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Review Completion Date / Stamped Date	
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Applicant	bluebird bio
Established Name	elivaldogene autotemcel
(Proposed) Trade Name	SKYSONA
Pharmacologic Class	Gene Therapy
Dosage Form(s) and Route(s) of Administration	A cell suspension for intravenous infusion.
Dosing Regimen	The minimum recommended dose is 5.0×10^6 CD34+ cells/kg.
Indication(s) and Intended Population(s)	To slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

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GLOSSARY

ABCD1	ATP-binding cassette, subfamily D member 1
ALD	Adrenoleukodystrophy
ALDP	adrenoleukodystrophy protein
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ANC	absolute neutrophil count
ATP	adenosine triphosphate
BLA	biologics license application
CALD	cerebral adrenoleukodystrophy
cDNA	complementary deoxyribonucleic acid
CI	confidence interval
DMC	data monitoring committee
EDT	Eastern Daylight Time
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GVHD	chronic graft versus host disease
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
ITT	Intent-to-treat
IV	intravenous
lovo-cel	lovotibeglogene autotemcel
MDS	myelodysplastic syndrome
MECOM	MDS1 and EVI1 complex locus protein EVI1
MFDs	major functional disabilities
MRI	magnetic resonance imaging
NEP	Neutrophil Engraftment Population
NFS	Neurologic Function Score
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PMISP	Particular Matter Involving Specific Parties
SAEs	Serious Adverse Events
SD	standard deviation
TEAEs	Treatment Emergent Adverse Events
TP	Transplant Population
TPES	Strictly ALD-102-Eligible Transplant Population
TRM	transplant-related morbidity and mortality
UK	United Kingdom
US	United States
VCN	vector copy number
VLCFAs	very long-chain fatty acids

1. Executive Summary

This biologics license application (BLA) is for approval of SKYSONA which is an adenosine triphosphate (ATP)-binding cassette, subfamily D member 1 (*ABCD1*) gene addition therapy indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

The primary evidence to support the safety and effectiveness of the product is based on the final analysis results of the pivotal study ALD-102. ALD-102 is an international, open-label, multi-site, single-arm, single dose, phase 2/3 study to evaluate the efficacy and safety of HSC transduced with Lenti-D Lentiviral Vector for the treatment of CALD. The primary efficacy endpoint was the proportion of subjects who had none of the 6 major functional disabilities (MFDs), were alive, did not receive a second allogeneic hematopoietic stem cell transplantation (allo-HSCT) or rescue cell administration, and had not withdrawn or been lost to follow-up at Month 24 (i.e., Month 24 MFD-free survival). The six MFDs were defined as (1) loss of communication, (2) cortical blindness, (3) requirement for tube feeding, (4) total incontinence, (5) wheelchair dependence, (6) or complete loss of voluntary movement. The study success criterion was proposed as the lower bound of the 2-sided 95% exact confidence interval (CI) of Month 24 MFD-free survival had to exceed a clinical benchmark of 50%.

Thirty-two subjects with CALD were enrolled and treated with SKYSONA. All were male and aged between 3 and 13 years at time of consent. Twenty-nine out of 32 (90.6%) subjects achieved Month 24 MFD-free survival (95% CI: 75%, 98%). Of 32 subjects, 31 subjects remained alive at the end of the trial, so the Kaplan-Meier analysis estimated overall survival rate at Month 24 after drug product infusion was 96.7% (95% CI: 78.6%, 99.5%).

In terms of safety, the primary safety endpoint was the proportion of subjects who experience either acute (\geq Grade II) or chronic graft versus host disease (GVHD) by Month 24. No subjects experienced acute or chronic GVHD by Month 24. One death was reported at approximately 22 months after drug product infusion. There were no treatment-emergent events of interest reported. No subjects experienced malignancy or human immunodeficiency virus (HIV) infection.

One integrated efficacy analysis was performed by incorporating data from an additional study: Study ALD-103, a hybrid prospective-retrospective observational study in boys who were treated more recently with allo-HSCT (between 2013 and 2019). The integrated analysis was to compare ALD-102 outcomes with ALD-103 by using a Cox regression model. For MFD-free survival, the hazard ratio (ALD-102 vs. ALD-103) was 0.229 (95% CI: 0.060, 0.868). For overall survival, the hazard ratio was 0.119 (95% CI: 0.014, 1.020).

In summary, the primary efficacy analysis of study ALD-102 shows that the success criterion was met. In the integrated analyses, the comparisons between

the ALD-102 and ALD-103 based on the MFD-free survival and overall survival also support the effectiveness of SKYSONA.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Adrenoleukodystrophy (ALD) is a rare, X-linked disease, caused by a defect in the *ABCD1* gene which encodes adrenoleukodystrophy protein (ALDP). ALDP is a peroxisomal transport protein involved in the degradation of very long-chain fatty acids (VLCFAs). Dysfunction of ALDP results in accumulation of VLCFAs, primarily in the adrenal glands and white matter of the brain and spinal cord. The incidence of ALD among newborn males has been estimated as approximately 1 in 10,000 to 1 in 21,000 (Bezman et al. 2001; Taylor and Lee 2019). CALD, the most severe manifestation of ALD, affecting approximately 40% of boys with ALD typically during childhood, is characterized by rapidly progressive cerebral demyelination leading to progressive, irreversible loss of neurologic function and death.

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

There is currently no treatment approved for CALD in the United States (US); the current standard of care for treatment of children with CALD is allo-HSCT. Allo-HSCT has been shown to have a beneficial effect on clinical indices of disease and long-term survival. Although allo-HSCT can stabilize neurologic disease if performed at the early stage of cerebral involvement, it has significant limitations. Donor availability and transplant-related risks (transplant-related morbidity and mortality [TRM], GVHD, graft rejection, and long-term use of immunosuppression) limit its broader use.

Allo-HSCT is ideally performed using an HLA-matched sibling HSC donor who does not carry the mutation; however, a matched sibling donor is only available for $\leq 30\%$ of patients. Thus, alternatives are necessary for the majority of children with CALD. Current options include allo-HSCT with cells derived from an HLA-mismatched related donor, or from a matched or mismatched unrelated donor, including banked cord blood.

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

SKYSONA was granted an orphan drug designation for the treatment of ALD on 19 April 2012 (#12-3682), received a Rare Pediatric Disease Designation on 09 August 2017 (#RPD 2016-79), and was granted a Breakthrough Therapy Designation on 21 May 2018.

In a Type-C meeting (CRMTS# 11016) on February 22, 2018, The Food and Drug Administration (FDA) expressed concern about possible bias in assessing major functional disabilities. In a Type-B meeting (CRMTS# 11453) on November 15, 2018, the FDA agreed with the primary clinical efficacy endpoint. In a pre-BLA meeting (CRMTS# 13347) on 21 June 2021, the applicant received final guidance from the FDA to submit the BLA.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without unreasonable difficulty.

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

5.1 Review Strategy

Five clinical studies submitted in this BLA contain efficacy and safety information: efficacy and safety data from Study ALD-102, long-term data from Study LTF-304, interim efficacy and safety data from Study ALD-104, contemporaneous external control data from Study ALD-103, and historical control data from Study ALD-101. Study ALD-102 is the pivotal study and is the focus of this memo. An integrated efficacy analysis was performed to further support the efficacy of SKYSONA.

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

I reviewed the following documents and datasets for the BLA.

- BLA 125755/0
 - Module 1.14 Labeling
 - Module 2.7.3 Summary of Clinical Efficacy
 - Module 5.2 Tabular Listing of all Clinical Studies
 - Module 5.3.5.2 Study Reports
 - ALD-102: study report body, protocol, SAP
 - Module 5.3.5.2 Data Files
 - ALD-102: adsl.xpt, adefeff.xpt
 - Module 5.3.5.4 Other Study Reports
 - ALD-103: study report body, protocol
 - Module 5.3.5.4 Data Files
 - ALD-103: adsl.xpt, adefeff.xpt
- 125755/55
 - Module 5.3.5.3 Reports of Analyses of Data from More Than One Study
- 125755/79
 - Module 5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3 Table of Studies/Clinical Trials

The submitted clinical studies in this BLA are summarized in Table 1.

Table 1 Summary of clinical studies in the BLA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Admin'n	Number of Subjects	Diagnosis of Patients	Treatment	Study Status; Type of Report
Eli-cel								
Efficacy and safety	ALD-102	Efficacy and safety	Open-label, multi-center, single arm, externally controlled	eli-cel drug product; $\geq 5.0 \times 10^6$ CD34+ cells/kg; Intravenous infusion	32 treated	Patients ≤ 17 years of age with CALD	Single dose	Completed; Final Report (full)
Efficacy and safety	ALD-104	Efficacy and safety	Open-label, multi-center, single arm, uncontrolled	eli-cel drug product; $\geq 5.0 \times 10^6$ CD34+ cells/kg; Intravenous infusion	23 treated	Patients ≤ 17 years of age with CALD	Single dose	Ongoing; Interim Report (safety focus)
Efficacy and safety	LTF-304	Long-term follow-up from parent studies; safety and efficacy	Long-term follow-up, single arm, uncontrolled	N/A (subjects dosed in prior studies)	27 enrolled	Patients ≤ 17 years of age with CALD treated with eli-cel in parent study	N/A	Ongoing; Interim Report (full)
Allogeneic								
Efficacy and safety: Historical Control	ALD-101	The natural history of disease in untreated subjects with CALD;	Retrospective, non-interventional, data collection study	N/A	137 (72 untreated; 65 allo-HSCT treated)	Patients ≥ 3 and ≤ 15 years of age with CALD	N/A	Completed; Final Report (full)
Safety and efficacy: External concurrent control	ALD-103	Safety and efficacy of allo-HSCT in subjects with CALD	Retrospective and prospective, data collection study	N/A	59 allo-HSCT treated	Patients ≤ 17 years of age with CALD	N/A	Completed; Final Report (full)

Abbrev.: CALD, cerebral adrenoleukodystrophy; HSCT, hematopoietic stem cell transplant; N/A, not applicable

Source: Original BLA 125755; Module 5.2 Tabular Listing of all Clinical Studies.

5.4 Consultations

5.4.1 Advisory Committee Meeting

The Advisory Committee meeting took place on June 9, 2022. Three clinical questions were discussed in the meeting and listed as follows.

- 1) The eli-cel [SKYSONA] efficacy data are difficult to interpret due to problems with the benchmark calculation, issues of comparability between populations, potential bias, concerns regarding imputation methods, few events during a limited duration of follow-up, and limited sample size for treatment and control populations.
 - a) Please discuss the limitations of the primary and secondary efficacy endpoint data, and whether the data support the presence of a clinically meaningful benefit of SKYSONA.
 - b) Please discuss the population(s) (e.g., children without a matched and willing sibling donor, children without a matched donor) in which the efficacy data are, or are not, supportive of a clinically meaningful benefit.

Summary of Discussion: The committee agreed with the concerns regarding data but found that the data does support efficacy of SKYSONA in the proposed patient population without a matched sibling donor and those without an unrelated matched donor. The panel thought that a 24-month time period for the primary efficacy endpoint was appropriate. They suggested that analysis should be ongoing for patients receiving SKYSONA and compared against patients receiving a bone-marrow transplant to continue to evaluate the risk-benefit of treatment with SKYSONA.

- 2) Three SKYSONA-treated subjects have developed myelodysplastic syndrome [MDS]. Subjects with sickle cell disease treated with a related product, lovotibeglogene autotemcel (lovo-cel), have been diagnosed with myeloid malignancies. Please discuss the extent to which the myeloid malignancies associated with lovo-cel raise concerns regarding risk for hematologic malignancy with SKYSONA.

Summary of Discussion: The panel did not think that the lovo-cel data should negatively impact the SKYSONA analysis as the products are used in two different settings. The analysis for each concern two different diseases, different indications, and two different products.

- 3) SKYSONA has a risk of hematologic malignancy, a potentially fatal adverse event. The number of cases of malignancy (currently 3/67, or 4%) seems likely to increase over time. In addition to the three recognized cases of MDS, there are at least four other subjects with concern for impending MDS. Although the clinical significance is unclear, 98% of subjects in the SKYSONA study population have vector integration sites in MDS1 and EVI1 complex locus protein EVI1 (MECOM), a proto-oncogene. Please discuss the risk of insertional oncogenesis in patients with early active childhood CALD treated with SKYSONA.

Summary of Discussion: The committee acknowledged the risk of MDS for patients treated with SKYSONA and felt that historical data of MDS in pediatric patients may not translate to patients in this setting who will have the same limited pool of donors to treat their MDS. However, given the current risks of GVHD related toxicity and untreated CALD disease, the benefit is still favorable. The panel agreed with the need for continued monitoring and detailed surveillance which should include sequencing analysis of integration sites, biopsies to identify MDS, and early intervention for cases of MDS.

Voting Questions for BLA 125755:

1. Are the lovo-cel safety data relevant to the safety assessment of SKYSONA?

The results of the vote were as follows: Yes=1; No=13; Abstain=1.

2. Do the benefits of SKYSONA outweigh the risks, for the treatment of any sub-population of children with early active CALD?

The results of the vote were as follows: Yes=15; No=0; Abstain=0.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 ALD-102 (August 21, 2013-March 26, 2021)

6.1.1 Objectives

- Evaluate the efficacy of SKYSONA in subjects with CALD
- Evaluate the safety of SKYSONA in subjects with CALD

6.1.2 Design Overview

Study ALD-102 was an international multi-site, non-randomized, open-label, single-dose, phase 2/3 study in male subjects with CALD treated with SKYSONA. Initially, the treatment schedule was staggered: the second subject began myeloablative conditioning only after the data monitoring committee (DMC) reviewed safety and neutrophil engraftment data for the first subject. After the DMC also reviewed data for the second subject, parallel drug product treatment occurred with additional subjects.

The study had 4 distinct stages, as follows.

Stage 1: Screening to determine eligibility

Stage 2: Autologous CD34+ cell collection, transduction, disposition of SKYSONA, and re-confirmation of eligibility

Granulocyte colony-stimulating factor (G-CSF) (filgrastim or lenograstim) was used for HSC mobilization. Depending on CD34+ cell count on the day of collection, plerixafor could be given for up to four days to augment mobilization. Apheresis was used to harvest peripheral blood mononuclear cells (PBMCs). The harvested cells were enriched for CD34+ cells, transduced with Lenti-D LVV, stored frozen in cryopreservation solution in the vapor phase of liquid nitrogen while aliquots were tested to ensure they meet product quality specifications, and then shipped to the treatment site.

Stage 3: Myeloablative and lymphodepleting conditioning and infusion of SKYSONA

Subjects did not begin conditioning until drug product was dispositioned for clinical use and was at the site. A four-day course of busulfan was followed by a rest day and then a four-day course of cyclophosphamide, followed by a rest day, before SKYSONA infusion. On Study Day 1, defined as the day of drug product infusion, thawed SKYSONA was administered via IV infusion as a single dose of $\geq 5.0 \times 10^6$ CD34+ cells/kg.

Stage 4: Follow-up through Month 24

Subjects were to be followed until approximately 24 months after SKYSONA infusion (Month 24 Visit) in this study. Subsequently, after provision of written informed consent (and assent if applicable), subjects are to be followed for up to an additional 13 years in Study LTF-304, for a total of 15 years after drug product infusion.

6.1.3 Population

Key inclusion criteria:

- Male and ≤ 17 years of age.
- Active CALD as defined by elevated VLCFA levels, and brain MRI demonstrating Loes score between 0.5 and 9 (inclusive) on the 34-point scale and gadolinium enhancement (GdE+) of demyelinating lesions; and (Inclusion criterion).
- Neurologic Function Score (NFS) of ≤ 1 .

Key exclusion criteria:

- A recipient of an allogeneic transplant or previous gene therapy.
- Having a willing 10/10 HLA-matched sibling donor (excluding female heterozygotes).

6.1.4 Study Treatments or Agents Mandated by the Protocol

SKYSONA is an autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector that encodes an *ABCD1* complementary deoxyribonucleic acid (cDNA) for human ALDP, suspended in cryopreservation solution. Each drug product was prepared individually for each subject using their autologous cells and labelled to identify the relevant subject number. More than one drug product lot could have been required to reach the minimum cell dose, however each subject in Study ALD-102 required only one lot of drug product. On Study Day 1, subjects received intravenous (IV) administration of SKYSONA as a single dose of $\geq 5.0 \times 10^6$ CD34+ cells/kg.

6.1.6 Sites and Centers

The study involved eight clinical sites in Argentina, Australia, France, Germany, United Kingdom (UK), and US and three of them are in the US.

6.1.7 Surveillance/Monitoring

A DMC composed of members with appropriate scientific and medical expertise to monitor the study was convened before the study started. The DMC reviewed safety and neutrophil engraftment data of Subject 1 prior to proceeding with the transplant of Subject 2; and data of Subject 2 prior to allowing the transplant of subsequent subjects. The DMC had the right to recommend halting the study at any time due to concerns for the safety of the subjects.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects who were alive and had none of the defined MFDs at Month 24 Visit (Month 24 MFD-free survival). MFDs were defined as (1) loss of communication, (2) cortical blindness, (3) tube feeding, (4) total incontinence, (5) wheelchair dependence, and (6) complete loss of voluntary movement.

For success, the lower bound of the 2-sided 95% exact CI of Month 24 MFD-free survival for the cohort had to exceed a clinical benchmark of 50%. This clinical benchmark was derived from the natural history study ALD-101. In this study, 4 of

19 GdE+ untreated subjects remained MFD-free and alive within 2 years of their first GdE+ MRI. Thus, the Month 24 MFD-free survival rate in untreated GdE+ subjects was 21% (95% CI: 6.1%, 45.6%).

Reviewer Comment:

1. *In the IND meeting (CRMTS 11016) that took place on February 22, 2018, the applicant was seeking comments from the Agency about whether the selected benchmark value (50%) is adequate to establish a clinical meaningful comparison for the primary efficacy endpoint. FDA answered that using this approach, data from both the ALD-102 and ALD-103 (will be discussed in Section 6.2) studies could in principle support the conclusion that treatments are superior to those of untreated patients. However, the validity of this approach should depend on demonstration that baseline clinical and demographic data (as well as background care) are sufficiently similar.*
2. *There are two concerns raised by the clinical reviewer:*
 - a. *The population in Study ALD-101 had higher-risk baseline characteristics, making it not comparable at baseline to subjects treated with SKYSONA in Study ALD-102.*
 - b. *The benchmark was not determined a priori as the Applicant had already collected 24 months of data on 17 (53%) subjects treated with SKYSONA in Study ALD-102.*

Secondary Efficacy Endpoints

The secondary efficacy endpoints included the following:

- MFD-free survival over the study period
- Overall survival (OS)
- Proportion of subjects who demonstrated resolution of gadolinium positivity on MRI (GdE-) at the Month 24 Visit
- Time to sustained resolution of gadolinium positivity on MRI (GdE-). Sustained is defined as gadolinium resolution without a subsequent evaluation indicating gadolinium positivity
- Change in total NFS from Baseline to Month 24

Primary Safety Endpoint

The primary safety endpoint was the proportion of subjects who experienced either acute (\geq Grade II) or chronic GVHD by Month 24.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size

The sample size for this study was not determined by a formal statistical method due to the rarity, severity, and rapidly progressive nature of CALD. Initially, in accordance with the advice from the FDA (CRMS # 9978, 17 November 2015), it was agreed that analysis of the primary efficacy endpoint in 17 subjects would be the basis for determining success of the study.

Analysis Populations

The Intent-to-treat (ITT) Population:

The ITT population consisted of subjects who initiated any study procedures, beginning with mobilization by G-CSF.

The Transplant Population (TP):

The TP consisted of subjects who received SKYSONA. This population was to be used for the analyses of all efficacy endpoints and some of the safety endpoints, including the primary safety endpoint.

Primary Efficacy Endpoint Analysis

For the primary analysis, the number and percent of subjects who achieved Month 24 MFD-free survival are presented and with the 2-sided exact 95% CI from Clopper-Pearson method for the TP population. The success criterion was defined as the lower bound of the 95% CI of Month 24 MFD-free survival is > 50%.

Secondary Efficacy Endpoint Analysis

- For categorical variables, the exact 2-sided 95% CI from Clopper- Pearson method was planned.
- For continuous variables, 2-sided 95% CI of the mean was planned.
- For time-to-event variables, the Kaplan-Meier method was planned.

Missing data

There is no imputation plan for missing data. Subjects who discontinued prior to the Month 24 were to be considered treatment failures in the primary efficacy analysis.

Interim Analysis

No interim analyses were planned.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The summary of each population is presented in Table 2.

Table 2 Populations Enrolled

	Initial Cohort	Overall Cohort
ITT	17	32
TP	17	32

Source: Original BLA 125755; Module 5.3.5.2 CSR Study ALD-102 – Table 6.

6.1.10.1.1 Demographics

The subjects were all male as expected because CALD is an X-linked disease. Median (min, max) age at drug product infusion was 6 (4, 14) years of age. Fifteen (47%) of subjects were White, another 10 (31%) did not report race. The other baseline characteristics and demographic data in the TP population are described in Table 3 and Table 4, respectively.

Table 3 Baseline Characteristics, TP Population

	Initial Cohort (N=17)	Overall Cohort (N=32)
Age at informed consent (years)		
Median	6	6
Min, Max	4, 13	3,13
Age at diagnosis of CALD (years)		
Median	6	6
Min, Max	3,13	1,13
Age at SKYSONA infusion (years)		
Median	6	6
Min, Max	4,14	4,14
Weight at screening (kg)		
Median	25.1	25.0
Min, Max	16.3, 44.3	14.3, 54.0
Height at screening (m)		
Median	1.187	1.178
Min, Max	1.020, 1.511	0.975, 1.553
Body mass index at screening (kg/m²)		
Median	18.1	17.9
Min, Max	12.5, 22.9	12.5, 24.6

Source: Original BLA 125755; Module 5.3.5.2 CSR Study ALD-102 – Table 8.

Table 4 Demographics, TP Population

	Initial Cohort (N=17)	Overall Cohort (N=32)
Age at informed consent category (years), n (%)		
≥ 2 to < 6	7 (41)	14 (44)
≥ 6 to < 12	9 (53)	17 (53)
≥ 12 to < 18	1 (6)	1 (3)
Sex, n (%)		
Male	17 (100)	32 (100)
Race, n (%)		
White	9 (53)	15 (47)
Black or African American	0	1 (3)
Asian	0	1 (3)
Other	3 (18)	5 (16)
Not Reported	5 (29)	10 (31)
Ethnicity, n (%)		
Hispanic	7 (41)	12 (38)
Non-Hispanic	8 (47)	17 (53)
Not Reported	2 (12)	3 (9)

Source: Original BLA 125755; Module 5.3.5.2 CSR Study ALD-102 – Table 8.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The baseline NFS was 0 in 31/32 (96.9%). Other summary statistics for medical characteristics are presented in Table 5.

Table 5 Medical/Behavioral Characterization, TP Population

	Initial Cohort (N=17)	Overall Cohort (N=32)
Family history, n (%)	11 (64.7)	19 (59.4)
Method of diagnosis, n (%)		
VLCFA Testing	16 (94.1)	29 (90.6)
ABCD1 Genotyping	10 (58.8)	21 (65.6)
MRI with Gadolinium Contrast	13 (76.5)	23 (71.9)
Signs and symptoms, n (%)		
Adrenal insufficiency	14 (82.4)	27 (84.4)
Seizures	0	1 (3.1)
Gait disturbance	1 (5.9)	1 (3.1)
Other	2 (11.8)	3 (9.4)
Baseline Neurologic Function Score		
0	17 (100.0)	31 (96.9)
1	0	1 (3.1)
Baseline Loes score		
Median	2	2
Min, Max	1.0, 7.5	1.0, 9.0
Baseline Loes pattern^a, n (%)		
Pattern 3 and/or 4 only	2 (11.8)	3 (9.4)
Patterns include 1, 2, 5 ^b	15 (88.2)	29 (90.6)
Time from informed consent to drug infusion (days)		
Median	67	67
Min, Max	58, 89	58, 89
Time from diagnosis of CALD to drug infusion (months)		
Median	5.8	5.8
Min, Max	2.5, 17.2	2.5, 26.8

^a Loes Patterns: 1 = Parietal-occipital; 2 = Frontal; 3 = Pyramidal tracts involvement; 4 = Cerebellar white matter involvement; 5 = Combined parieto-occipital and frontal white matter involvement.

^b Patterns include 1,2,5. Subjects with this pattern may also have 3, 4 or other.

Source: Original BLA 125755; Module 5.3.5.2 CSR Study ALD-102 – Table 9.

6.1.10.1.3 Subject Disposition

Of the 35 subjects who were screened, 32 were eligible for treatment and enrolled. Of the 32 eligible subjects, 17 were in “Initial Cohort” and 15 subjects were in additional cohort. In the Overall Cohort, 29 subjects completed the study and 3 subjects discontinued. Of the 29 subjects, 15 subjects were in “Initial Cohort” and 14 are in additional cohort. The reasons for discontinuation were: Subject (b) (6) in

“Initial Cohort” died on-study at approximately 22 months after drug product infusion; and Subjects (b) (6) (“Initial Cohort”) and (b) (6) (“Additional Cohort”) discontinued to receive allo-HSCT approximately 13 months and 16 months after drug product infusion, respectively.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The summary of primary endpoint analysis is provided in Table 6. In the Overall Cohort, 29 (90.6%) of subjects infused with SKYSONA met Month 24 MFD-free survival (95% CI: 75%, 98%).

Table 6 Summary of Primary Endpoint Analysis, TP Population

	Initial Cohort (N=17)	Overall Cohort (N=32)
Month 24 evaluable subjects	17	32
Month 24 MFD-free survival		
n (%)	15 (88.2)	29 (90.6)
Exact 95% CI	(63.6, 98.5)	(75.0, 98.0)

Source: Original BLA 125755; Module 5.3.5.2 CSR Study ALD-102 – Table 20.

Reviewer Comment:

During the review, the chemistry, manufacturing and control (CMC) reviewer was not able to establish comparability of products for six subjects in this study, so these subjects were excluded from the efficacy analysis. After removing the 6 subjects, 23 of the 26 evaluable subjects (88.5%) met Month 24 MFD-free survival (95% CI: 69.8%, 97.6%).

6.1.11.2 Analyses of Secondary Endpoints

For MFD-free at 24 months after SKYSONA infusion, three events had occurred between 279 and 493 days after drug product infusion. The Kaplan-Meier estimated MFD-free survival rate at 24 months after drug product infusion in the Overall Cohort was 90.6% (95% CI: 73.7%, 96.9%). The restricted mean MFD-free survival time within the 24-month period was estimated to be 23 months.

For overall survival rate at 24 months after drug product infusion, one death had occurred after drug product infusion. The Kaplan-Meier estimated overall survival rate at 24 months after drug product infusion in the Overall Cohort was 96.7% (95% CI: 78.6%, 99.5%). The restricted mean MFD-free survival time within the 24-month period was estimated to be 23.9 months.

6.1.11.3 Subpopulation Analyses

Subpopulation analyses by sex and age were not performed because all subjects were male and aged between 3 and 13 years of age. In addition, because there were too few subjects in relevant subgroups in the study to assess by race, the subpopulation analysis by race was not performed as well.

6.1.12 Safety Analyses

6.1.12.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects who experienced either acute (\geq Grade II) or chronic GVHD by Month 24. No subjects experienced GVHD, so the proportion of subjects with either acute (\geq Grade II) or chronic GVHD was 0/32 subjects (exact 95% CI: 0.0%, 10.9%).

6.1.12.3 Deaths

One death was reported during the study. Please refer to Section 6.1.10.1.3. An additional death, Subject (b) (6), occurred after receiving allo-HSCT off study (on Day 495 after the first drug infusion). This event was not included in the clinical database.

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

Twenty-one subjects (including the subject who died) experienced 44 SAEs during the study. The majority of events were treatment emergent, but two events of Adrenal insufficiency and one event of Vascular device infection and Procedural pain occurred prior to SKYSONA infusion. One SAE, an event of Cystitis viral (Grade 3), was assessed as possibly related to SKYSONA. All other SAEs were assessed as not related or unlikely related to SKYSONA.

Twenty subjects experienced treatment-emergent SAEs. Treatment-emergent SAEs that occurred in more than 1 subject included Febrile neutropenia (8/32, 25.0%), Pyrexia (6/32, 18.8%), and Vascular device infection (2/32, 6.3%). All SAEs had resolved at the time of the last subject last visit, with the exception of events in Subject (b) (6) that were ongoing at the time of his death.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no treatment-emergent events of interest reported. No subjects experienced malignancy or HIV infection.

6.2 Study ALD-103 (April 10, 2015-December 6, 2019)

6.2.1 Objectives

- Evaluate the safety of allo-HSCT in subjects with CALD
- Evaluate the efficacy of allo-HSCT in subjects with CALD

6.2.2 Design Overview

ALD-103 was a multi-site, global, prospective, and retrospective data collection study designed to evaluate outcomes of allo-HSCT in male subjects \leq 17 years of age with CALD. Three cohorts were included: (1) Retrospective Cohort (Died Before Study Enrollment). (2) Partial Retrospective/Prospective Cohort (Enrollment Before Month 24 Study Visit). (3) Prospective Cohort (Enrollment Before allo-HSCT). Retrospective subjects were \leq 17 years of age at the time of treatment; prospective subjects were \leq 17 years of age at the time of consent. This study did not involve the use of an investigational drug or medicinal product. Suitability for allo-HSCT and the choice of the treatment protocol utilized for these subjects were determined by the subjects' treating physicians per their institutional policies/protocols and other local treatment guidelines.

6.2.3 Population

Key eligibility criteria included: Male and ≤ 17 years of age at the time of treatment, for retrospective and partial prospective/retrospective subjects, or at the time of parental/guardian consent and, where appropriate, subject assent, for prospective subjects, and had a confirmed diagnosis of CALD as defined by abnormal VLCFA profile and cerebral lesion on brain MRI.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Not applicable. This was an observational, data collection study.

6.2.6 Sites and Centers

The study involved 18 clinical sites in Argentina, Italy, France, Germany, UK, Netherlands, Canada, Spain, and US and seven of them are in the US.

6.2.8 Endpoints and Criteria for Study Success

Efficacy Endpoints:

- Proportion of MFDs (defined as any of the following: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement)
- Change from Baseline in Loes score
- Change from Baseline in NFS
- Frequency and timing of resolution of gadolinium enhancement on MRI, if applicable
- MFD-free survival
- Overall survival

Reviewer Comment:

This study was designed to collect data on CALD patients eligible for allo-HSCT, using a study design consistent with that described in Study ALD-102, so there is no specific primary efficacy endpoint for this study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size

No formal sample size calculations have been performed.

Analysis Populations

The Intent-to-treat (ITT) population:

The ITT population consisted of subjects who initiated conditioning that including retrospective and partially retrospective subjects who were enrolled after allo-HSCT.

The Transplant Population (TP):

The TP consisted of subjects who received allo-HSCT. This population will be used for the analyses of all efficacy and safety endpoints.

Strictly ALD-102-Eligible Transplant Population (TPES):

For the efficacy comparison with SKYSONA, an analysis population, TPES, was defined as all subjects who received an allo-HSCT infusion and at Baseline had NFS ≤ 1 , Loes score ≥ 0.5 and ≤ 9 , and GdE+.

Efficacy Endpoint Analysis

- For categorical variables, the number and percentage of subjects were presented, along with the exact 2-sided 95% CI using the Clopper-Pearson method.
- For continuous variables (not time-to-event), the number of observations, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum values were presented, along with 2-sided 95% CIs of the mean.
- For time-to-event variables, the Kaplan-Meier was used.

Missing data

There is no imputation plan for missing data.

Interim Analysis

No interim analyses were planned.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The summary of each population is presented in Table 7.

Table 7 Populations Enrolled

	Overall
ITT	59
TP	59
TPES	27

Source: Adapted from Original BLA 125755; Module 5.3.5.4 CSR Study ALD-103 – Table 8.

6.2.10.1.1 Demographics

At the time of first allo-HSCT, the median (min, max) age of subjects in the TP was 8.0 (2, 14) years old and most subjects (51/59, 86.4%) were White (Table 8). The other key demographic data in the TP population are described in Table 8.

Table 8 Summary of Key Demographics (TP)

	TP (N=59)
Age at first allo-HSC infusion (years)	
n	59
Median	8
Min, Max	2,14
Age at first allo-HSC infusion (years), n (%)	
< 2	0
≥ 2 to < 6	7 (11.9)
≥ 6 to < 12	49 (83.1)
≥ 12	3 (5.1)
Age at diagnosis of CALD (years)	
n	59
Median	7
Min, Max	0,14
Race, n (%)	
White	51 (86.4)
Black or African American	2 (3.4)
Asian	1 (1.7)
Other	3 (5.1)
Not reported	2 (3.4)
Ethnicity, n (%)	
Hispanic	12 (20.3)
Non-Hispanic	32 (54.2)
Not reported	15 (25.4)

Source: Original BLA 125755; Module 5.3.5.4 CSR Study ALD-103 – Table 12.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Some key baseline disease characteristics are summarized for the TP in Table 9.

Table 9 Summary of Baseline Characteristics (TP)

	TP (N=59)
Method of diagnosis, n (%)	
VLCFA testing	54 (91.5)
ABCD1 genotyping	39 (66.1)
MRI with gadolinium contrast	44 (74.6)
Family history, n (%)	31 (52.5)
Baseline neurologic function score, n (%)	
0	43 (72.9)
1	7 (11.9)
> 1 and ≤ 4	4 (6.8)
> 4	1 (1.7)
Missing	4 (6.8)
Signs and symptoms, n (%)	
Adrenal insufficiency	44 (74.6)
Seizures	1 (1.7)
Hyperactivity	6 (10.2)
Gait disturbance	5 (8.5)
Vision problems	3 (5.1)
Hearing problems	7 (11.9)
Swallowing difficulty	0
Other	17 (28.8)
Baseline Loes score	
n	56
Median	4.25
Min, Max	0.0, 18.5
Baseline Loes pattern^a, n (%)	
1	36 (61.0)
2	4 (6.8)
3	4 (6.8)
4	1 (1.7)
5	3 (5.1)
Other	7 (11.9)
5, Other	1 (1.7)
Missing	3 (5.1)
Baseline GdE status, n (%)	
GdE+	39 (66.1)
GdE-	13 (22.0)
Missing	7 (11.9)

^a Loes Patterns: 1 = Parietal-occipital; 2 = Frontal; 3 = Pyramidal tracts involvement; 4 = Cerebellar white matter involvement; 5 = Combined parieto-occipital and frontal white matter involvement.

Source: Original BLA 125755; Module 5.3.5.4 CSR Study ALD-103 – Table 12.

6.2.10.1.3 Subject Disposition

59 subjects were enrolled in Study ALD-103. Of these 59 subjects, 7 subjects were in Retrospective Cohort, 26 subjects were in Partial Retrospective / Prospective Cohort, and 26 subjects were in Prospective Cohort. After receiving the first allo-HSCT treatment, 12 subjects completed Month 48 visit, 12 subjects died, and 9 subjects received the second allo-HSCT treatment. Of these nine subjects, two subjects completed Month 48 visit, three subjects were dead, and one received the third allo-HSCT treatment.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of some key endpoint(s)

Evaluable subjects who completed the Month 24 Visit in the first allo-HSCT Period were included in the analyses. Eighteen subjects were evaluable in the TPES population and 44 were evaluable in the TP population. The results for some key efficacy parameters are summarized in Table 10.

Table 10 Key Efficacy Results (TP and TPES)

	TPES	TP
Evaluable subjects ^a	18	44
Proportion of Month 24 MFD-free survival		
n (%)	14 (77.8)	28 (63.6)
Exact 95% CI	(52.4, 93.6)	(47.8, 77.6)
Kaplan-Meier estimated overall Month 24 MFD-free survival rate^b		
% (95% CI)	75.9 (53.4, 88.6)	64.8 (50.8, 75.8)
Kaplan-Meier estimated Month 24 overall survival rate		
% (95% CI)	86.2 (62.6, 95.4)	75.8 (61.7, 85.2)
Sustained resolution of GdE+ by Month 24^c		
Evaluable subjects 13 24		
n (%)	11 (84.6)	18 (75.0)
Exact 95% CI	(54.6, 98.1)	(53.3, 90.2)
NFS at Month 24, n (%)		
Evaluable subjects	12	26
0	11 (91.7)	17 (65.4)
1	1 (8.3)	6 (23.1)
> 1 and ≤ 4	0	2 (7.7)
> 4	0	1 (3.8)
Loes Score at Month 24		
Evaluable subjects 13 26		
Median (min, max)	2 (0, 15)	2 (0, 17)

^a A subject is Month 24 evaluable if he satisfies any of the following: completed the Month 24 Visit in the first allo-HSCT Period within the protocol defined Visit window; was followed for at least 730 days; or discontinued study for reasons other than study termination or was lost to follow-up, and would have been followed for at least 730 days at data cut if still in study.

^b Deaths, MFDs, and second allo-HSC infusions are considered events. Subjects who did not experience any event are censored at the time of last contact.

^c Sustained GdE+ is defined as having at least 2 GdE- results by MRI without a subsequent evaluation indicating gadolinium positivity.

Source: Original BLA 125755; Module 5.3.5.4 CSR Study ALD-103 – Table 32.

6.2.12 Safety Analyses

6.2.12.3 Deaths

Fifteen subjects (15/59, 25.4% subjects) died in Study ALD-103, including 12 deaths during the first allo-HSCT Period and 3 deaths during the second allo-HSCT Period. Deaths included 9 events of TRM.

6.2.12.4 Nonfatal Serious Adverse Events (SAE)

Forty-three (72.9%) subjects experienced at least 1 SAE and all reported SAEs were Grade 3 or higher. The most common SAEs category was Infections and infestations (22/59 [37.3%] subjects).

Of 59 subjects in the TP, 38 (64.4%) subjects experienced treatment emergent Adverse Events (TEAEs) in Blood and lymphatic system disorders. 35 (59.3%) subjects experienced TEAE in Infection and infestations.

6.2.12.5 Adverse Events of Special Interest (AESI)

No subjects experienced HIV infection or malignancies.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Integrated Analysis with ALD-102 and ALD-103

7.1.1 Methods of Integration

The following criteria were applied to select the eligible subjects from ALD-103 to be compared with the subjects in ALD-102.

- NFS \leq 1 at Baseline
- 0.5 \leq Loes score \leq 9 at Baseline
- GdE+ at Baseline

Of the 59 subjects, 27 subjects (TPES-103) were selected from ALD-103 to do the comparison with ALD-102.

7.1.2 Demographics and Baseline Characteristics

Demographics were compared between ALD-102 and TPES-103. Median age at first HSC infusion were similar. ALD-102 subjects tended to be slightly younger at time of HSC infusion than TPES-103 subjects. For ALD-102 subjects, the median time in months from diagnosis to treatment is slightly longer than TPES-103 subjects. Other key demographics and baseline characteristics are presented in Table 11 and Table 12 respectively.

Table 11 Demographics

	ALD-102 (N=32)	TPES-103 (N=27)
Age at first HSC infusion (years)		
n	32	27
Median	6	8
Min, Max	4, 14	5, 11
Age at first HSC infusion category, n (%)		
≥2 to <6	14 (43.8)	3 (11.1)
≥6 to <12	17 (53.1)	24 (88.9)
≥12 to <18	1 (3.1)	0
≥18	0	0
Age at CALD diagnosis (years)		
n	32	27
Median	6	7
Min, Max	1, 13	0, 11
Race, n (%)		
White	15 (47)	25 (93)
Black or African American	1 (3)	0
Asian	1 (3)	0
Other	5 (16)	2 (7)
Not provided/ unknown/ not reported	10 (31)	0
Ethnicity, n (%)		
Hispanic	12 (38)	7 (26)
Non-Hispanic	17 (53)	11 (41)
Not provided/ Unknown/ Not reported	3 (9)	9 (33)

Source: Original BLA 125755; Module 2.7.3 Summary of Clinical Efficacy – Table 5.

Table 12 Baseline Disease Characteristics

	ALD-102 (N=32)	TPES-103 (N=27)
Time from CALD diagnosis to treatment (months)		
n	32	27
Mean (SD)	7.1 (5.07)	12.6 (21.98)
Median	5.8 (3.7, 8.5)	3.5 (2.0, 9.2)
Min, Max	2.5, 26.8	0.6, 78.0
Baseline NFS, n (%)		
0	31 (96.9)	26 (96.3)
1	1 (3.1)	1 (3.7)
> 1 to ≤ 4	0	0
> 4	0	0
Baseline Loes score		
n	32	27
Median	2	3
Min, Max	1, 9	1, 9

Source: Original BLA 125755; Module 2.7.3 Summary of Clinical Efficacy – Table 6.

7.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for the integrated analysis was the proportion of subjects who were alive and had none of the defined MFDs at Month 24 Visit. Meanwhile, a hazard ratio of ALD-102 vs. TPES-103 was provided based on Cox regression model. Of the 27 TPES subjects, 18 subjects were evaluable for this efficacy analysis. The hazard ratio was 0.229 (95% CI: 0.060, 0.868) that indicates that SKYSONA has lower risk of MFD than allo-HSCT. The summary of analysis is provided in Table 13.

Table 13 Summary of Primary Endpoint Analysis

	ALD-102	TPES-103
Number of subjects evaluable^a	32	18
Month 24 MFD-free survival		
n (%)	29 (90.6)	14 (77.8)
Exact 95% CI	75.0, 98.0	52.4, 93.6
Hazard Ratio (95% CI)^b		0.229 (0.060, 0.868)

^a Evaluable subjects are defined as subjects who have been followed for 24 months or have discontinued from the study but would have been followed for 24 months if still on the study.

^b The hazard ratio is based on Cox regression model.

Source: Original BLA 125755; Module 2.7.3 Summary of Clinical Efficacy – Table 7 & 9.

Reviewer Comment:

After discussing with the clinical team, the concerns for the comparability between these two studies are as follows:

- 1. The principal comparator allo-HSCT data in Study ALD-103 were partially collected retrospectively that could introduce bias.*
- 2. The subjects in ALD-103 were somewhat older and had higher Loes scores than the ALD-102 population at baseline, raising concerns about comparability.*

When conducting the analysis with Loes score and age at diagnosis as covariates in the Cox model, the Hazard Ratio (95% CI) becomes 0.218 (0.04, 0.903). I also conducted a few additional analyses with different covariates and the results are similar.

7.1.5 Analysis of Overall Survival

The key secondary efficacy endpoint for the integrated analysis was overall survival. A Cox regression model was applied. Twenty-seven (27) TPES subjects from Study 103 were used in this analysis. The hazard ratio was 0.119 (95% CI :0.014, 1.020) that indicates that SKYSONA has lower risk of death than allo-HSCT. This estimate is likely unstable, however, due to the small number of events. The summary of analysis is provided in Table 14.

Table 14 Summary of Secondary Endpoint Analysis

	ALD-102 (N=32)	TPES-103 (N=27)
Events, n (%)		
Death	1 (3.1)	5 (18.5)
Overall Survival (months)		
Median (95% CI)	- (-, -)	- (33.1, -)
Hazard Ratio (95% CI)^a		0.119 (0.014, 1.020)

^a The hazard ratio is based on Cox regression model.

Source: Original BLA 125755; Module 2.7.3 Summary of Clinical Efficacy – Table 12.

Reviewer Comment:

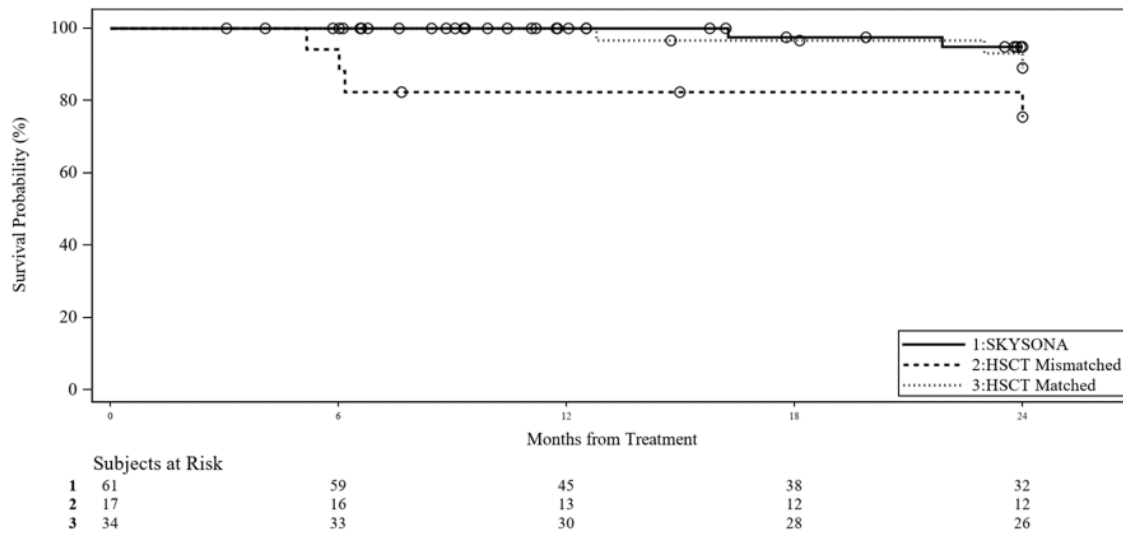
I also conducted additional analyses for the overall survival endpoint. With Loes score and age at diagnose as covariates in the Cox model, the HR (95% CI) becomes 0.072 (0.006, 0.876). This estimate is also likely unstable due to the small number of events. I also conducted a few additional analyses with different covariates and the results are similar.

7.2 Integrated Analysis with ALD-102 and ALD-104 vs. ALD-103 and ALD 101

In labeling meetings between FDA and the applicant, additional information related to the efficacy of SKYSONA was requested by the clinical team to combine the subjects in ALD-102 with another open-label, single-arm, ongoing study (ALD-104) that included a total of 35 subjects with early active CALD treated with SKYSONA. Referring to the discussion in Section 6.1.11.1, 26 subjects were included from ALD-102. With the combined efficacy population (N=61), the Kaplan-Meier estimated 24-month overall survival rate was 95% (95% CI: 81%, 99%). Please refer to the clinical review memo for more details.

Another comparison was requested by the clinical team to assess the difference among SKYSONA subjects, allo-HSCT from a HLA-mismatched donor (N=17), and allo-HSCT from a HLA-matched donor (N=34) subjects in overall survival in the first 24 months following treatment. The allo-HSCT subjects were from ALD-103 and a natural history study ALD-101. Figure 1 presents the results. Please refer to the clinical review memo for more details.

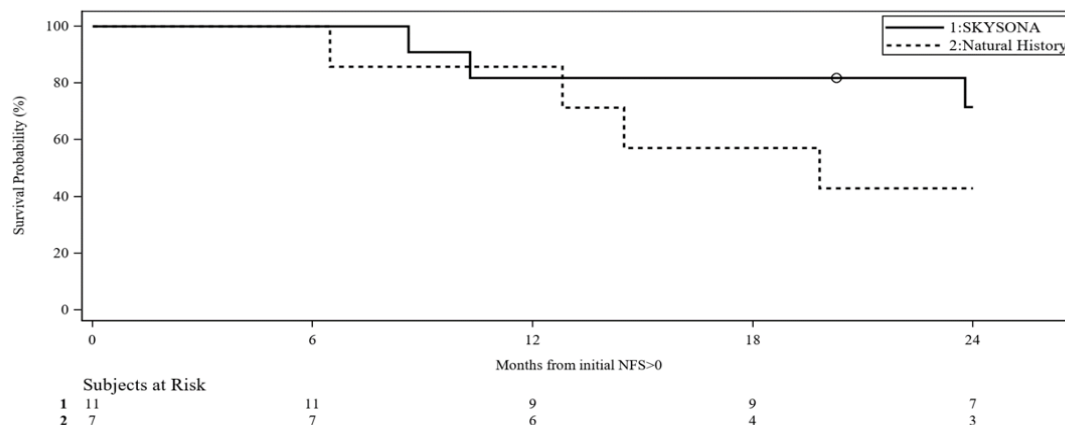
Figure 1 Kaplan-Meier Curve of Overall Survival Between SKYSONA and allo-HSCT Treated Populations



7.3 Integrated Analysis with ALD-102 and ALD-101

Another efficacy comparison requested by the clinical team in the labeling meetings was MFD-free survival from onset of symptoms ($NFS \geq 1$). To be included in the analysis, subjects had to have $NFS = 1$ at baseline or $NFS = 0$ at baseline and have developed symptoms ($NFS \geq 1$) during the course of follow-up in the study and been followed at least 24 months after initial $NFS \geq 1$ or have had an event (MFD or death). Eleven subjects from ALD-102 were selected to compare with 7 subjects from the natural history study ALD-101. Figure 2 presents the Kaplan-Meier estimated MFD-free survival at Month 24 from time of first $NFS \geq 1$. Please refer to the clinical review memo for more details.

Figure 2 Kaplan-Meier Curve of MFD-free Survival in Symptomatic Patients of SKYSONA, and Natural History Populations



Reviewer Comment:

There are clear statistical limitations to both of the integrated analyses in sections 7.2 and 7.3, including their post-hoc nature, and the use of subsets of subjects from non-randomized trials and historical control data with limited sample size. Therefore, no inferential claims are being made, and the results of these analyses will be used only descriptively in product labeling.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

SKYSONA is a gene therapy indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral CALD. The primary evidence to support the safety and effectiveness of the product is based on the final analysis results of the pivotal study ALD-102.

For efficacy assessment, the primary efficacy endpoint was the proportion of Month 24 MFD-free survival. Thirty-two subjects with CALD were enrolled and treated with SKYSONA. All were male and aged between 3 and 13 years. Twenty-nine out of 32 (90.6%) subjects achieved Month 24 MFD-free survival (exact 95% CI: 75%, 98%). The lower bound of the exact 95% CI exceeded a clinical benchmark of 50%. The overall survival rate at 24 months after drug product infusion was 96.7% (95% CI: 78.6%, 99.5%).

In terms of safety, the primary safety endpoint was the proportion of subjects who experience either acute (\geq Grade II) or chronic GVHD by Month 24. No subjects experienced acute or chronic GVHD by Month 24. One death was reported at approximately 22 months after drug product infusion. There were no treatment-emergent events of interest reported. No subjects experienced malignancy or HIV infection.

One integrated efficacy analysis was performed by incorporating data from an additional study: Study ALD-103, a hybrid prospective-retrospective observational study in boys who were treated more recently with allo-HSCT (between 2013 and 2019).

The integrated analysis was to compare ALD-102 and ALD-103 by using a Cox regression model. For MFD-free survival, the hazard ratio (ALD-102 vs. ALD-103) was 0.229 and 95% CI was (0.060, 0.868). For Overall Survival, the hazard ratio was 0.119 and 95% CI was (0.014, 1.020).

10.2 Conclusions and Recommendations

The primary efficacy analysis of study ALD-102 shows that the success criterion was met. In the integrated analyses, the comparisons between the ALD-102 and ALD-103 based on the MFD-free survival and overall survival also support the effectiveness of SKYSONA.