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Division / Office	Division of Clinical Evaluation Oncology/ Office of Therapeutic Products
Clinical Reviewer(s)	Katherine Barnett (Efficacy) Abigail Johnson (Safety)
Project Manager	Tigist Assefa
Priority Review	Yes
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
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Applicant	Adaptimmune, Inc
Established Name	afamitresgene autoleucel
(Proposed) Trade Name	TECLERA
Pharmacologic Class	Melanoma-associated antigen A4 (MAGE-A4) directed, genetically modified autologous T cell immunotherapy
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)
Recommended Indication(s)/Population(s)	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

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GLOSSARY

Abbreviation	Definition
AESI	Adverse event of Special Interest
BLA	Biologics Licensure Application
BOR	Best overall response
CI	Confidence interval
CR	Complete Response
CRS	Cytokine release syndrome
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HR	Hazard ratio
IRC	Independent Review Committee
ITT	Intent-to-treat
IND	Investigational new drug
KM	Kaplan-Meier
MEGA-A4	melanoma-associated antigen A4
mITT	Modified intent-to-treat
MRCLS	myxoid/round cell liposarcoma
NA	Not applicable
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event
SD	Stable Disease
SS	synovial sarcoma
STD	Standard deviation
STS	soft-tissue sarcoma
TTR	Time to response
US	United States

1. EXECUTIVE SUMMARY

Afamitresgene autoleucel is a melanoma-associated antigen A4 (MAGE-A4) directed genetically modified autologous T-cell immunotherapy. This Biologics License Application (BLA) seeks licensure of afamitresgene autoleucel for the treatment of adults with unresectable or metastatic synovial sarcoma (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.

In support of this application, the Applicant submitted the safety and efficacy data from the Study ADP-0044-002. Study ADP-0044-002 is a single-arm, open-label, multi-cohort, multicenter, multiregional Phase 2 study that enrolled subjects 16 to 75 years old with HLA-A*02 positive, MAGE-A4 expressing, advanced synovial sarcoma or myxoid/round cell liposarcoma (MRCLS) who previously received either an anthracycline- or ifosfamide-containing regimen. This study is composed of three independent cohorts (Cohorts 1, 2, and 3). From Cohort 1, a total of 52 subjects with SS were enrolled and underwent leukapheresis, and 44 subjects (84.6%) received afamitresgene autoleucel, which provides the primary evidence of efficacy for the product. From Cohorts 1 and 2, 80 subjects with SS were included in the primary safety analysis. The pre-specified primary efficacy endpoint is overall response rate (ORR), which is defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial response (PR), as assessed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

During the review of the initial efficacy data submitted, several data quality and study conduct issues were identified by the FDA clinical review team, such as measurement errors resulting in inaccurate target lesion measurements, inconsistencies in adherence to RECIST v.1.1, and inconsistencies in the implementation response adjudication. These issues, when evaluated in the context of the small sample size and low prevalence of responders of Cohort 1, raised concerns about the reliability of the ORR and DOR results. FDA therefore requested an independent, third-party re-review of response assessment for the 44 SS subjects in Cohort 1 using a different, blinded, IRC imaging vendor. Results summarized in this memo are based on this independent re-review IRC data with a cut-off date of March 29, 2023.

The ORR as assessed by re-review was 43.2% (19/44; 95% CI: 28.3%, 59.0%). The lower limit of the 95% exact Clopper-Pearson confidence interval (CI) of 28.3% exceeded the pre-specified response rate of 18% under the null hypothesis. Two (4.5%) subjects had a best response of CR, and 17 (38.6%) subjects had a best response of PR. The median duration of response (DOR) was 6.0 months (95% CI: 4.6, NR) for all responders with a median follow-up time of 21.9 months.

Deaths occurred in 54.4% (24/44) of treated SS subjects in Study ADP-0044-002 Cohort 1. All deaths reported after the cell infusion were due to disease deterioration under the study. In the primary safety analysis set including both Cohort 1 and Cohort 2 for

subjects with SS (n=80), 37 subjects (46.3%) died and 31 subjects (38.8%) reported treatment-emergent serious adverse events (SAEs). The most frequently reported treatment-emergent SAEs were respiratory, thoracic and mediastinal disorders (10, 12.5%) and infections and infestations (8, 10.0%).

Study ADP-0044-002 Cohort 1 met the efficacy criterion for the ORR primary endpoint, rejecting the null hypothesis and demonstrating durability of response. The statistical analysis results provide sufficient evidence to support the safety and effectiveness of afamitresgene autoleucel for the proposed indication in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

SS is a type of soft tissue sarcoma 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]. 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].

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Pazopanib is the only FDA-approved therapy for patients with advanced soft-tissue sarcomas (STS) who have received prior systemic therapy. 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 PFS of 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm (hazard ratio [HR]: 0.35, 95% CI: 0.26, 0.48). In the subgroup of SS patients, median PFS was 4.1 months in the pazopanib arm versus 0.9 months in the placebo arm (HR: 0.45, 95% CI: 0.19, 0.98). For STS overall, ORR for pazopanib was 4% (95% CI: 2.3%, 7.9%) with a median DOR of 9 months (95% CI: 3.9, 9.2). ORR was not reported for the subgroup of SS. Pazopanib was not associated with an 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.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this BLA.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Submission
December 28, 2016	IND 17235: ADP-0044-001 Phase 1 study in adults subjects with advanced solid tumors. Safe to proceed.
March 2019	Initiated ADP-004-002 Phase 2 study
August 26, 2019	Granted Orphan Drug Designation
November 27, 2019	Granted Regenerative Medicine Advanced Therapy designation
October 13, 2022	Pre-BLA meeting
December 5, 2023	Final module of rolling BLA received
January 10, 2023	BLA filed. The filing met priority review criteria.
May 20, 2024	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.
August 2, 2024	PDUFA Action Date

(Source: FDA assessment aid; FDA statistical reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Cohort 1 of Study ADP-0044-002, which is the focus of this review memo.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes the review of clinical study reports and data sets submitted in modules 2 and 5 of BLA 125789/0 (original data) and BLA 125789/58 (independent re-review data).

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the clinical trials relevant to this BLA submission.

Table 2. Studies in the BLA application

Study code	Study population	Study design	# of subjects treated
ADP-0044-002 (Cohort 1: pivotal)	HLA-A*02:01P, HLA-A*02:03P or HLA-A*02:06P positive adult patients with MAGE-A4 expressing metastatic or inoperable (advanced) SS or MRCLS.	Phase 2 single-arm, open-label study	Cohort 1: n=52 44 SS patients Cohort 2: n=36 36 SS patients (safety only)
ADP-0044-001 (supportive)	HLA-A*02 positive (and HLA-A*02:05P negative) adult patients with MAGE-A4 inoperable locally advanced or metastatic tumors.	Phase 1, open-label, dose escalation study	n=38 16 SS patients

(Source: Summary of Clinical Efficacy Table 1; FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study # ADP-0044-002

6.1.1 Objectives

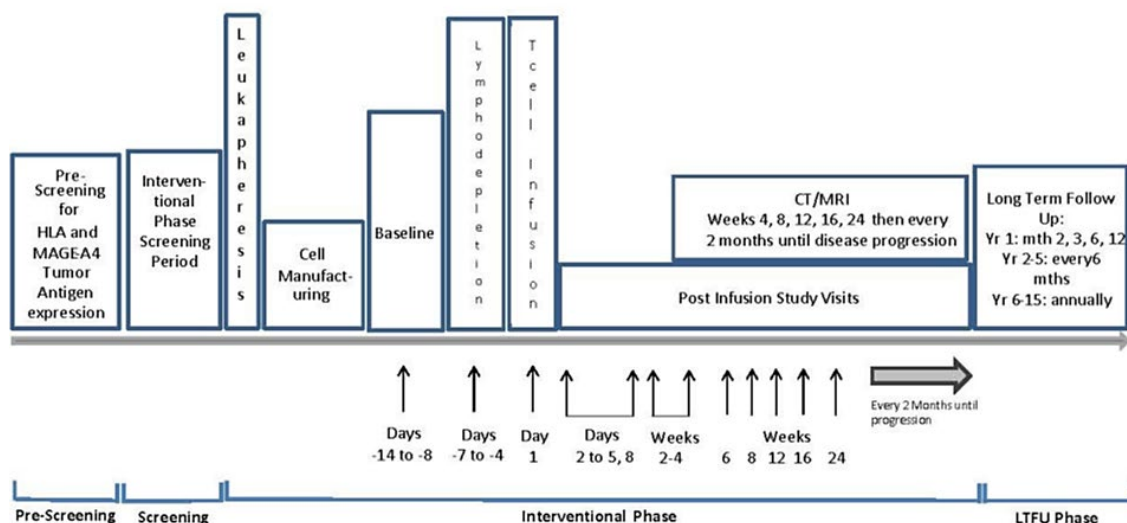
Primary: To evaluate the efficacy of afamitresgene autoleucel (i.e., measured by ORR)

Secondary objectives included assessing safety, tolerability and efficacy of afamitresgene autoleucel (i.e., measured by DOR, time to response, etc.), and characterizing the in vivo cellular pharmacokinetics profile of ADP-A2M4 cells.

6.1.2 Design Overview

Study ADP-0044-002 is a Phase 2, single-arm, open-label, multicenter clinical study of afamitresgene autoleucel in HLA-A*02 positive subjects with MAGE-A4 expressing advanced SS or MRCLS, who have received at least one line of prior systemic therapy. This study is composed of three independent cohorts (Cohorts 1, 2, and 3): enrollment and dosing are complete in Cohort 1, enrollment is complete in Cohort 2, and enrollment will be complete in July, 2024 in Cohort 3 per Applicant. Cohorts 2 and 3 have subjects with SS only. The primary evidence of efficacy for afamitresgene autoleucel is based on data from subjects with SS in Cohort 1 of Study ADP-0044-002. Figure 1 below gives the overview of study design schematic.

Figure 1. Study design schematic



(Source: Study ADP-0044-002 CSR Section 6.1)

6.1.3 Population

Key elements of eligibility criteria are listed below.

- Eligible subjects were ≥ 16 and ≤ 75 years and must have diagnosis of advanced (metastatic or inoperable) SS or myxoid liposarcoma / MRCLS (Cohort 1 only) confirmed by cytogenetics. Cohorts 2 and 3 have subjects with SS only.
- 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.
- Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

Reviewer's Note #1: ADP-0044-002 Cohort 1 also included subjects with myxoid liposarcoma/MRCLS; however, those subjects were not included in the primary efficacy analysis. In addition, the protocol allowed inclusion of pediatric subjects 16 years or older, but no pediatric subjects were enrolled in Cohort 1.

6.1.4 Study Treatments or Agents Mandated by the Protocol

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.

6.1.6 Sites and Centers

Twenty-five (25) study sites in US, Canada and Europe.

6.1.7 Surveillance/Monitoring

A Data Safety Monitoring Board (DSMB) was implemented for this study for Cohort 1 and consisted of two experienced oncologists who are independent of the study and an independent statistician.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was ORR, defined as the proportion of subjects with a CR or PR, per IRC using RECIST v1.1.

The study protocol also included several secondary efficacy endpoints: time to response (TTR), DOR, CR, PR, stable disease (SD), or progressive disease (PD), PFS, OS, and ORR per IRC using RECIST v1.1 across cohorts.

Reviewer's Note #2: FDA's primary determination of efficacy is based on confirmed ORR by IRC, further supported by DOR.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

Statistical hypothesis:

The analysis of the primary efficacy endpoint ORR was performed by testing

$H_0: p \leq 18\%$ vs. $H_1: p > 18\%$.

Note: The null hypothesis rate of 18% was justified as follows: The historical ORR for second-line metastatic soft-tissue sarcoma patient populations ranges from 4%-13%¹. To account for the potential variability in historical control response rate, a more conservative historical ORR of 18% was determined for therapies administered in the second-line metastatic SS setting and chosen for the hypothesis testing.

Analysis populations:

- *Intention-to-treat (ITT) set:* all subjects who were enrolled in the trial.
- *Modified intention-to-treat (mITT) set:* all ITT subjects who received T cell infusion.

Statistical methods:

The primary efficacy analyses were conducted in the mITT set. For the primary analysis, independent re-review IRC assessment of disease status would be used.

Primary endpoint

The primary efficacy endpoint, ORR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval (CI).

¹ Applicant's protocol Section 4.2

Secondary endpoints

For time-to-event endpoints, the Kaplan-Meier (KM) method was used to estimate the median along with the 95% CI. The reverse KM method was used to estimate the median follow-up time with the 95% CI. For binary endpoints, the number and proportion of subjects who were evaluated as CR, PR, SD, or PD were tabulated.

Interim analyses:

There was no interim analysis planned/performed for this study.

Sample size and power calculation:

A sample size of 45 subjects in Cohort 1 was calculated to provide approximately 93% power to exclude a 18% ORR if the true rate was 40% at a two-sided alpha level of 0.05.

Sensitivity and supplemental analyses:

- Sensitivity analyses of the primary and secondary efficacy endpoints were performed based on the response determined by investigator assessment
- Supplemental efficacy analyses were performed based on the ITT set

Subgroup analyses:

In the mITT set for Cohort 1, subgroup analyses were performed on the following variables based on patient's baseline status:

- Age: < 40 versus ≥ 40 years
- Sex: male versus female
- Geographical region: North America versus Europe
- Prior systemic lines of Therapy: ≤ 2 lines versus ≥ 3 lines
- H Score: < 200 versus ≥ 200
- Baseline sum of diameter: SLD < 100 mm versus SLD ≥ 100 mm
- Bridging therapy: Yes versus No
- Transduced cell dose: $< 7B$ versus $\geq 7B$
- CRS Any Grade: Yes versus No
- Time from initial diagnosis to cell infusion (A): ≤ 24 months versus > 24 months
- Time from initial diagnosis to cell infusion (B): ≤ 30 months versus > 30 months

Missing data:

Subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered as non-responders. For assessment of DOR, if a subject was known to be alive and progression-free, DOR was censored on the day of the last adequate tumor assessment; if a subject missed 2 or more consecutive post-baseline tumor assessments and the following assessment was a PD, or if a subject missed 2 or more consecutive post-baseline tumor assessments and then died, DOR was censored on the date of the last adequate tumor assessment.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

For analyses of efficacy and safety of subjects with SS in Study ADP-0044-002 Cohort 1, Table 3 summarizes the study analysis sets. Leukapheresed set (i.e., ITT set) included 52 subjects. Of 52 subjects, 45 (86.5%) subjects underwent lymphodepletion, and 44 (84.6%) subjects received afamitresgene autoleucel that constituted the primary efficacy set (i.e., mITT set).

Table 3. Analysis sets

Analysis Set	N (%)
Leukapheresed set (ITT set)	52 ^a
lymphodepletion set	45 (86.5%)
mITT set	44 (84.6%) ^b

a Fifty-two (52) subjects with SS were enrolled in ADP-0044-002 Cohort 1 and underwent leukapheresis. One subject (Subject (b) (6)) was initially enrolled in Cohort 1 and underwent leukapheresis. After slow progression of pulmonary metastases, this subject ultimately received treatment with volumetric-modulated arc therapy and did not receive afamitresgene autoleucel. The investigator's intent was to reassign this subject to Cohort 2, but this subject never received treatment. This subject is included in the ITT population by FDA analysis.

b For the 8 subjects who did not receive afamitresgene autoleucel, the reasons were: death from cancer under study (n=3), loss of eligibility prior to lymphodepletion (n=3), physician decision (n=1), and withdrawal by subject (n=1).

(Source: FDA statistical reviewer's summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for subjects with SS in Cohort 1 in the ITT set and mITT set, respectively. Subjects' demographics were generally similar between these two analysis sets.

Table 4. Demographics in the ITT and mITT sets for SS subjects in Cohort 1

	ITT set, n=52	mITT set, n=44
Age (years)		
Mean (STD)	40.6 (12.9)	41.0 (13.1)
Median (min, max)	40.5 (19, 73)	40.5 (19, 73)
Sex n (%)		
Female	25 (48.1%)	22 (50.0%)
Male	27 (51.9%)	22 (50.0%)
Race n (%)		
White	47 (90.4%)	39 (88.6%)
Black or African American	2 (3.8%)	2 (4.5%)
Asian	3 (5.8%)	3 (6.8%)
Ethnicity n (%)		
Hispanic or Latino	4 (7.7%)	2 (4.5%)
Not Hispanic or Latino	42 (80.8%)	38 (86.4%)
Not reported	6 (11.5%)	4 (9.1%)
Geographical Region		
North America	34 (65.4%)	31 (70.4%)
Europe	18 (34.6%)	13 (29.6%)

(Source: FDA statistical reviewer's summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 shows the baseline characteristics for subjects with SS in Cohort 1 in the ITT set and mITT set, respectively. There were no outstanding differences with respect to subject baseline characteristics between these two analysis sets.

Table 5. Baseline characteristics in the ITT and mITT sets for SS subjects in Cohort 1

	ITT set, n=52	mITT set, n=44
Prior systemic lines of therapy, n (%)		
1	8 (15.4%)	7 (15.9%)
2	17 (32.7%)	14 (31.8%)
3	12 (23.1%)	9 (20.5%)
4+	15 (28.8%)	14 (31.8%)
Bridging therapy, n (%)		
Yes	18 (34.6%)	16 (36.4%)
No	34 (65.4%)	28 (63.6%)
Time from initial diagnosis to cell infusion (months)		
Mean (STD)	55.5 (52.9)*	55.5 (52.9)
Median (min, max)	41.2 (7.2, 256.9)*	41.2 (7.2, 256.9)
Stage of cancer at last staging, n (%)		
Stage II	3 (5.8%)	2 (4.5%)
Stage III	1 (1.9%)	1 (2.3%)
Stage IV	41 (78.8%)	35 (79.5%)
Unknown	7 (13.5%)	6 (13.6%)

* Eight (8) subjects did not receive the cell infusion in the ITT set. The results presented in ITT set were based on 44 treated subjects (i.e., mITT set)

(Source: FDA statistical reviewer's summary)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date March 29, 2023, out of the 44 treated subjects with SS in Cohort 1 (i.e., mITT set), 6 were still ongoing and 38 had discontinued. Among the 38 subjects who discontinued, the most common reason for discontinuation was progressive disease (n = 30).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Due to data quality and study conduct issues identified during the review of the initial efficacy data submitted, FDA requested an independent, third-party re-review of response assessment for the 44 subjects in Cohort 1 using a different, blinded, IRC imaging vendor. The FDA's primary efficacy evaluation was based upon the independent re-review of response assessment.

In the mITT set of 44 subjects, 19 subjects (43.2%; 95% CI: [28.3%, 59.0%]) had a BOR of CR or PR, as determined by re-review IRC assessment. The lower limit of the 95% exact Clopper-Pearson CI for ORR was 28.3% which is above the pre-specified null hypothesis rate of 18%. Among the 19 responders, 2 subjects (4.5%) had a best response of CR, and 17 (38.6%) subjects had a best response of PR.

FDA also performed the sensitivity analysis based on investigator assessment: The ORR is 40.9% (18/44; 95% CI: [26.3%, 56.8%]) per investigator assessment. The lower limit of the 95% exact Clopper-Pearson confidence interval was 26.3% exceeding the pre-specified null rate of 18%. Among the 18 responders, 2 subjects (4.5%) had a best response of CR, and 16 (36.4%) subjects had a best response of PR.

6.1.11.2 Analyses of Secondary Endpoints

Table 6 below summarizes results from different type of responses in the mITT set for the subjects with SS in Cohort 1 per independent re-review and Table 7 shows the responses based on investigator assessment in the mITT set.

Table 6. Summary of different response by independent re-review

Parameter	mITT, n=44
CR	2 (4.5)
PR	17 (38.6)
SD	20 (45.5)
PD	5 (11.4)

(Source: FDA statistical reviewer's analysis)

Table 7. Summary of different response by investigator assessment

Parameter	mITT, n=44
CR	2 (4.5)
PR	16 (36.4)
SD	19 (43.2)
PD	7 (15.9)

(Source: FDA statistical reviewer's analysis)

DOR

Table 8 summarizes the DOR results for treated subjects with SS in Cohort 1 per re-review IRC and investigator assessment, respectively.

Table 8. DOR results in the mITT set in subjects with SS in Cohort 1

	Re-review IRC	Investigator
Number of subjects 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)		
median	6.0	14.4
95% CI	(4.6, NR)	(6.0, NR)
range	(1.9, 36+)	(1.9, 31.3+)
Median follow-up time (months)	21.9	28.2
Percentage of subjects with response duration (%)*		
≥ 6 months	45.6	64.9
≥ 12 months	39.0	53.1
≥ 24 months	39.0	33.2

*The estimated percentage of subjects with response duration ≥ 6 , ≥ 12 , and ≥ 24 months was presented with 95% CIs using the KM method.

(Source: FDA statistical reviewer's analysis)

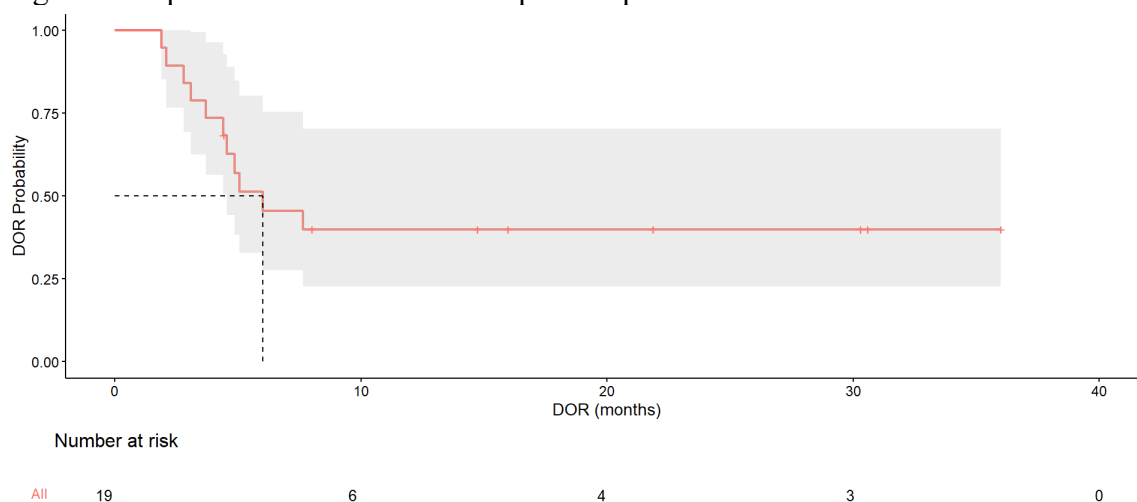
Reviewer's Note #3: Per FDA review team, DOR results of one subject were adjudicated:

- Subject (b) (6) - no imaging between Month 8 and Month 18. Therefore, this subject was censored at Month 8 per FDA adjudication. This subject was censored due to end of intervention before PD at Month 22 by the Applicant.
- The DOR analyses in this memo were based on FDA adjudicated data.

For analysis of DOR per re-review IRC assessment, the overall median was 6.0 months with a lower 95% limit of 4.6 months and an unattainable upper limit. The median follow-up time was 21.9 months. For analysis per investigator assessment, the overall median of DOR was 14.4 months with a lower 95% limit of 6.0 months and an unattainable upper limit.

Figures 2 below shows the Kaplan-Meier curve of DOR per independent re-review.

Figure 2. Kaplan-Meier curves of DOR per independent re-review



(Source: FDA statistical reviewer's analysis)

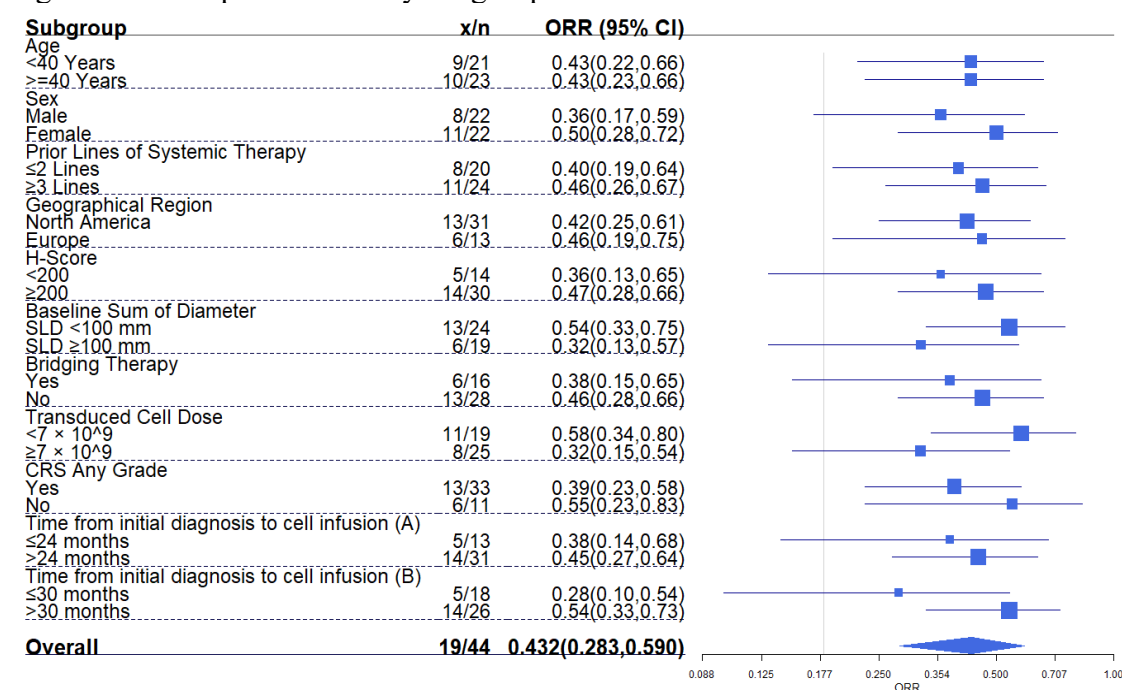
TTR

For analysis of TTR per independent re-review, the overall median was 4.9 weeks with a lower 95% limit of 4.4 weeks and an upper 95% limit of 8 weeks. For analysis per investigator assessment, the overall median of TTR was 5.1 weeks with a lower 95% limit of 4.3 weeks and an upper 95% limit of 11.3 weeks.

6.1.11.3 Subpopulation Analyses

Figure 4 shows the forest plot of ORR in the mITT set for subjects with SS in Cohort 1 by some important baseline characteristics. Although the lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is below the null hypothesis rate of 18% in some subgroups, it is not possible to draw definitive conclusions due to the small sample size in these subgroups.

Figure 3. Forest plot of ORR by subgroups



*One subject in the mITT set has missing baseline sum of diameter.
(Source: FDA statistical reviewer's analysis)

6.1.11.4 Dropouts and/or Discontinuations

Table 9 summarizes subjects with discontinuations from the study. The reasons for dropouts and discontinuations included deaths, content withdrawal, lost to follow-up, etc. Among the 44 subjects with SS in Cohort 1, 28 (63.6%) subjects discontinued the study.

Table 9. Subjects with discontinuations

Status	mITT, n=44 n (%)
Subjects discontinued from study	28 (63.6)
Primary reason for discontinuation from study	
Death	24 (54.5)
Lost to follow-up	1 (2.3)
Noncompliance with study requirements	1 (2.3)
Withdrawal by subject	2 (4.5)

(Source: FDA reviewer's summary)

6.1.12 Safety Analyses

This section summarizes safety results of Study ADP-0044-002 Cohort 1 (and Cohort 2) for subjects with SS.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data.

6.1.12.3 Deaths

Deaths reported in the study are listed in Table 10. Among the 44 treated subjects with SS in Cohort 1, 24 (54.4%) subjects died post the cell infusion. All these 24 deaths were due to disease under study. Among 80 treated subjects with SS in both Cohorts 1 and 2, 37 (46.3%) subjects died post the cell infusion, and 36 (45.0%) deaths were due to disease under study.

Table 10. Deaths reported

	mITT, n=44 n (%)	Safety set, n=80 n (%)
Subject status		
Dead	24 (54.4)	37 (46.3)
Alive at last contact; follow-up ongoing	16 (36.4)	36 (45.0)
Alive at last contact; lost to follow-up/study withdrawal	4 (9.1)	7 (8.7)
Primary cause of death		
Disease under study	24 (54.5)	36 (45.0)
Adverse event	0	0
Others	0	1 (1.3; due to COVID-19)

(Source: FDA clinical review)

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

The Applicant reported 31 (38.8%) subjects who had at least one treatment-emergent non-fatal SAEs in the treated subjects with SS in both Cohort 1 and Cohort 2 (n=80). The most frequently reported treatment-emergent SAEs were respiratory, thoracic and mediastinal disorders (10, 12.5%) and infections and infestations (8, 10.0%).

Table 11. Nonfatal SAEs reported in $\geq 5\%$ of treated subjects

System Organ Class Preferred Term	SS, n=80 n (%)
Any treatment-emergent SAE	31 (38.8)
Blood and lymphatic system disorders	4 (5.0)
Anemia	3 (3.8)
Neutropenia	1 (1.3)
Immune system disorders	6 (7.5)
Cytokine release syndrome	6 (7.5)
Infections and infestations	8 (10.0)
COVID-19	1 (1.3)
COVID-19 pneumonia	1 (1.3)
Empyema	2 (2.5)
Pneumonia	2 (2.5)
Sepsis	1 (1.3)
Staphylococcal abscess	1 (1.3)
Respiratory, thoracic and mediastinal disorders	10 (12.5)
Dyspnea	1 (1.3)
Hemoptysis	1 (1.3)
Pleural effusion	4 (5.0)
Pneumothorax	2 (2.5)
Pulmonary embolism	2 (2.5)
Vascular disorders	4 (5.0)
Deep vein thrombosis	2 (2.5)
Hemorrhage	1 (1.3)
Superior vena cava occlusion	1 (1.3)

(Source: FDA clinical review memo)

6.1.12.5 Adverse Events of Special Interest (AESI)

CRS occurred most frequently in 73.8% (=59/80) of treated SS subjects in Cohorts 1 and 2. See FDA clinical review memo for details.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Afamitresgene autoleucel is a MAGE-A4 directed genetically modified autologous T-cell immunotherapy. This BLA seeks licensure of afamitresgene autoleucel for the treatment of adults 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.

The primary source of evidence to support the efficacy of this application is the Cohort 1 of a single-arm, open-label, multi-cohort, multicenter, multiregional Phase 2 study (Study ADP-0044-002). A total of 52 subjects with SS in Cohort 1 were enrolled and underwent leukapheresis, 45 subjects (86.5%) received lymphodepletion, and 44 subjects (84.6%)

received afamitresgene autoleucel constituting the primary evidence of efficacy for the product.

The ORR as assessed by independent re-review was 43.2% (19/44; 95% CI: 28.3%, 59.0%) and the lower limit of the 95% exact Clopper-Pearson CI was 28.3% which was above the pre-specified null hypothesis rate of 18%. Two (4.5%) subjects had a best response of CR, and 17 (38.6%) subjects had a best response of PR. The median DOR was 6.0 months (95% CI: 4.6, NR) for all responders with a median follow-up time of 16.1 months (95% CI: 8.0, 30.5).

Deaths occurred in 54.4% (24/44) of treated SS subjects in Study ADP-0044-002 Cohort 1 and all deaths reported after the cell infusion were due to disease under the study. In the primary safety analysis set including both Cohort 1 and Cohort 2, 31 of 80 subjects (38.8%) reported treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs were respiratory, thoracic and mediastinal disorders (10, 12.5%) and infections and infestations (8, 10.0%).

10.2 Conclusions and Recommendations

Study ADP-0044-002 Cohort 1 met the efficacy criterion for the primary endpoint ORR, rejecting the null hypothesis and demonstrating durability of response. The statistical analysis results provide sufficient evidence to support the safety and effectiveness of afamitresgene autoleucel for the proposed indication in this BLA.