



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

PHARMACOVIGILANCE PLAN REVIEW FOR ORIGINAL BLA

From: Alisha Thomas, MD, MPH
Medical Officer, Pharmacovigilance Branch 3 (PB3)
Division of Pharmacovigilance (DPV)
Office of Biostatistics and Pharmacovigilance (OBPV),
CBER, FDA

To: Anna Kwilas, PhD
Chair of the Review Committee
Office of Tissues and Therapies

Through: Manette Niu, MD, MPH
Acting Branch Chief, PB3
DPV, OBPV, CBER, FDA

Meghna Alimchandani, MD
Deputy Director, DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Applicant: bluebirdbio, Inc

Product: Skysona (elivaldogene autotemcel)

Application Number: BLA/ STN 125755\0

Proposed Indication: Skysona is indicated for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have an available and willing human leukocyte antigen-matched sibling hematopoietic stem cell donor

Submission Date: October 18, 2021

Action Due Date: September 16, 2022

1 Objective

The sponsor, bluebird bio, Inc., submitted an original BLA 125755/0 seeking licensure for a novel gene therapy product, Skysona (elivaldogene autotemcel), for the proposed treatment of cerebral adrenoleukodystrophy. Based on the safety profile of Skysona (elivaldogene autotemcel), this review assesses the adequacy of the pharmacovigilance plan proposed by the sponsor for post-marketing safety monitoring, and to identify potential safety concerns that may require additional postmarketing safety surveillance, studies, or other pharmacovigilance activities, should this product be approved.

2 Product Information

Background

Adrenoleukodystrophy (ALD) is a rare, X-linked, metabolic disease in which dysfunction or lack of the ALD protein (ALDP) is caused by mutations in the ATP-binding cassette, subfamily D member 1 (ABCD1) gene.¹ ALDP is a peroxisomal transport protein involved in the transport and degradation of very long chain fatty acids VLCFAs.² Defective function of ALDP leads to the accumulation of VLCFAs, which occurs in plasma and all tissue types but most prominently in the adrenal cortex 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.^{3,4} The cerebral form (CALD) develops in approximately 40% of boys with ALD, and there are no major differences in incidence rates of ALD in countries around the world.^{5,6}

CALD is the most severe form of ALD, affecting approximately 40% of boys with ALD, typically during childhood. CALD is characterized by rapidly progressive cerebral demyelination leading to progressive, irreversible loss of neurologic function and death.² If untreated, nearly half of patients with CALD die within 5 years of symptom onset.^{7,8} Monitoring of white matter involvement by magnetic resonance imaging (MRI) is used to objectively determine the onset of CALD signs and identify patients at high risk for rapid progression. Disease progression and neurologic decline in patients with CALD have been documented in natural history studies; patients experience critical deficits across multiple neurological domains within a short period after onset of clinical symptoms.⁹ In children diagnosed with CALD, learning and behavioral problems are often observed at the time of disease onset in early- to mid-childhood (median age 7 years) with progressive gait, vision, and hearing impairments within 6 to 15 months of symptom onset.⁹ This is typically followed by rapid neurologic functional decline (CSR ALD-101).²

There are no approved treatments for CALD in the US. Allogeneic hematopoietic stem cell transplant (allo-HSCT) can stabilize deterioration of neurological function, with the best outcomes observed in patients treated at the early stages of cerebral involvement. The goal of treatment for CALD is to stabilize neurologic function by delaying or, ideally, preventing the development of impairments which compromise the ability to function independently. There is currently no treatment approved for CALD in the US. Initially, the only treatment available was supportive care. Later, in an attempt to modify the body's production of VLCFAs, a dietary mixture of 4:1 glyceryl trioleate and glyceryl trierucate was developed. This mixture, called Lorenzo's oil, was developed and tested

clinically, but ultimately was shown to have minimal effect in stabilizing neurologic disease.¹⁰⁻¹² Allo-HSCT was developed as a therapeutic option with the best outcomes observed if it is performed at the early stages of cerebral involvement^{2,13,14} and using a donation from a sibling who is HLA-matched to the patient (a matched sibling donor [MSD]). Allo-HSCT is thought to enable migration of donor-derived cells into the brain, which include donor-derived macrophages and/or microglial cells that express functional ALDP and function normally, thereby stopping further demyelination.¹⁵ Early identification and intervention relative to CALD onset are necessary for favorable outcomes. In studies of allo-HSCT for CALD, the 5-year overall survival rates ranged from 89% to 94% for early disease, compared with 45% to 90% for advanced disease^{8,13,16} (CSR ALD-101). Disease stage is assessed by a clinical neurological examination and brain MRI assessments, and early disease is often considered to include a neurologic function score (NFS) of ≤ 1 and a Loes score of ≥ 0.5 and ≤ 9 . The Loes score is a 34-point imaging-based severity scale based on the location and extent of central nervous system involvement and presence of either focal or global atrophy. The neurologic function score (NFS) is a 25-point composite scale that assess functional disabilities.¹⁷

Although allo-HSCT has been reported to stabilize neurologic disease, the full effects of transplant are not immediately apparent; demyelinating lesions usually continue to progress for 12 to 18 months post-transplant with corresponding clinical progression observed¹⁹⁻²². Treatment with allo-HSCT carries several immunologic risks, which necessitate immunosuppressive therapy for several months and sometimes for years after transplant, depending on the degree of incompatibility between the host and donor cells.²³ These risks are decreased in patients who receive cells from a HLA-MSD (CSR ALD-101), but fewer than 30% of patients have an available MSD¹³. These risks can be avoided by using eli-cel, which uses autologous cells. Graft versus Host Disease (GVHD), a severe autoimmune response in which donor immune cells react to the patient's tissues, is the most serious complication of allo-HSCT, because it is not only life-threatening, but also the principal reason of a long-lasting poor quality of life. GVHD can be either acute (usually within the first 100 days post-transplant) or chronic (occurring after 100 days).²⁴ The need for immunosuppression to prevent or treat GVHD following allo-HSCT is associated with a prolonged continuous risk of opportunistic infections as well as additional serious side effects.²⁵ Death due to transplant-related mortality (TRM) is another risk of allo-HSCT, which may be caused by GVHD, infection, organ toxicity, or other causes.²⁶ Malignancies have been observed in patients with inborn errors of metabolism after treatment with conditioning and allo-HSCT.²⁷ There is a high unmet medical need for efficacious therapies for CALD that have an improved safety profile compared to allo-HSCT.

Product description

Skysona is a genetically modified autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with lentiviral vector (LVV) encoding ABCD1 complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein (ALDP).

Peripheral blood mononuclear cells are collected by apheresis from each patient following mobilization at one of the bluebird bio-Qualified Treatment Centers (QTCs). The autologous hematopoietic progenitor cells obtained by apheresis (HPC-A) are then shipped to the drug product manufacturing facility. Subsequent to a complete blood count and CD34+ cell enumeration, the HPC-A is enriched for cells expressing CD34 (CD34+) using the (b) (4). The CD34+ cell-enriched population is stimulated ex vivo with a mixture of recombinant human cytokines to facilitate cell growth. Next, the cells are transduced with Lenti-D LVV in the cytokine mixture with the addition of a transduction enhancer. After transduction, the cells are washed, (b) (4) in the cryopreservation solution, and filled in bags before (b) (4) freezing to -140°C. The drug product is stored at that temperature prior to disposition. Following lot release, the eli-cel drug product is maintained at ≤ -140°C through storage and shipping to the QTC until the day of infusion, when it is thawed and infused intravenously as a single dose without additional processing steps at the clinical site.

Proposed dosing regimen(s) and formulation(s)

Skysona is indicated for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have an available and willing HLA-matched sibling HSC donor. Skysona is an autologous CD34+ cell-enriched population containing HSCs transduced with lentiviral vector that encodes an ABCD1 cDNA for human ALDP, suspended in (b) (4) cryopreservation solution. The drug product is supplied as a sterile cell suspension for intravenous infusion in (b) (4) 20 ml Fluorinated-Ethylene-Propylene bags. The minimum recommended dose of Skysona is 5×10^6 CD34+ cells/kg patient weight.

3 Pertinent Regulatory History

Table 1: Pertinent Regulatory History (Table 16: Regulation Interaction Summary, Appendix 1, Clinical Overview)

Dates	Details
September 13, 2010	<p>Pre-IND meeting. FDA agreed with:</p> <ul style="list-style-type: none"> i) single trial in pediatric CALD patients, ii) proposed composite primary endpoints (provided clinically meaningfulness is demonstrated), iii) historical data analysis to identify alternative endpoints, iv) equal distribution of trial subjects among trial centers, and v) staggered enrolment to confirm engraftment. <p>FDA commented that the adequacy of the single trial design is dependent on historical control data and knowledge of disease natural history and recommended conducting a natural history study to support clinical development</p>
March 05, 2012	<p>A Type B pre-IND meeting was held. FDA agreed:</p> <ul style="list-style-type: none"> (i) that MRI scoring system is a valuable tool in assessing disease progression,

	(ii) with studying gadolinium enhancement (GdE), but not as a key secondary endpoint. FDA expressed concern on use of NFS at Month 24 as a proposed primary endpoint in Study ALD-102 and recommended defining a few rapidly changing, clinically meaningful endpoints. FDA commented on overall study design of Study ALD-102, its extension study, LTF-304, and the use of Study ALD-101 as a historical comparator to measure efficacy outcomes. FDA recommended a trial comparing survival against a benchmark derived from robust natural history data.
April 09, 2012	In the US, Skysona was granted an orphan drug designation for the treatment of ALD on 19 April 2012 (#12-3682)
March 27, 2013	Investigational New Drug Application 15433 for the use of Skysona in the treatment of CALD was filed to the FDA.
March 27, 2015	A Type C meeting was held to address quality issues
November 17, 2015	A Type C meeting was held. FDA agreed that: i) design of study LTF-304 is acceptable, ii) if the magnitude of the treatment effect is large, outcomes from ALD-102 compared with data derived from a newly designed study, ALD-103 (a retrospective/prospective observation study of allo-HSCT treatment), and ALD-101 may be sufficient to support a BLA. FDA commented that safety should be formally compared and should feature prominently in hierarchy of outcomes. Regarding fluctuations observed in subjects' Loes score, FDA recommended that two neuroradiologists score each MRI for each subject and made recommendations for statistical analyses (primary endpoint analysis of MFD-free survival at Month 24). FDA disagreed that enrolling subjects in an under-powered non-inferiority study would provide more compelling data than comparisons between Studies ALD-102, ALD-103 and ALD-101.
August 09, 2017	Skysona received a Rare Pediatric Disease Designation on 09 August 2017 (#RPD 2016-79),
February 22, 2018	A Type C meeting was held to discuss the approach to provide primary evidence of effectiveness to support a future BLA filing. FDA acknowledged the selected benchmark value to be clinically meaningful, provided recommendations on the proposed statistical analyses of the primary efficacy and safety endpoints, confirmed adequacy of proposed clinical package to support BLA, and confirmed eli-cel may meet the requirements for priority review.
May 21, 2018	Skysona was granted a Breakthrough Therapy Designation.
November 15, 2018	A Type B/CMC meeting was held. FDA agreed with statistical analyses plans for Studies ALD-102, LTF-304 and ALD-103. Recommendations were made on approach to further support MFD consistency assessment. Additional discussions took place on proposed pharmaceutical package for BLA. FDA requested that data from 2 supplemental DP PPQ runs at Lonza Pearland using patient material be included in the BLA, in addition to the planned healthy donor DP PPQ runs.

September 16, 2020	Type B meeting
January 15, 2021	The proposed CMC process performance qualification package discussion.
July 16, 2021	Skysona was approved for the treatment of patients less than 18 years of age with early CALD without an MSD by the European Commission.
July 22, 2021	bluebird Bio submitted the original Biologics License Application (BLA) package.
January 11, 2022	A major amendment was submitted providing a substantial amount of new data and a new analysis of studies.

4 Materials Reviewed

Materials reviewed in support of this assessment include:

Document	STN	Date Received
Pharmacovigilance Plan for elivaldogene autotemcel, Version 1.0	Module 1.16.1, 125755/0/002	18 Oct 2021
Annotated Draft Labeling Text	Module 1.14.1.2, 125755/0/002)	18 Oct 2021
Introduction	Module 2.2, 125755/0/000	22 Jul 2021
Nonclinical Overview	Module 2.4, 125755/0/000	22 Jul 2021
Clinical Overview	Module 2.5, 125755/0/002	18 Oct 2021
Summary of Clinical Safety	Module 2.7.4, 125755/0/002	18 Oct 2021
Summary of Clinical Safety Late Breaking Safety Listings	Module 2.7.4, 125755/0/002	18 Oct 2021
BLA correspondence of "Notification of a Serious Adverse Event (SAE) Report of Myelodysplastic syndrome (MDS)" sent on December 03, 2021	Module 1.2, 125755/0/003	03 Dec 2021
Information request response #1: major amendment part 1	Module 1.11.3, 125755/0/07	03 Jan 2022
Information request response #1: major amendment part 2	Module 1.11.3, 125755/0/09	14 Jan 2022
Information request response #5: protocol revision of how secondary malignancies are reported and tissue collection; update on subject (b) (6)	Module 1.11.3, 125755/0/24	01 Mar 2022
Information request response #9: platelet engraftment	Module 1.11.3, 125755/0/30	25 Mar 2022
Information request response #12: add malignancies as primary endpoints to REG-502	Module 1.11.3, 125755/0/37	08 Apr 2022

Information request response #18: date of final protocol submission; reason for EU removal	Module 1.11.3, 125755/0/45	22 Apr 2022
Information request response #21: request to add platelet engraftment failure to PVP	Module 1.11.3, 125755/0/52	11 May 2022
Information request response #36: increasing REG-502 sample size to 60	Module 1.11.3 125755/0/79	15 Jul 2022
Clinical Information request response #49: multiple amendments to REG-502 protocol	Module 1.11.3 125755/0/103	August 30, 2022
Clinical Information request response #59: multiple amendments to REG-502 protocol	Module 1.11.3 125755/0/114	September 09, 2022
Study Protocol Registry REG-502	Module 5.3.5.4, 125755/0/002	18 Oct 2021
Overall Subject-specific narratives	Module 5.3.5.3, 125755/0/002	18 Oct 2021
Summary of Clinical Safety Narratives	Module 5.3.5.3, 125755/0/002	18 Oct 2021
Clinical Study Report ALD-102, Section 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	Module 5.3.5.2, 125755/0/002	18 Oct 2021
Clinical Study Report ALD-104, Section 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	Module 5.3.5.2, 125755/0/002	18 Oct 2021
Clinical Study Report LTF-304, Section 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	Module 5.3.5.2, 125755/0/002	18 Oct 2021
Monthly and Malignancy Report for eli-cel 1	Module 1.11.3 125755/0/009	10 Jan 2022
Monthly and Malignancy Report for eli-cel 2	Module 1.11.3 125755/0/014	01 Feb 2022
Monthly and Malignancy Report for eli-cel 3	Module 1.11.3 125755/0/023	01 Mar 2022
Monthly and Malignancy Report for eli-cel 4	Module 1.11.3 125755/0/033	01 Apr 2022
Monthly and Malignancy Report for eli-cel 5	Module 1.11.3 125755/0/046	01 May 2022
Monthly and Malignancy Report for eli-cel 6	Module 1.11.3 125755/0/062	01 Jun 2022
Monthly and Malignancy Report for eli-cel 7	Module 1.11.3 125755/0/074	01 July 2022
Monthly and Malignancy Report for eli-cel 8	Module 1.11.3 125755/0/087	01 Aug 2022
3 Month Safety Update Report	Module 1.11.3 125755/0/010	21 Jan 2022
3 Month Safety Update to 1 July 2022	Module 1.11.3 125755/0/086	29 Jul 2022

5 Clinical Safety Database

The clinical program for Skysona consisted of 5 studies: one completed study (Study ALD-102), 2 ongoing studies from the Skysona clinical development program (Study ALD-104, the long-term follow-up Study LTF-304), a contemporaneous external control study (Study ALD-103) and an additional retrospective historical control (Study ALD-101). The table below describes the clinically relevant safety studies ALD-102, ALD-104, and LTF-304 and their populations.

Table 2: Clinical program

Study	Description	Subjects Description
ALD-102 (complete)	A Phase 2/3 study to evaluate the efficacy and safety of Skysona. Subjects underwent myeloablative conditioning with busulfan and cyclophosphamide.	<ul style="list-style-type: none"> 32 enrolled subjects with CALD all treated with Skysona. All 32 subjects in the study were male with median age of 6 years (range=4-14 years) at time of drug product infusion. Subjects were predominantly White (15/32 [47%], 31% not reporting race).
ALD-104 (ongoing)	A Phase 3 study to evaluate the efficacy and safety of Skysona. Subjects underwent myeloablative conditioning with busulfan and fludarabine.	<ul style="list-style-type: none"> 28 enrolled male subjects; 23 subjects treated with Skysona, 5 patients untreated. All 28 subjects in the study were male, the median age was 7 years (range=5-13 years) at time of providing informed consent/assent and product infusion. Subjects were predominantly White (18/28 [64%]; 29% not reporting race).
LTF-304 (ongoing)	A 15-year long-term follow up study monitoring the safety and continued efficacy of Skysona administered in parent clinical studies	<ul style="list-style-type: none"> 27 enrolled subjects all treated with Skysona, all from ALD-102 All subjects were male, the median age was 6 (range=3-13 years) at time of informed consent in the parent study. Subjects were predominantly White (12/27, 44.4%); Hispanics (10/27, 37.0%), Black 1/27 (3.7%), Asian 1/27 (3.7%), and the remaining subjects not reporting race (9/27, 33.3%) or identified as "Other" (4/27, 14.8%).

Reviewer comment: Our review focused on the safety data from the clinical studies ALD-102 and ALD-104 and the long-term study LTF-304. The data from Study ALD-101 (natural history study) or ALD-103 (stem cell transplant study) were not evaluated

because of lack of comparability due to differences in the way safety data was recorded and evaluated.

Demographics:

The study populations of ALD-102 and ALD-104 consisted of 55 subjects who received Skysona. All 55 Skysona subjects were male with a median age at first HSCT of 6 years old (range=4-14 years) and included White (n=31, 56%), Black/African American (n=2, 4%), Asian (n=1, 2%), Other (n=5, 9%), or not reported (n=16, 29%) [Hispanic (n=15, 27%), non-Hispanic (n=33, 60%), or not reported (n=7, 13%)].

Summary of All Treatment-Emergent Adverse Events (TEAEs):

In the clinical trials Study 102 and 104, all subjects (55/55) experienced at least 1 TEAE. The most common AEs reported in >10% of subjects are shown in Table 3:

Table 3: Adverse Events Occurring in $\geq 10\%$ of Subjects by SOC, PT (From Table 13 in Summary of Clinical Safety)

System Organ Class Preferred Term	(n=55) n (%), Number of events
Blood and lymphatic system disorders	55 (100.0), 353
Thrombocytopenia	53 (96.4), 99
Anemia	45 (81.8), 75
Neutropenia	45 (81.8), 85
Febrile neutropenia	42 (76.4), 47
Leukopenia	15 (27.3), 37
Lymphopenia	4 (7.3), 5
Gastrointestinal disorders	55 (100.0), 353
Stomatitis	48 (87.3), 57
Vomiting	16 (29.1), 20
Abdominal pain	15 (27.3), 18
Diarrhoea	13 (23.6), 14
Nausea	12 (21.8), 7
Constipation	7 (12.7), 7
Skin and subcutaneous tissue disorders	45 (81.8), 77
Alopecia	41 (74.5), 41
Pruritis	7 (12.7), 7
Skin hyperpigmentation	7 (12.7), 7
Rash	4 (7.3), 4
Metabolism and nutrition disorders	30 (54.5), 58
Decreased appetite	17 (30.9), 20
Hypokalemia	13 (23.6), 15
Hypophosphataemia	8 (14.5), 9
Hypomagnesaemia	2 (3.6), 2
Nervous system disorders	26 (47.3), 56
Headache	10 (18.2), 10
General disorders and administration site conditions	24 (43.6), 35

Pyrexia	18 (32.7), 25
Catheter site pain	0
Respiratory, thoracic, and mediastinal disorders	23 (41.8), 28
Epistaxis	11 (20.0), 11
Cough	6 (10.9), 6
Injury, poisoning and procedural complications	18 (32.7), 24
Allergic transfusion reaction	6 (10.9), 6
Procedural pain	2 (3.6)
Investigations	13 (23.6), 27
Alanine aminotransferase increased	7 (12.7), 7
Aspartate aminotransferase increased	4 (7.3), 5
Vascular disorders	9 (16.4), 12
Hypertension	5 (9.1), 6

Deaths

There were a total of 2 deaths in study ALD-102, both of which occurred in patients who received Skysona. The first patient (Subject (b) (6)) received Skysona but was later discontinued from the study at the investigator's discretion to receive allo-HSCT. He died on Rel Day 495 from multiorgan failure related to organ toxicity from the chemotherapy shortly after withdrawing from the study. Per the Investigator, due to restrictions placed on communication of information regarding a subject withdrawn from a study, the events leading to the subject's death were not provided. The Investigator assessed the death as not related to eli-cel but related to "complications from allogeneic transplantation." The second subject (Subject (b) (6)) experienced neurological decompensation caused by CALD progression starting 2 weeks after treatment with Skysona, leading to spastic tetraparesis. The patient also had a concomitant infection of adenovirus. Both factors likely led to rhabdomyolysis, acute kidney injury, hepatic failure, and finally death from cardiorespiratory arrest on Rel Day 666. Both deaths were not considered to be related to Skysona administration.

There were no deaths reported in study ALD-104 or LTF-304.

Other Serious Adverse Events (SAEs):

Table 4 details the serious treatment-emergent adverse events (TEAEs) that were reported in studies ALD-102, ALD-104, and LTF-304. The most commonly reported PTs were: pyrexia (n=17, 30.9%), febrile neutropenia (n=11, 20.0%), seizure (n=11, 20.0%), neurological decompensation (n=5, 9.1%), and vascular device infection (n=3, 5.4%).

Table 4: Treatment-Emergent Serious Adverse Events by SOC, PT (Listings in CSR for ALD-102, ALD-104, LTF-304, Monthly Safety Update, Data Lock Point (DLP) July 1, 2022)

Preferred Terms	ALD-102 (n, events)	ALD-104 (n, events)	LTF-304 (n, events)	Total* (n, events)
Blood/Lymphatic	7, 7	7, 7	1, 1	15, 15
Febrile neutropenia	7, 7	4, 4	0, 0	11, 11
Myelodysplastic syndrome	0, 0	1, 1	1, 1	2, 2

Pancytopenia	0, 0	2, 2	0, 0	2, 2
Cardiac disorders	1, 1	1, 1	0, 0	2, 2
Cardio-respiratory arrest	1, 1	0, 0	0, 0	1, 1
Sinus bradycardia	0, 0	1, 1	0, 0	1, 1
Congenital, familial, and gene disorders	0, 0	0, 0	1, 1	1, 1
Developmental hip dysplasia	0, 0	0, 0	1, 1	1, 1
Endocrine disorders	2, 2	0, 0	0, 0	2, 2
Adrenal insufficiency	2, 2	0, 0	0, 0	2, 2
Eye disorders	0, 0	0, 0	1, 1	1, 1
Visual impairment	0, 0	0, 0	1, 1	1, 1
Gastrointestinal disorders	3, 3	2, 2	0, 0	5, 5
Abdominal pain	1, 1	0, 0	0, 0	1, 1
Constipation	0, 0	1, 1	0, 0	1, 1
Stomatitis	1, 1	1, 1	0, 0	2, 2
Vomiting	1, 1	0, 0	0, 0	1, 1
General disorders and administration site conditions	7, 7	10, 10	4, 4	21, 21
Catheter site haemorrhage	0, 0	1, 1	0, 0	1, 1
Complication associated with device	0, 0	1, 1	0, 0	1, 1
Disease progression	0, 1	1, 1	0, 0	1, 1
Fatigue	0, 0	0, 0	1, 1	1, 1
Pyrexia	7, 7	7, 7	3, 3	17, 17
Hepatobiliary disorders	1, 1	0, 0	0, 0	1, 1
Acute hepatic failure	1, 1	0, 0	0, 0	1, 1
Infections & Infestations	9, 9	8, 8	1, 1	18, 18
Bacteraemia	0, 0	1, 1	0, 0	1, 1
COVID-19	0, 0	1, 1	0, 0	1, 1
Cystitis viral	1, 1	0, 0	0, 0	1, 1
Gastroenteritis	1, 1	1, 1	0, 0	2, 2
Influenza	1, 1	0, 0	0, 0	1, 1
Otitis media	1, 1	0, 0	0, 0	1, 1
Pseudomonal bacteraemia	0, 0	2, 2	0, 0	2, 2
Septic shock	0, 0	0, 0	1, 1	1, 1
Sinusitis	1, 1	0, 0	0, 0	1, 1
Stenotrophomonas infection	0, 0	1, 1	0, 0	1, 1
Streptococcal bacteraemia	0, 0	1, 1	0, 0	1, 1
Vascular device infection	3, 3	0, 0	0, 0	3, 3
Viral infection	1, 1	0, 0	0, 0	1, 1
Viral upper respiratory infection	0, 0	1, 1	0, 0	1, 1
Injury, poisoning and procedural complications	3, 3	1, 1	0, 0	4, 4
Anaphylactic transfusion reaction	0, 0	1, 1	0, 0	1, 1

Head injury	1, 1	0, 0	0, 0	1, 1
Procedural pain	1, 1	0, 0	0, 0	1, 1
Spinal fracture	1, 1	0, 0	0, 0	1, 1
Investigations	0, 0	1, 1	0, 0	1, 1
Transaminases increased	0, 0	1, 1	0, 0	1, 1
Metabolism and nutrition disorders	1, 1	1, 1	0, 0	2, 2
Decreased appetite	1, 1	0, 0	0, 0	1, 1
Diabetes mellitus	0, 0	1, 1	0, 0	1, 1
Musculoskeletal and connective tissue disorders	1, 1	0, 0	0, 0	1, 1
Rhabdomyolysis	1, 1	0, 0	0, 0	1, 1
Nervous system disorders	6, 6	2, 2	10, 10	18, 18
Dyskinesia	1, 1	0, 0	0, 0	1, 1
Myelitis transverse	0, 0	1, 1	0, 0	1, 1
Neurological decompensation	4, 4	1, 1	0, 0	5, 5
Seizure	1, 1	0, 0	10, 10	11, 11
Psychiatric disorders	0, 0	3, 3	2, 2	5, 5
Autism spectrum disorder	0, 0	1, 1	0, 0	1, 1
Aversion	0, 0	1, 1	0, 0	1, 1
Depression	0, 0	0, 0	1, 1	1, 1
Suicidal ideation	0, 0	0, 0	1, 1	1, 1
Tic	0, 0	1, 1	0, 0	1, 1
Renal and urinary disorders	1, 1	0, 0	0, 0	1, 1
Acute kidney injury	1, 1	0, 0	0, 0	1, 1
Respiratory, thoracic and mediastinal disorders	1, 1	0, 0	0, 0	1, 1
Respiratory distress	1, 1	0, 0	0, 0	1, 1
Vascular disorders	0, 0	0, 0	1, 1	1, 1
Hypotension	0, 0	0, 0	1, 1	1, 1

* Multiple cases in 102 and 104 continued into 304. Totals reflect cumulative data.

There were no AEs leading to withdrawal or discontinuation in Studies ALD-102 and ALD-104.

Adverse Events of Special Interest (AESIs):

A review of ALD-102/104, and Study LTF-304 to identify TEAEs of interest included AEs of Special Interest (AESIs) associated with the use of Skysona, and risks potentially associated with ex-vivo viral vector gene therapy are listed below.

Neutrophil Engraftment Failure

Neutrophil engraftment (NE) was defined as 3 consecutive absolute neutrophil counts $\geq 0.5 \times 10^9$ cells/L (after initial post-infusion nadir) obtained on different days by 42 days post-HSCT (Rel Day 43). All subjects achieved neutrophil engraftment by Rel Day 42.

Platelet Engraftment Failure

Platelet engraftment (PE) was defined by the Sponsor as “3 consecutive platelet counts $\geq 20 \times 10^9$ cells/L obtained on different days while no platelet transfusions are administered for 7 days immediately preceding and during the evaluation period.” In an IR response (STN 125755/0/30, received March 25, 2022), the Sponsor clarified that the ‘evaluation period’ refers to the time during which each subject has platelet counts potentially contributing to the determination of platelet engraftment; platelet counts obtained within 7 days after a platelet transfusion are not used to determine platelet engraftment. The sponsor’s ALD-102 and ALD-104 statistical analysis plans state that subjects followed for 24 months without achieving the requisite 3 platelet counts above 20×10^9 cells/L in the absence of transfusions would be shown as not achieving platelet engraftment.

Using the standard definition of 42 days for the evaluation period,²⁸ of 55 patients, 14 (25.5%) achieved PE after Relative (Rel) Day 42. This includes 5 subjects who had platelet counts $\leq 20 \times 10^9$ cells/L after Day 42, and 9 who had platelet counts $\geq 20 \times 10^9$ cells/L while receiving platelet transfusions. Data on these subjects are provided in Table 5 below.

Table 5: Platelet values for patients achieving platelet engraftment after Day 42

Subject No.	Platelet nadir ($\times 10^9$) (Relative [Rel] Day)	Platelet engraftment count ($\times 10^9$) (Rel Day)	Most recent platelet count ($\times 10^9$) (Rel Day)	Bleeding TEAEs ($\times 10^9$) (Rel Day)
(b) (6)	7.0 (D8, D18)	21 (D55)	249 (Y7)	None
	5.0 (D34)	50 (D44)	179 (Y6)	Epistaxis (D7-22) Haematochezia (D7-14)
	5.0 (D7)	88 (D47)	344 (Y6)	None
	7.0 (D14, D18)	54 (D60)	184 (Y4)	Epistaxis (D9-9)
	6.0 (D31)	33 (D49)	292 (D889)	Epistaxis (D7-15)
	4.0 (D36)	53 (D104)	142 ^{1,2} (D959) 26 ³ (D891)	None
	5.0 (D11)	31 (D108)	100 ¹ (D805)	None
	5.0 (D10)	46 (D48)	242 (D918)	Epistaxis (D14-15)
	3.0 (D48)	22 (106)	41 ^{1,2} (D625) 146 ³ (D552)	Epistaxis (D8-17) Post-allo HSCT: (D584, 590, 592-595, 607-608, 612-622)
	7.0 (D11)	41 (D49)	269 (D567)	None
	9.0 (D22, D30)	27 (D50)	306 (D357)	None
	7.0 (D10, D13)	22 (D48)	95 (D169)	None
	12.0 (D17)	24 (D53)	126 (D192)	None
	10.0 (D14)	68 (D58)	139 (D177)	None

¹Platelet count derived from the safety database

²Reflects platelet count post allo-HSCT for treatment of MDS

³Reflects platelet count preceding allo-HSCT for treatment of MDS

Three subjects treated with Skysona achieved PE after Rel Day 100: Subject (b) (6) (PE on Rel Day 108), Subject (b) (6) (PE on Rel Day 104; persistent thrombocytopenia at Month 24, bone marrow biopsy: dysplastic megakaryocytes), and Subject (b) (6) (PE on Rel Day 106, bone marrow biopsy: markedly hypocellular marrow (10-20%) with dysmegakaryopoiesis). The two latter subjects were subsequently diagnosed with MDS.

Insertional oncogenesis

Upon transduction, lentiviral vectors integrate into the DNA of target cells, thus, there exists a risk for insertional oncogenesis, also described in the 2020 FDA Guidance *Long Term Follow-Up After Administration of Human Gene Therapy Products* (available at <https://www.fda.gov/media/113768/download>). After engraftment of transduced HSCs, a progenitor cell derived from a transduced HSC could undergo preferential expansion, resulting in the presence of a predominant clone in the peripheral blood. This expansion may be without clinical consequences (benign clonal expansion) or result in malignancy (insertional oncogenesis, manifest as MDS, leukemia, and/or lymphoma). Hematologic assessments (e.g., integration site analysis [ISA]) remain the standard means by which subjects are screened and evaluated for hematologic malignancy. Supplementary ISA determines the polyclonality of the reconstituted hematopoietic system in subjects who receive Skysona in clinical trials. Although ISA can be used to assess clonal contribution, it cannot provide a determination of whether a predominant clone is an expression of benign clonal expansion or is associated with malignancy as clinical data are required to inform clinical treatment decisions.

Subjects were monitored by ISA every 6 months for the first 5 years post-Skysona administration, and then at Years 7, 10, and 15. The total number of unique mappable integration sites (IS) detected in each subject was variable, both within and between subjects, with the highest total number of unique mappable IS at any single time point ranging from 552 to 15683 per subject. Of the Top 10 IS genes, IS in the SMG6 and MECOM genes were the most frequently detected and were present among the Top 10 for at least one timepoint in 36 (76.6%) and 24 (51.1%) subjects, respectively. To investigate if vector insertion could be associated with dysregulation of SMG6 gene expression, the most frequent SMG6 IS was engineered into cultured CD34+ cells in an in vitro assay. The presence of an internal MNDU3 promoter was not associated with dysregulation of SMG6 gene expression. Transcription analyses on 3 subjects with predominant clones that contained an IS in the MECOM gene showed increased MECOM mRNA levels in these 3 clones (Subjects (b) (6)). IS in the MECOM gene have been associated with malignancy in gene therapy studies using gamma-retroviral vectors.²⁹

Four subjects had ISA results that met criteria for a predominant clone after treatment with Skysona:

- Subject (b) (6) is an 11-year-old male who did not have hematological manifestations. He first demonstrated a predominant clone of CD15+ at year 5

but prior to that his studies showed an insertion in ACER3 (a gene associated with AML and leukodystrophy) and RFX3 (a gene coding for transcription factors). At month 54, there was an insertion in MECOM gene, a proto-oncogene associated with myeloproliferative neoplasms. As of the most recent visit at Year 6.5, the clone remained predominant and while no MDS diagnosis was given, a bone marrow biopsy did show 30-40% hypocellularity.

- Subject (b) (6) is a 15-year-old male whose first assessment at Month 6 revealed the predominant clone in peripheral blood leukocytes. This subject had a hematologic manifestation in the form of pancytopenia (inclusive of persistent thrombocytopenia and delayed platelet engraftment). MECOM insertion was noted in both the predominant clone and in dysplastic megakaryocytes. At the most recent reported visit at Month 24, the clone remained predominant, there was significant bone marrow hypocellularity at 70%, and a diagnosis of MDS was made.
- Subject (b) (6) is a 12-year-old male who also showed a predominant clone at Month 6. He had atypical megakaryotes and presented with thrombocytopenia and delayed platelet engraftment. He had mild hypocellularity (10-20%) in the bone marrow with dysmegakaryopoiesis at month 12. At the most recent visit at Month 14, the clone remained predominant and at Month 15 a diagnosis of MDS was made.
- Subject (b) (6) is a 12-year-old male who presented 7.5 years after Skysona transplant with fatigue, pallor, and petechiae and was found to be both thrombocytopenic and anemic. A bone marrow biopsy showed 15-20% myeloblasts and 3% in the peripheral blood. Based on this, a diagnosis of MDS was made. ISA results showed clones with insertion in PRDM16 (83.5% clonal contribution in blood, 84.1% in bone marrow), GAB3 (76.6% in blood, 86.8% in marrow), and SNX12 (54.9% in blood, 59.8% in marrow). PRDM16 has been associated with MDS and AML.

Prolonged cytopenias

This important identified risk is defined as Grade 3 or higher cytopenia on or after Rel Day 60 (60 days after receiving Skysona). It occurred in 15/52 (28.8%) subjects as a decrease in neutrophils (21.2%), platelets (15.4%), or hemoglobin (1.9%). On or after relative day 100, 7/47 (14.9%) subjects had Grade 3 or higher cytopenia, including decreased platelet count (8.5%) or decreased neutrophil count (10.6%); no subjects had decreased hemoglobin (0%). The subjects with prolonged thrombocytopenia did not report bleeding AEs but 5 of the 11 subjects with prolonged neutropenia reported infection, 2 of which were opportunistic (*Pseudomonas* bacteremia and Human Herpesvirus 6) infections.

Serious infections

Infections of any grade occurred in 51%. Important infections diagnosed within the first 3 months after treatment with Skysona were BK cystitis, Cytomegalovirus reactivation, Human Herpesvirus-6 viremia, Candidiasis, and pneumonia. Epstein-Barr virus reactivation was diagnosed as late as 18 months after treatment with Skysona. Serious

infections involving adenovirus include a case of transverse myelitis at 6 months that was attributed to adenovirus and entero/rhinovirus infection, and a fatal adenovirus infection at 21 months in a patient with CALD progression who developed multisystem organ failure.

Grade 3 or higher infections occurred in 31% of all patients (12% bacterial, 3% viral, and 9% unspecified). The most common Grade 3 or higher infections were vascular device infections (7% of patients) diagnosed as late as 6 months after treatment with Skysona, and bacteremias (6% of patients) diagnosed as late as 8 months after treatment with Skysona.

Opportunistic infections in 4 subjects were identified as events of interest: 1 subject experienced a serious TEAE of viral cystitis, 1 subject experienced Pseudomonal bacteraemia, 1 subject experienced Pseudomonal bacteraemia and Stenotrophomonas infection, and 1 subject experienced Human Herpesvirus 6 infection.

Reviewer Comment:

There were no deaths related to administration of Skysona.

With regards to SAEs, the blood/lymphatic disorder PTs, pyrexia, and most infectious PTs were related to conditioning. The infectious PTs likely not related were: gastroenteritis, influenza, sinusitis, and viral infections, though conditioning may have weakened the subjects' immunity, increasing the likelihood of infections. Other related PTs were procedural pain and decreased appetite. All neurologic and psychiatric PTs were related to underlying CALD progression.

The presence of predominant clones demonstrating insertion in MECOM and PDRM16, both associated with MDS, as well as elevated vector copy numbers suggests that these cases of MDS were most likely mediated by lenti-D LVV insertion.

6 Summary of Prior Marketed Experience

Not applicable. The product has not been previously approved or used outside of the clinical trials. This is a first in-class product.

7 Applicant's Pharmacovigilance Plan

The applicant's pharmacovigilance plan (PVP) is outlined in the table below.

Table 5: Pharmacovigilance Plan from Applicant Risk Management Plan

Type of Risk	Potential Safety Concern	Planned pharmacovigilance Activity
Identified	Insertional oncogenesis	<ul style="list-style-type: none">• Enhanced pharmacovigilance activity (updates will be reported in yearly PSURs)• Black box warning and Section 5.1 of product label (under hematologic malignancy)

		<ul style="list-style-type: none"> • Post-approval study REG-502
Identified	Prolonged cytopenias	<ul style="list-style-type: none"> • Routine pharmacovigilance • Section 5.3 of product label • Post-approval study REG-502
Potential	Neutrophil engraftment failure	<ul style="list-style-type: none"> • Routine pharmacovigilance • Section 5.5 of product label • Post-approval study REG-502
Potential	Lack or loss of response to gene therapy	<ul style="list-style-type: none"> • Routine pharmacovigilance
Missing Information	Long-term safety and efficacy	<ul style="list-style-type: none"> • Routine pharmacovigilance • Post-approval study REG-502
Missing Information	Pregnancy (including partner pregnancy)	<ul style="list-style-type: none"> • Routine pharmacovigilance • Section 8.1 of product label • Post-approval study REG-502

Individual Case Safety Reports (ICSRs) from postmarketing sources (spontaneous, solicited, literature, and regulatory authorities) will be collected, investigated, and submitted to the FDA as defined in 21 CFR 600.80. Submission of 15-day Alert reports and periodic safety reports will proceed according to the reporting requirements delineated in 21 CFR 600.80(c). Routine activities planned for Skysona include monthly signal detection, quarterly aggregate review of safety data, safety evaluation and updates to the product information using a dedicated cross-functional internal Safety Management Committee. The applicant label provides instructions specific to the identified and potential risks, as well as missing information.

In addition to routine pharmacovigilance and labeling, the applicant has two activities that they consider part of risk minimization. The first risk minimization activity is the use of Quality Treatment Centers (QTCs), which serve as the sites of apheresis, cell therapy, and transplantation qualified by the sponsor. QTCs ensure the chain of identity of patients' cells in the transfer to the manufacturing site and return back to the appropriate QTC. The second risk minimization activity is routine risk communication, which include HCP-specific educational brochure and website, caregiver-specific educational brochure and website, the patient packet insert, and patient advocacy groups.

Safety-related postmarketing requirement (PMR) study

FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at <https://www.fda.gov/media/113768/download> recommends 15-year long term follow up for products with integrating vectors. In keeping with this Guidance, and the important identified risk of insertional oncogenesis and secondary malignancies with this product, the sponsor proposed conducting a long-term follow up study for patients receiving the product in the post-licensure setting (REG-502 study).

As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for

Developing Post-marketing Requirements and Commitments, a Sentinel Sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with Skysona. As outlined in the Sentinel Sufficiency memorandum, the CBER Sentinel Team has determined that CBER Sentinel will not be sufficient to characterize the serious risk of secondary malignancy/insertional oncogenesis with 15 years of follow-up. Additionally, collection of tissue samples is needed for further characterization of this risk, and this is not feasible in claims-based system data sources used by the CBER Sentinel program. Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA.

Therefore, the REG-502 study was presented as a safety postmarketing requirement (PMR) to assess the serious risk of secondary malignancies, at the CBER Safety Working Group meeting on April 28, 2022. The Safety Working Group concurred with need for this safety-related PMR study. On July 8, 2022, the Sponsor was notified by FDA of a postmarketing requirement (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA) to conduct a postmarketing, prospective, multi-center, observational study to assess the long-term safety of Skysona and the risk of secondary malignancies occurring after treatment with Skysona, and that FDA would be providing additional recommendations for study protocol REG-502. Acknowledgment for this PMR and its study milestone dates was received on July 15, 2022.

Table 6: Postmarketing Study

Study Name	Description
A Prospective, Multicenter, International, Observational, Long-Term Safety and Effectiveness Study of Patients with Cerebral Adrenoleukodystrophy Treated with Elivaldogene autotemcel or Allogeneic Hematopoietic Stem Cell Transplantation (REG-502)	An international, observational study designed to evaluate long-term outcomes of patients with CALD treated with eli-cel or allo-HSCT

REG-502 is a long term 15-year observational cohort study following patients post-treatment. This study will include two cohorts:

- The Skysona cohort will comprise patients treated with Skysona who are enrolled through either the European Society for Blood and Marrow Transplantation (EBMT) or Center for International Blood and Marrow Transplant Research (CIBMTR) transplant registries in the European Economic Area (EEA) and the US, respectively.
- The allo-HSCT cohort will comprise patients with CALD treated with allo-HSCT who are enrolled through either the EBMT (EEA) or CIBMTR (US) registries.

This is a 15-year long term study. Initially the sponsor proposed to enroll 60 patients in the Skysona cohort and 25 in the allo-HSCT arm.

The objectives of the study are:

- To describe the safety outcomes of patients with CALD treated with eli-cel or allo-HSCT (primary objective)

- To describe the effectiveness outcomes of patients treated with eli-cel or allo-HSCT (primary objective)
- To describe the baseline characteristics of patients with CALD treated with eli-cel or allo-HSCT (secondary objective)
- To characterize hematologic malignancy secondary to LVV insertional oncogenesis, including risk factor identification, clinical progression of disease over time (from pre-diagnosis through treatment), characterization of response vs refractoriness to treatment including risk of relapse and death, and characterization of molecular changes involved in the progression to malignancy

The safety variables that are collected in this observational registry will include the following:

- AEs:
 - Neutrophil engraftment failure
 - Malignancy
 - Newly acquired HIV-1, or -2
 - Autoimmune disorders
 - Opportunistic infections
 - Grade 3 cytopenias >60d s/p eli-cel infusion
- Eli-cel related adverse events as assessed by the treating HCP
- All SAEs, regardless of relationship to eli-cel
- Neutrophil engraftment, defined as ANC $>0.5 \times 10^9/L$
 - Evidence of neutrophil engraftment
 - Date of neutrophil engraftment
- Platelet engraftment, defined as platelet count $>20 \times 10^9/L$
 - Evidence of platelet engraftment
 - Date of platelet engraftment
- Acute and chronic graft versus host disease (aGVHD and cGVHD)
- Malignancy
 - Evidence of new malignancy
 - Malignancy diagnosis (type)
 - Date of malignancy diagnosis
 - If malignancy is considered donor/cell product derived
- Graft failure
- All-cause mortality
- Date of death
 - Primary cause of death
 - Transplant-related mortality
- Second transplant (or additional transplants)
 - Evidence of new hematopoietic stem cell transplant (HSCT) since date of last report
 - Date of additional HSCT
 - aGVHD, including date of diagnosis/onset and maximum overall grade
 - cGVHD, including date of diagnosis/onset, maximum extent, maximum score
 - Graft failure, primary and secondary

- Treatment characteristics:
 - Mobilization regimen
 - Mobilization agent(s) and dose administered
 - Mobilization dates
 - Number of collections
 - Conditioning regimen
 - Conditioning agent(s) and dose administered
 - Conditioning dates
 - Dose administered
 - Eli-cel drug product characteristics
 - Dose, Lot
 - Vector copy number (VCN)
 - Cell concentration
 - %LVV+ cells in DP
 - %ALDP+ cells
 - Reason for discontinuation, if applicable

FDA has required and the sponsor agreed to include the following:

- Complete bone marrow biopsy reports.
 - All bone marrow biopsies will include core and aspirate to assess cellularity, fibrosis, and other relevant tests deemed by pathology, flow cytometry, conventional karyotyping, NGS, and ISA.
 - Fluorescence In Situ Hybridization (FISH) will be included if CBC or karyotype is abnormal. FISH will include a myeloid panel as well as probes for genes that have been implicated in LVV-mediated malignancy, such as MECOM.
 - The Next generation sequencing (NGS) panel must be appropriate for age and include coverage for gene mutations expected in myeloid and lymphoid malignancies.
 - A single hematopathologist will perform centralized, independent review of all bone marrow biopsies and peripheral blood smears
 - RNA sequencing will ensure the use of spike-in controls to allow proper normalization of gene expression.
- HSCT details, including cell source (e.g., cord, peripheral, or bone marrow), relationship (e.g., none, paternal, or sibling), HLA matching, and timing.
- Conditioning including dose and timing (e.g., chemotherapy, immunosuppressives, total body irradiation).
- Clinical course including serious adverse events and details/cause of any death.
- In the event of relapse, provide timing, treatment, and outcome
- Conditioning regimen details (number of cells administered, drug product VCN, percent of vector-containing cells, and vector copies per transduced cell)
- Hematopoietic recovery details (CBC data collected for the duration of a subject's enrollment in the study and all transfusions and growth factor administrations)

FDA has required and the sponsor agreed to include the following as part of routine assessments:

- Upon enrollment into the study, the following tests will be performed for all subjects to understand baseline risk for developing malignancy and to allow for comparison to future samples:
 - Hematopathology review of peripheral blood smear
 - Complete count with differential
- During the first year after eli-cel:
 - Monthly complete blood count with differential
 - Peripheral blood ISA and VCN at Months 6, 9, and 12
 - Bone marrow biopsy with ISA and hematopathology review of peripheral blood smear at Months 6 and 12
- During Years 2 through 10 after eli-cel - Every 4 months:
 - Complete blood count with differential and hematopathology review of peripheral blood smear
 - Peripheral blood ISA and VCN
- During Years 11 through 15 after eli-cel – Every 6 months:
 - Complete blood count with differential and hematopathology review of peripheral blood smear
 - Peripheral blood ISA and VCN

FDA has required and the sponsor agreed to include the following to be performed in response to abnormal findings:

- After the first year, for any CBC abnormality that is of Grade 2 or higher severity based on CTCAE classification, CBC should be repeated within one month
- Bone marrow biopsies with ISA of bone marrow will be performed at 4-month intervals for the following:
 - Any two consecutive CTCAE grade II CBC values, adjusted for age
 - Any transfusion requirement
 - Abnormal results from the most recent bone marrow biopsy.
 - ISA relative frequency of $\geq 5\%$ at two consecutive time points in a gene with known biological relevance to carcinogenesis
 - ISA relative frequency of $\geq 10\%$ at two consecutive time points in a gene not known to have biological relevance to carcinogenesis
- For ISA relative frequency of $\geq 5\%$ at two consecutive time points in a gene with known biological relevance to carcinogenesis, gene expression studies will be performed
- For multiple integration sites within a clone, the following testing will be performed:
 - Bone marrow biopsies will be performed for persistent, unexpected, abnormalities of peripheral blood cell counts, particularly in the setting of persistent oligoclonality

The applicant has requested that study investigators report all SAEs, including malignancies to them within 24 hours of awareness of diagnosis. The sites will be notified that expedited reporting is necessary to facilitate prompt initiation of obtaining clinical samples for further investigation and be trained to submit the AE/SAE report form and forward it to the applicant to ensure timely reporting. Upon receipt of the SAE

for a newly diagnosed malignancy, the applicant will facilitate collection of clinical samples if clinically feasible (which may include blood, bone marrow aspirate, or biopsy of the neoplastic tissue or autopsy tissue) for analysis (including ISA if feasible) to investigate whether the lentiviral vector integration could have contributed to the malignancy. Results of laboratory assessments will be included in the study dataset and findings will be shared with the Agency as required by pharmacovigilance safety reporting requirements.

Reviewer comment: Following additional recommendations, the sponsor agreed to increase the target enrollment for REG-502 to 120 patients. The Sponsor acknowledged that, by not including baseline bone marrow biopsy and aspirate and skin biopsy for germline mutations, the assumption will be that all hematological malignancies that are developed after the treatment and during the period of observation will be attributed to Skyona. The Sponsor will submit an amended protocol for the REG-502 study post approval to reflect the above changes.

8 Analysis of Applicant's Pharmacovigilance Plan

The applicant has outlined the important identified and potential risks safety specifications of the submitted pharmacovigilance plan. The applicant has proposed labeling which provides information on the risks and techniques and warning signs to minimize the risks.

Safety Issues identified in the Pharmacovigilance Plan:

- Insertional oncogenesis: In clinical trials, 4 subjects developed a predominant clone, leading to MDS in 3 of them. Based on the ISA for 2 MDS cases demonstrating insertion in the MECOM gene and in the PDRM16 gene in the third case, it is likely that the MDS events were related to receipt of Skysona. The sponsor will submit all ICSRs of hematologic malignancy in the post-marketing setting to FDA within 15 days of receipt. In addition, if a hematologic malignancy is detected in a patient who received Skysona in the post marketing setting, HCPs are instructed through product labeling to contact the sponsor for instructions on collection of blood samples for further testing. Enrollees in the post-approval study will have ISAs periodically performed as screening for concerning genetic insertions and determining clonality as described in Section 7 of this memo. The Sponsor will report updates on all cases of predominant clones and their laboratory tests (blood counts, bone marrow biopsies, ISA results) in yearly PSURs. Skin biopsies will also be collected to determine germline mutations. This risk is included in Section 5.1 of Warnings and Precautions under "Hematologic Malignancy" and as a black box warning.
- Prolonged cytopenias: In clinical trials, 15/52 (28.8%) subjects reported a Grade 3 or higher cytopenia more than 60 days after receiving Skysona. While thrombocytopenias did not lead to bleeding episodes, the neutropenic episodes did coincide with opportunistic infections. The product label recommends blood counts as well as screening for symptoms. In addition, the PMR will obtain screening blood counts and peripheral blood smears at increasing intervals as

outlined in Section 7 of this memo. This risk will be added to the product label under 5.3 of Warnings and Precautions

- Neutrophil engraftment failure: Though this potential risk did not occur during clinical trials, the product label recommends monitoring for absolute neutrophil count. The PMR will also be assessing for engraftment failure based on complete blood counts collected every 6 months. This risk will be included in the product label under 5.5 of Warnings and Precautions.
- Platelet engraftment failure: The standard definition for platelet engraftment failure allows a 42-day period for engraftment. This differs from Sponsor's definition which allows 2 years for engraftment. In an IR sent to the Sponsor CBER requested that the Sponsor change their engraftment evaluation period to 42 days and to add platelet engraftment failure as an identified risk to the PVP. The Sponsor declined both requests (STN 125755/0/30, received March 25, 2022). Delayed Platelet Engraftment will be added to the product label under the 5.4 of Warnings and Precautions section.
- Lack or loss of response to gene therapy: The sponsor defines this risk as undetectable VCN (<0.0003 copies per diploid genome) in peripheral blood cells for 2 consecutive measurements at least 1 month apart. There were no cases of this in the clinical trials, and this potential risk is not mentioned in the product label. Enrollees in the post-approval study will have bloodwork obtained periodically as outlined in Section 7.

Reviewer Comment:

The applicant PVP adequately reflects the safety concerns based on the clinical trial experience. The important identified risk of insertional oncogenesis is a serious and important adverse event that can occur post-administration of the product, as evidenced in the clinical trials.

On April 28, 2022, the safety-related post-marketing requirement of REG-502 was presented to CBER's Safety Working Group (SWG). The SWG concurred with the recommendation of OBPV and OTAT to require a 15-year safety-related PMR to assess the risk of secondary malignancies. Similarly, on June 9, 2022, the Cellular, Tissue, and Gene Therapies Advisory Committee determined that the benefits of Skysona outweigh the risks and agreed a study was necessary for better characterization of the risk of hematologic malignancy.

9 DPV CONCLUSIONS

Based on review of available data, there is a safety signal from the clinical trials for Skysona which warrants a FDAAA Title IX post-marketing requirement (PMR) study to assess the safety outcomes of Skysona for the serious risk of insertional oncogenesis and secondary malignancies, and the long-term safety of the product including prolonged cytopenia. The review team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product, The sponsor has proposed to conduct

a long-term follow up safety study for subjects treated with Skysona. This study will collect blood samples/tissue samples as needed to test for gene expression studies and peripheral blood counts, bone marrow biopsies, and skin biopsies for germline mutations. The risks of treatment with Skysona will be mitigated through risk communication and risk minimization measures as recommended in the USPI, including a black box warning for hematologic malignancy and by routine and enhanced pharmacovigilance activities.

10 DPV RECOMMENDATIONS

Should the product be approved, the sponsor's PVP which includes conducting a 15-year observational study as a post-marketing requirement assessing the serious risk of insertional oncogenesis and secondary malignancies and long-term safety of Skysona, routine and enhanced pharmacovigilance and AE reporting in accordance with 21 CFR 600.80, is acceptable. The available data does not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) at this time.

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon content and language. Please see the approval letter for the PMR study milestone dates.

References:

1. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. *Brain*. 1997;120 (Pt 8):1485-1508. doi:10.1093/brain/120.8.1485.
2. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. *Nat Clin Pract Neurol*. 2007;3(3):140-151. doi:10.1038/ncpneuro0421.
3. Bezman L, Moser AB, Raymond GV, et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. *Ann Neurol*. 2001;49(4):512-517.
4. Taylor JL, Lee S. Lessons Learned from Newborn Screening in Pilot Studies. *N C Med J*. 2019;80(1):54-58. doi:10.18043/ncm.80.1.54.
5. Bezman L, Moser HW. Incidence of X-linked adrenoleukodystrophy and the relative frequency of its phenotypes. *Am J Med Genet*. 1998;76(5):415-419.
6. Wiesinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. *Appl Clin Genet*. 2015;8:109-121. Published 2015 May 2. doi:10.2147/TACG.S49590
7. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol*. 2007;6(8):687-692. doi:10.1016/S1474-4422(07)70177-1.
8. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2019;25(3):538-548. doi:10.1016/j.bbmt.2018.09.036.
9. Suzuki Y, Takemoto Y, Shimozaawa N, et al. Natural history of X-linked adrenoleukodystrophy in Japan. *Brain Dev*. 2005;27(5):353-357. doi:10.1016/j.braindev.2004.09.008.
10. Aubourg P, Adamsbaum C, Lavallard-Rousseau MC, et al. A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med*. 1993;329(11):745-752. doi:10.1056/NEJM199309093291101.
11. Rizzo WB. Lorenzo's oil--hope and disappointment. *N Engl J Med*. 1993;329(11):801-802. doi:10.1056/NEJM199309093291110.
12. van Geel BM, Assies J, Haverkort EB, et al. Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". *J Neurol Neurosurg Psychiatry*. 1999;67(3):290-299. doi:10.1136/jnnp.67.3.290.
13. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood*. 2011;118(7):1971-1978. doi:10.1182/blood-2011-01-329235.
14. Kühl JS, Kupper J, Baqué H, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. *JAMA Netw Open*. 2018;1(3):e180769. Published 2018 Jul 6. doi:10.1001/jamanetworkopen.2018.0769.

15. Asheuer M, Pflumio F, Benhamida S, et al. Human CD34+ cells differentiate into microglia and express recombinant therapeutic protein. *Proc Natl Acad Sci U S A*. 2004;101(10):3557-3562. doi:10.1073/pnas.0306431101
16. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999 [published correction appears in *Blood*. 2004 Dec 15;104(13):3857]. *Blood*. 2004;104(3):881-888. doi:10.1182/blood-2003-10-3402
17. Kumar S, Sait H, Polipalli SK, Pradhan GS, Pruthi S, Kapoor S. Loes Score: Clinical and Radiological Profile of 22 Patients of X-Linked Adrenoleukodystrophy: Case Series from a Single Center. *Indian J Radiol Imaging*. 2021;31(2):383-390. doi:10.1055/s-0041-1734366.
18. Aubourg P, Blanche S, Jambaqué I, et al. Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. *N Engl J Med*. 1990;322(26):1860-1866. doi:10.1056/NEJM199006283222607.
19. Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. *Lancet*. 2000;356(9231):713-718. doi:10.1016/S0140-6736(00)02629-5.
20. Baumann M, Korenke GC, Weddige-Diedrichs A, et al. Haematopoietic stem cell transplantation in 12 patients with cerebral X-linked adrenoleukodystrophy. *Eur J Pediatr*. 2003;162(1):6-14. doi:10.1007/s00431-002-1097-3.
21. Beam D, Poe MD, Provenzale JM, et al. Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. *Biol Blood Marrow Transplant*. 2007;13(6):665-674. doi:10.1016/j.bbmt.2007.01.082.
22. Saute JA, Souza CF, Poswar FO, et al. Neurological outcomes after hematopoietic stem cell transplantation for cerebral X-linked adrenoleukodystrophy, late onset metachromatic leukodystrophy and Hurler syndrome. *Arq Neuropsiquiatr*. 2016;74(12):953-966. doi:10.1590/0004-282X20160155.
23. Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program*. 2008;134-141. doi:10.1182/asheducation-2008.1.134.
24. Carreras E, Dufour C, Mohty M, Kröger N, eds. *The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies*. 7th ed. Cham (CH): Springer; 2019.
25. Reddy SM, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. *Bone Marrow Transplant*. 2010;45(6):979-984. doi:10.1038/bmt.2010.35.
26. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363(22):2091-2101. doi:10.1056/NEJMoa1004383.
27. Wadhwa A, Chen Y, Holmqvist A, et al. Late Mortality after Allogeneic Blood or Marrow Transplantation for Inborn Errors of Metabolism: A Report from the Blood or Marrow Transplant Survivor Study-2 (BMTSS-2). *Biol Blood Marrow Transplant*. 2019;25(2):328-334. doi:10.1016/j.bbmt.2018.09.035

28. Ruggeri A, Labopin M, Sormani MP, et al. Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen. *Haematologica*. 2014;99(9):1509-1515. doi:10.3324/haematol.2014.109280.
29. Modlich U, Schambach A, Brugman MH, et al. Leukemia induction after a single retroviral vector insertion in Evi1 or Prdm16. *Leukemia*. 2008;22(8):1519-1528. doi:10.1038/leu.2008.118.