American, 5 (8.5%) Asian

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	Pediatrics (if any)	N/A
Dose(s) Included	2.68 to 10 x10 ⁹ MAGE-A4 TCR positive T-cells	
Exposure Metrics Explored (range)	NCA metrics for cellular persistence: C _{max} , AUC _{0-7D} , AUC _{0-28D} , AUC _{0-3M} , and AUC _{0-6M} NCA metrics for cytokines: C _{max} , AUC _{0-7D} , AUC _{0-28D}	
Covariates Evaluated	Demographic factors: age, body weight, BMI, BSA, Race (white vs non-white), Sex (male vs female), geographical region (North America vs Europe) Disease factors: MAGE-A4 H- score, ECOG status (0 versus 1), baseline tumor size (SLD of target lesions) Concomitant treatment/ pre-treatment: number of prior lines of systemic therapy, bridging therapy (binary), tocilizumab, G-CSF T-cell product characteristics: transduced cell dose, (b) (4) , transduction efficiency	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Cox PH model for PFS as a function of AUC _{0-6M} was developed. A logistic regression model for overall response rate (ORR) as a function of AUC _{0-6M} was developed.	
Model Parameter Estimates	The models for PFS and ORR had AUC _{0-6M} as the independent variable, but did not include any additional covariates.	
Model Evaluation	Cox PH Model for PFS: Covariate selection was based on forward inclusion with a significance level of p < 0.01 and backward elimination with a significance level of p < 0.001. In the forward selection of the modeling, baseline SLD was selected. However, after the backward step, baseline SLD was removed from the model. The final model was a time-to-event model for PFS as a function of AUC _{0-6M} with no covariates. The PH assumption was satisfied (p>0.01). Logistic Regression Model for Overall Response Rate: During the modeling, MAGE-A4 expression (H-score) was selected in the forward step but was removed in the backward step. The final model for overall response rate as a function of AUC _{0-6M} did not include any additional covariates.	
Covariates and Clinical Relevance	In the graphical analyses, the following were observed: Trend toward an increased probability of response and longer PFS with increased	

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	<p>afamitresgene autoleucel AUC_{0-3M} and AUC_{0-6M} (no trends with early exposure metrics (C_{max}, AUC_{0-7D}, and AUC_{0-28D}) were observed);</p> <p>Trend toward an increased probability of response, with increased age, body weight, and H-score, and a decreased probability of response with increased tumor baseline SLD;</p> <p>Older subjects and subjects with higher baseline body weight, higher H-score, and lower baseline SLD showed a trend toward longer PFS;</p> <p>Subjects who received a lower number of prior lines of systemic therapy had an increased probability of response and a trend toward longer PFS. Subjects who did not receive bridging therapy also had a trend toward longer PFS;</p> <p>T-cell product-related parameters had no impact on the probability of response or PFS.</p> <p>Based on these observations, the following covariates were evaluated in E-R models: Baseline body weight; Age; Baseline sum of the longest diameters; MAGE A4 H-score; Bridging therapy; Prior lines of systemic therapy; Dose. The model-based analyses (CPH model) did not identify any statistically significant predictors impacting the probability of response or the PFS, apart from afamitresgene autoleucel exposures.</p>	
Simulation for Specific Population	N/A	
Visualization of E-R relationships	<p>The benefit-risk balance across the dose range is illustrated in Figure 19 below, which integrates 2 logistic regression models:</p> <p>E-R efficacy: ORR as a function of persistence AUC_{0-6M}</p> <p>E-R safety: CRS Grade ≥3 as a function of persistence AUC_{0-7D}</p> <p>This illustrates that across the range of exposures achieved, subjects are expected to have a higher probability of response than the probability of experiencing a Grade ≥3 CRS event.</p>	
Overall Clinical Relevance for ER	E-R relationships with cell kinetic parameters indicated a relationship	

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	<p>between late afamitresgene autoleucel exposure metrics, AUC_{0-3M} and AUC_{0-6M}, and the probability of response (Figure 20) and PFS (Figure 21); however, the subgroup of SS subjects in the lowest quartiles of AUC_{0-3M} and AUC_{0-6M} also maintained a clinically meaningful ORR of 25%.</p> <p>No significant impact of TTR or DOR on the exposure metrics of cellular persistence was detected.</p> <p>Trends for cytokine exposure metrics with clinical endpoints are not expected to be clinically meaningful or actionable.</p>	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	<p>Across synovial sarcoma patients treated with TECELRA, median serum concentrations of cytokines and other soluble factors involved in cellular homeostasis, T-cell activation and inflammation (e.g. IFNγ, IL-6, IL-8, IL-15, and IL-2Rα) increased post-infusion, generally peaking between Days 3-8 (ADP-0044-002 CSR, Section 10.2.2).</p>	

Table 61: Applicant – Summary of Demographic Factors – SS Population

Demographic Factors	ADP-0044-001	ADP-0044-002 (SPEARHEAD-1)	Overall
N	16	43	59
Age (years)			
Mean (SD)	50.9 (13.3)	41.2 (13.2)	43.8 (13.8)
Median (IQR)	49.0 (41.3-57.5)	41.0 (31.0-46.0)	42.0 (33.0-51.0)
Min-max	31.0-76.0	19.0-73.0	19.0-76.0
Missing	0 (0%)	0 (0%)	0 (0%)
Body weight (kg)			
Mean (SD)	91.4 (23.8)	80.4 (18.5)	83.4 (20.5)
Median (IQR)	93.2 (82.0-98.8)	78.0 (68.8-92.1)	82.3 (69.6-97.6)
Min-max	42.9-149	45.9-120	42.9-149
Missing	0 (0%)	0 (0%)	0 (0%)
BMI (kg/m ²)			
Mean (SD)	30.2 (7.71)	27.3 (6.16)	28.1 (6.67)
Median (IQR)	28.8 (25.7-33.8)	25.8 (23.0-30.9)	26.7 (23.6-31.3)
Min-max	15.5-46.6	17.7-43.4	15.5-46.6
Missing	1 (6.25%)	2 (4.65%)	3 (5.08%)
BSA (m ²)			
Mean (SD)	2.04 (0.277)	1.92 (0.230)	1.95 (0.247)

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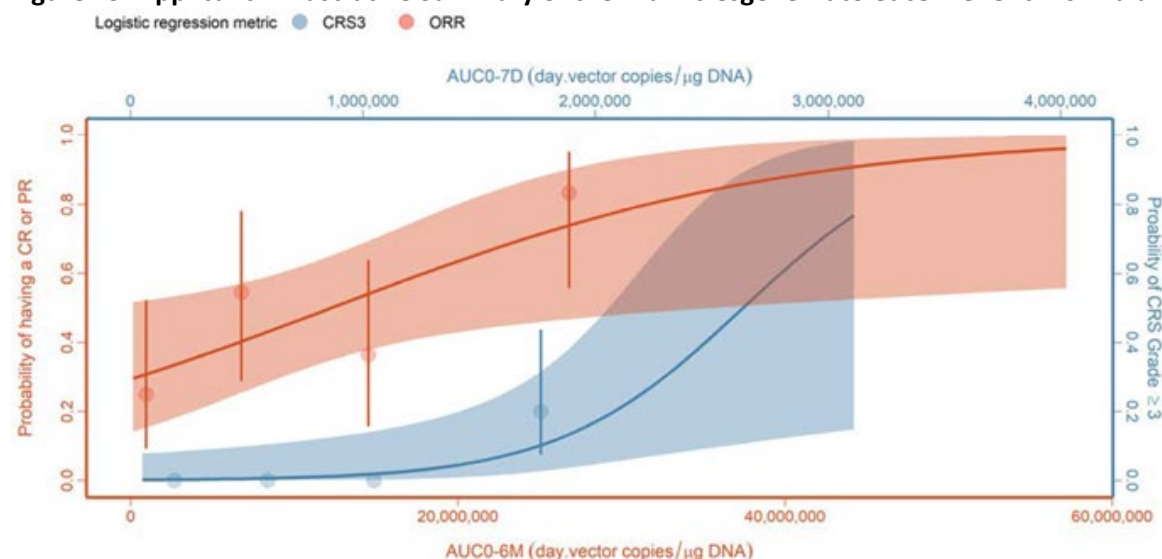
Demographic Factors	ADP-0044-001	ADP-0044-002 (SPEARHEAD-1)	Overall
Median (IQR)	2.04 (1.94-2.19)	1.94 (1.80-2.08)	1.97 (1.80-2.09)
Min-max	1.45-2.58	1.37-2.32	1.37-2.58
Missing	1 (6.25%)	2 (4.65%)	3 (5.08%)
Race group: White versus non-White			
White	14 (87.5%)	38 (88.4%)	52 (88.1%)
Non-White	2 (12.5%)	5 (11.6%)	7 (11.9%)
Race			
White	14 (87.5%)	38 (88.4%)	52 (88.1%)
Black or African American	-	2 (4.65%)	2 (3.39%)
Asian	2 (12.5%)	3 (6.98%)	5 (8.47%)
Sex			
Male	10 (62.5%)	21 (48.8%)	31 (52.5%)
Female	6 (37.5%)	22 (51.2%)	28 (47.5%)
Region			
North America	16 (100%)	31 (72.1%)	47 (79.7%)
Europe	-	12 (27.9%)	12 (20.3%)

Source: adap-adpa2m4-demo-ss-v8.Rmd, Reference: 40e1e3; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report, Table 10.

Notes: Numeric columns were formatted as mean (SD), median (IQR), and range (min-max).

Abbreviations: BMI=body mass index; BSA=body surface area; IQR=interquartile range; max=maximum; min=minimum; N= number of subjects with available information; SD=standard deviation; SS=synovial sarcoma

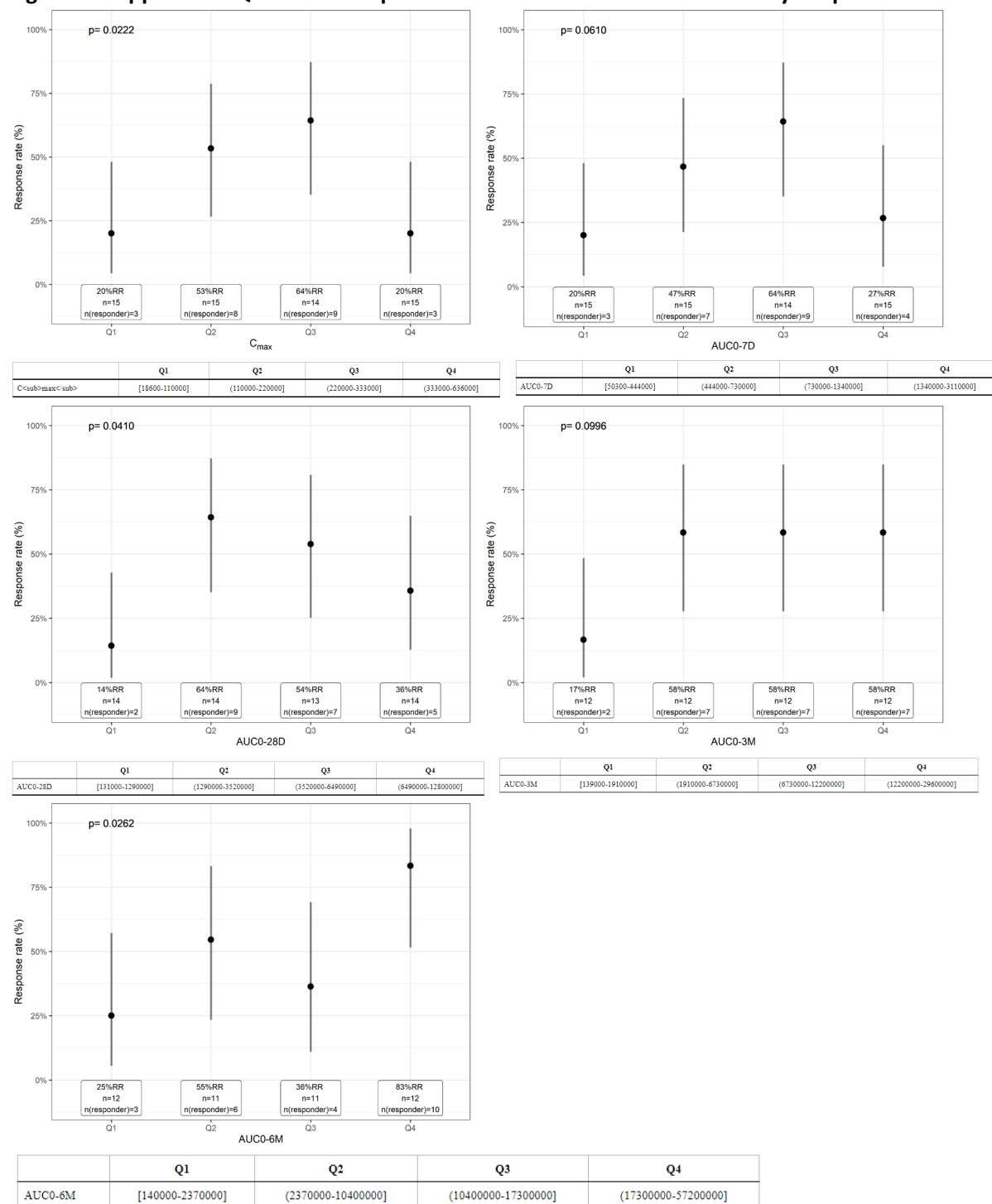
Figure 19: Applicant – Illustrative Summary of the Afamitresgene Autoleucel Benefit-Risk Balance



Source: adap-aspa2m4-logistic-regression-v6.Rmd, Reference: 0f3b26; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report, Figure 166

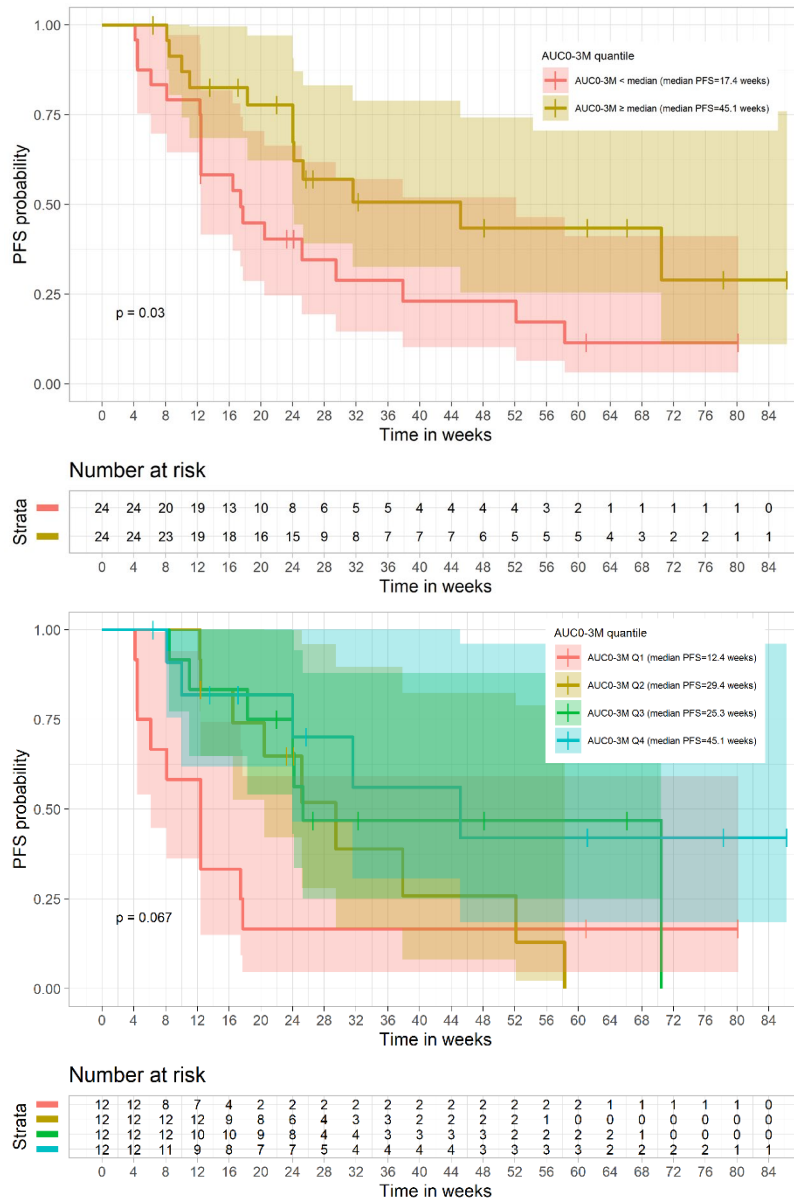
Abbreviations: AUC0-6M=area under the concentration-time curve from the time of dosing until Month 6 (Day 168) – for cellular persistence only; AUC0-7D=area under the concentration-time curve from the time of dosing until Day 7; CR=complete response; CRS=cytokine release syndrome; DNA=deoxyribonucleic acid; ORR=overall response rate; PR=partial response.

Figure 20: Applicant – Quartiles of Exposure Metrics of Cellular Persistence by Response Rate



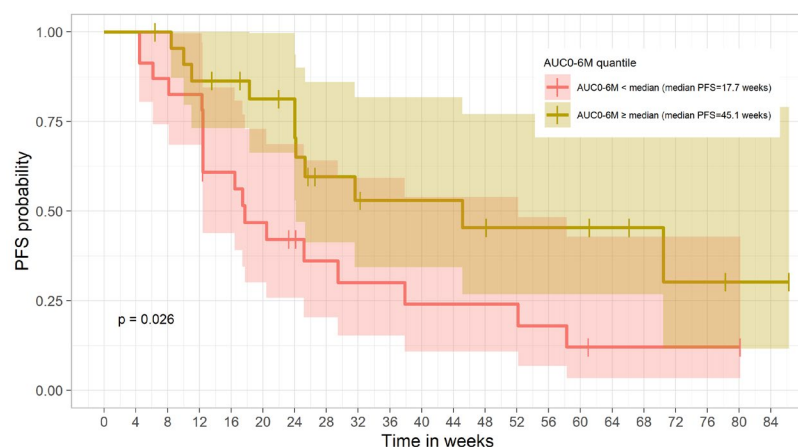
Source: adap-adpa2m4-orr-ss-v20.Rmd, Reference: 955c9f; d4e057; 91de64; b7f084; ddfd8c; ADAP-PMX-ADP-A2M4-2966
Modelling and Simulation Report, Figure 91.

Figure 21: Applicant – PFS Stratified by Median and Quartiles of Long-Term Exposure Metrics of Cellular Persistence



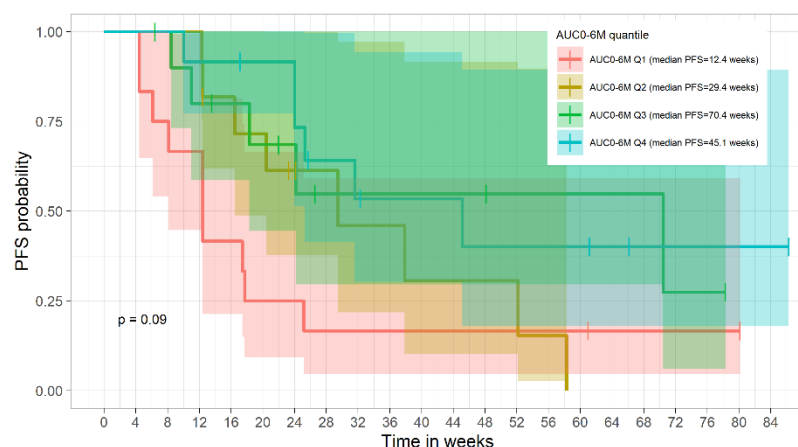
	Q1	Q2	Q3	Q4
AUC0-3M	[139000-1910000]	(1910000-6730000]	(6730000-12200000]	(12200000-29600000]

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Number at risk

Time in weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84
Strata	23	23	20	19	13	10	8	6	5	5	4	4	4	4	3	2	1	1	1	1	1	0
Strata	23	23	22	19	18	16	15	9	8	7	7	7	6	5	5	5	4	3	2	2	1	1



Number at risk

Time in weeks	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84
Strata	12	12	9	8	5	3	3	2	2	2	2	2	2	2	2	2	1	1	1	1	1	0
Strata	11	11	11	11	8	7	5	4	3	3	2	2	2	2	1	0	0	0	0	0	0	0
Strata	11	11	10	8	7	6	5	3	3	3	3	3	2	2	2	2	2	1	1	1	0	0
Strata	12	12	12	11	11	10	10	6	5	4	4	4	3	3	3	3	2	1	1	1	1	1

	Q1	Q2	Q3	Q4
AUC0-6M	[140000-2370000]	(2370000-10400000]	(10400000-17300000]	(17300000-57200000]

Source: adap-adpa2m4-pfs-ss-v18.Rmd, Reference: 387cda; ae6f6a; 1882d6; ead18f; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report, Figure 95.

19.4.2.3 ER (safety) Executive Summary

The FDA's Assessment:

[Refer to FDA Pharmacology/Toxicology and Clinical Pharmacology review memos for this BLA.]

19.4.2.4 ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Evaluate the relationship between exposure and safety, including an assessment of the impact of specified covariates on safety.
Study Included		Studies ADP-0044-002 and ADP-0044-001. Afamitresgene autoleucel cellular kinetics (C_{max} and AUC) were consistent between subjects with SS and other tumor types, supporting the pooling of data across tumor types for the cellular kinetic analyses.
Population Included		Primary analysis: subjects with advanced SS Secondary analysis: all subjects (any tumor type)
Endpoint		CRS: Grade ≥ 1 vs Grade < 1 CRS: Grade ≥ 2 vs Grade < 2 CRS: Grade ≥ 3 vs Grade < 3 CRS requiring tocilizumab: Yes/no ICANS: Yes/no
No. of Patients (total, and with individual PK)		Primary analysis: 59 subjects with SS Secondary analysis: 89 subjects (any tumor type)
Population Characteristics Table 61 Table 62	General	Primary analysis, as efficacy population (Table 61); secondary analysis (overall; Table 62): -Age median: 46 years (range: 19-78) -Weight median 78.0 kg (range: 68.5-95.7) -49 (55.1%) male; 40 (44.9%) female -79 (88.8%) White; 2 (2.25%) Black or African American; 6 (6.74%) Asian; 2 (2.25%) Missing.
	Organ impairment	N/A
	Pediatrics (if any)	N/A
	Geriatrics (if any)	13 subjects (14.6%), 6 with SS, aged ≥ 65 years old
Dose(s) Included		0.1 to 9.99×10^9 transduced cells
Exposure Metrics Explored		NCA metrics for cellular persistence: C_{max} , AUC _{0-7D} , AUC _{0-28D} , AUC _{0-3M} , and AUC _{0-6M} NCA metrics cytokines: C_{max} , AUC _{0-7D} , and AUC _{0-28D}
Covariates Evaluated		Demographic factors: age, body weight, BMI, BSA, Race (white vs non-white), Sex (male vs female), geographical region (North America vs Europe) Disease factors: MAGE-A4 H- score, ECOG status, baseline tumor size (SLD of target lesions) Concomitant treatment/ pre-treatment: number of prior lines of systemic therapy, bridging therapy (binary), tocilizumab, G-CSF T-cell product characteristics: dose; (b) (4) (b) (4), transduction efficiency
Final Model Parameters		Summary Acceptability [FDA's comments]
Model Structure		For CRS, an ordinal regression model was developed, with afamitresgene autoleucel

	AUC _{0-7D} as the independent variable	
Model Parameter Estimates	Table 63 shows the summary statistics of the ordinal regression model.	
Model Evaluation	Figure 22 presents the ordinal regression plots by grade of CRS grades by log AUC _{0-7D} of cellular persistence.	
Covariates and Clinical Relevance	Trend toward an increased probability of Grade ≥ 3 CRS and CRS requiring tocilizumab with increasing exposure (Figure 23). Caution is required when interpreting covariate associations due to the limited number of Grade ≥ 3 CRS. No extrinsic factors, including T-cell product-related parameters, showed trends with the probability of Grade ≥ 3 CRS and CRS requiring tocilizumab.	
Simulation for Specific Population	N/A	
Visualization of E-R relationships	Figure 24 presents the ordinal regression plots by predicted rates of CRS grades by log AUC _{0-7D} of cellular persistence.	
Overall Clinical Relevance for ER	Logistic regression analyses identified a relationship between Grade ≥ 3 CRS and afamitresgene autoleucel. In addition, relationships were identified between increasing afamitresgene autoleucel AUC _{0-7D} and increasing probability of CRS Grade ≥ 1 , CRS Grade ≥ 2 or CRS Grade ≥ 3 based on ordinal regression analyses. Throughout the range of exposures achieved over the proposed recommended dose range the probability of experiencing a Grade 2 or Grade 3 CRS event was lower than that of experiencing a Grade 1 CRS event. Markedly higher C _{max} , AUC _{0-7D} , and AUC _{0-28D} of all 3 key cytokines evaluated (GM-CSF, IL-6, and IFN γ) were observed in subjects who developed Grade ≥ 3 CRS (n = 3). While a higher incidence of Grade ≥ 3 CRS was observed in higher quartiles of early afamitresgene autoleucel exposure (C _{max} and AUC _{0-7D}) over the dose range, the overall incidence of Grade ≥ 3 CRS in the analysis population was low (3 of 59 SS subjects, i.e., 5.1%). Similarly, 3 of 89 across tumor types (and only 1 of 59 subjects with SS) experienced an any grade ICANS event, albeit these 3 subjects were in the upper half of afamitresgene autoleucel exposure.	

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Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Same as in E-R (efficacy).	

Table 62: Applicant – Summary of Demographic Factors – All Subjects

Demographic Factors	ADP-0044-001	ADP-0044-002 (SPEARHEAD-1)	Overall
N	38	51	89
Age (years)			
Mean (SD)	56.4 (12.6)	41.5 (12.9)	47.9 (14.7)
Median (IQR)	58.0 (48.3-65.5)	41.0 (31.0-46.5)	46.0 (38.0-60.0)
Min-max	31.0-78.0	19.0-73.0	19.0-78.0
Missing	0 (0%)	0 (0%)	0 (0%)
Body weight (kg)			
Mean (SD)	83.9 (22.5)	79.3 (17.6)	81.3 (19.9)
Median (IQR)	81.7 (68.6-98.3)	78.0 (68.8-89.4)	78.0 (68.5-95.7)
Min-max	42.9-149	45.9-120	42.9-149
Missing	0 (0%)	0 (0%)	0 (0%)
BMI (kg/m ²)			
Mean (SD)	27.4 (6.84)	27.0 (5.77)	27.1 (6.19)
Median (IQR)	26.0 (23.2-30.5)	25.7 (23.0-30.3)	25.8 (23.0-30.4)
Min-max	15.5-46.6	17.7-43.4	15.5-46.6
Missing	5 (13.2%)	2 (3.92%)	7 (7.87%)
BSA (m ²)			
Mean (SD)	1.93 (0.263)	1.90 (0.220)	1.91 (0.237)
Median (IQR)	1.93 (1.77-2.09)	1.94 (1.79-2.05)	1.93 (1.77-2.06)
Min-max	1.37-2.58	1.37-2.32	1.37-2.58
Missing	5 (13.2%)	2 (3.92%)	7 (7.87%)
Race group: White versus non-White			
White	35 (92.1%)	44 (86.3%)	79 (88.8%)
Non-White	3 (7.89%)	5 (9.80%)	8 (8.99%)
Missing	0 (0%)	2 (3.92%)	2 (2.25%)
Race			
White	35 (92.1%)	44 (86.3%)	79 (88.8%)
Black or African American	0 (0%)	2 (3.92%)	2 (2.25%)
Asian	3 (7.89%)	3 (5.88%)	6 (6.74%)
Missing	0 (0%)	2 (3.92%)	2 (2.25%)
Sex			
Male	22 (57.9%)	27 (52.9%)	49 (55.1%)
Female	16 (42.1%)	24 (47.1%)	40 (44.9%)
Region			
North America	38 (100%)	37 (72.5%)	75 (84.3%)
Europe	0 (0%)	14 (27.5%)	14 (15.7%)

Sources: adap-adpa2m4-demo-v8.Rmd, Reference: b3f72e; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report Table

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Notes: Numeric columns were formatted as mean (SD), median (IQR), and range (min-max).

Abbreviations: BMI=body mass index; BSA=body surface area; IQR=interquartile range; max=maximum; min= minimum;

N= number of subjects with available information; SD=standard deviation

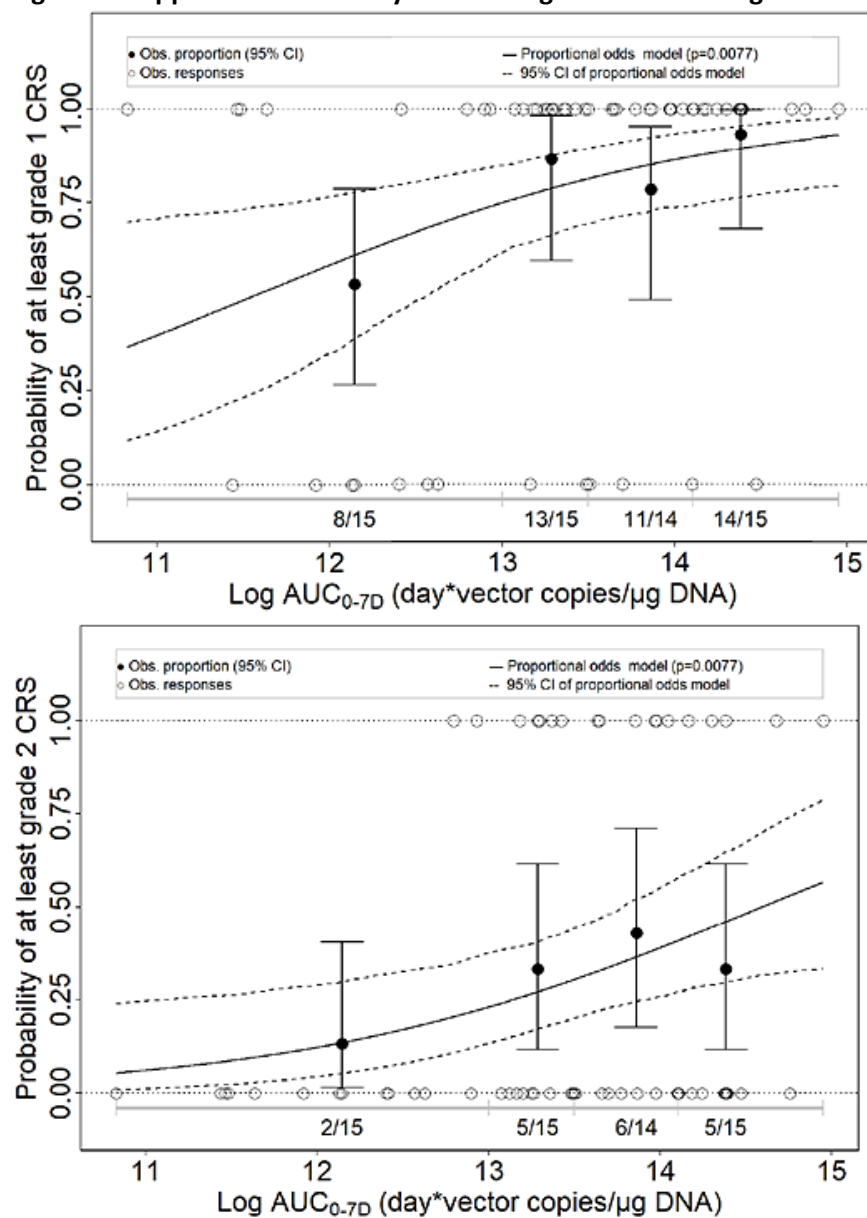
Table 63: Applicant – Summary of E-R Safety Ordinal Regression Modeling for Cellular Persistence and CRS Grades

	Value	p-value	OR	OR.low	OR.high
log_AUC07D	0.754447	0.00770569	2.12643	1.22082	3.70386
0 1	8.7125	0.0196519	6078.4	4.02581	9177518
1 2	11.009	0.00424642	60418.4	31.8938	114454210
2 3	13.1959	0.000773008	538131	245.55	1179332121

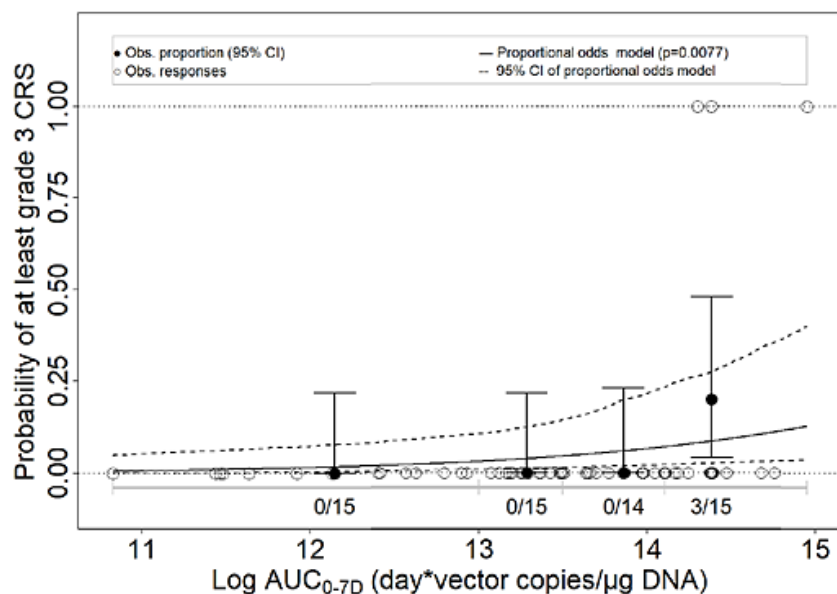
Source: ordinal_regression_safety_script_v3.R, Reference: 4500f9; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report, Table 20.

Abbreviations: AUC0-7D=area under the concentration-time curve from the time of dosing until Day 7; CRS=cytokine release syndrome; OR=odds ratio

Figure 22: Applicant – E-R Safety Ordinal Regression Modeling for Cellular Persistence and CRS Grades



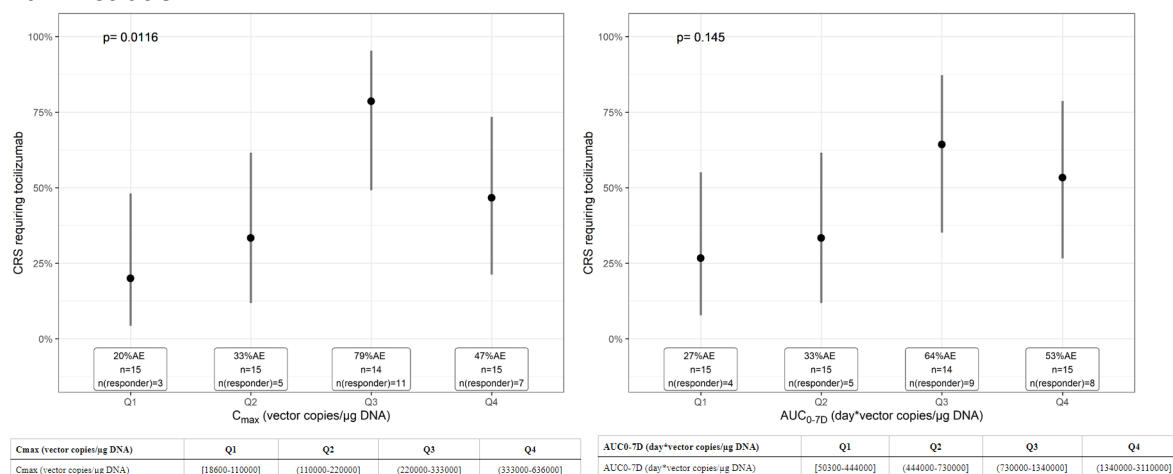
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Source: ordinal_regression_safety_script_v3.R, Reference: 35516a; d82d10; f44d66; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report, Figure 163.

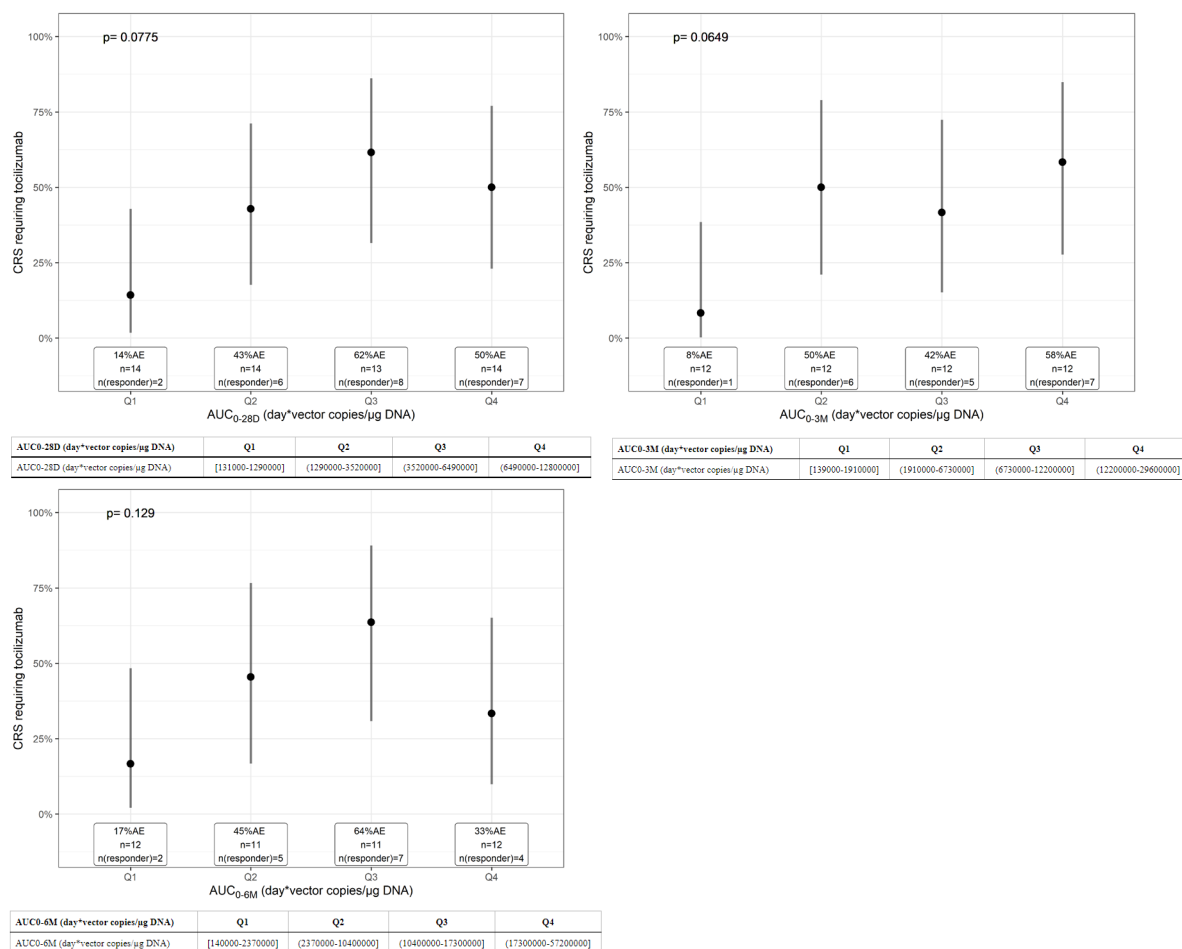
Abbreviations: AUC0-7D=area under the concentration-time curve from the time of dosing until Day 7; CRS=cytokine release syndrome.

Figure 23: Applicant – Cellular Persistence Quartiles of Exposure Metrics by Tocilizumab Administration



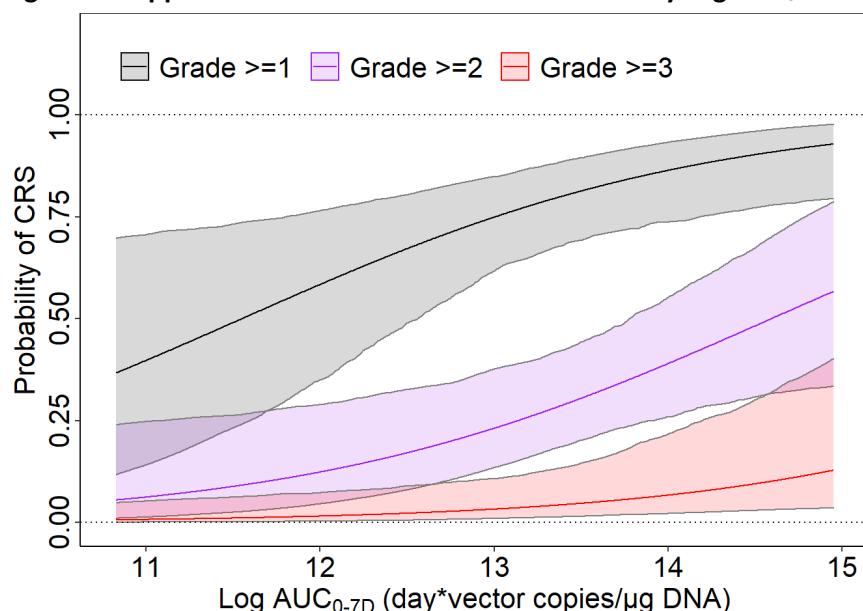
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TECELRA (afamitresgene autoleucel)



Source: adap-adpa2m4-safety-eda-ss-v7.Rmd, Reference: 5c30d6; c8df76; ab2052; a6c8c1; d5d9db; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report Figure 139.

Figure 24: Applicant – Predicted Rates of CRS Grades by Log AUC_{0-7D} of Cellular Persistence



Source: ordinal_regression_safety_script_v2.R, Reference: 4d4e9a; ADAP-PMX-ADP-A2M4-2966 Modelling and Simulation Report Figure 166.

19.4.2.5 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

In the efficacy E-R analysis population (SS-only subjects), no marked dose-response were observed with ORR, TTR, DOR, and PFS across the dose range. The incidence of Grade ≥ 3 CRS, a known class effect associated with T-cell therapy, was low across the dose range ($n=3$). The safety E-R analyses suggested that the probability of Grade ≥ 3 CRS was higher in doses $>5.13 \times 10^9$ transduced cells. However, due to the small number of subjects who developed a Grade ≥ 3 CRS in the analysis dataset ($n=3$), this finding is to be interpreted with caution. A similar trend toward an increased probability of CRS requiring tocilizumab was also observed in doses $>8.38 \times 10^9$ transduced cells.

The benefit-risk balance across the proposed dose range, shown in [Figure 19](#) (refer to "[Visualisation of E-R](#)" in 19.4.2.2), illustrates that across the range of exposures achieved, subjects are expected to have a higher probability of response than the probability of experiencing a Grade ≥ 3 CRS event.

Overall, efficacy and safety E-R analyses support the recommended afamitresgene autoleucel commercial dose range of 2.68 to 10×10^9 MAGE-A4 TCR positive T-cells.

The FDA's Assessment:

[Refer to FDA Clinical Pharmacology review memo for this BLA.]

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

[Results of safety analyses conducted by FDA are reported under [Section 8.2](#) of this memo.]