NEW DRUG APPROVAL

Brand Name	Skysona®
Generic Name	elivaldogene autotemcel
Drug Manufacturer	Bluebird bio, Inc.

New Drug Approval

FDA approval date: September 16, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 125755

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Adrenoleukodystrophy (ALD) is a rare genetic condition characterized by progressive loss of white matter in the nervous system and degradation of adrenal glands. It is caused by a mutation in the ABCD1 gene on the X-chromosome. Diagnosis can be established given clinical findings and elevated very long-chain fatty acids (VLCFA), and confirmed via genetic testing.

CALD is a rare genetic condition characterized by inflammatory demyelination in the central nervous system that primarily affects males, caused by a mutation in the ABCD1 gene, located on the X chromosome. The disease typically causes neurological symptoms in patients between 3 and 10 years of age and affected individuals die within 5 to 10 years of symptom onset unless they receive a hematopoietic stem cell transplant (HSCT) early in the disease process.

35% of affected males develop neurological symptoms between three and ten years of age. It almost never occurs before approximately two and a half to three years of age. Affected males will develop normally and then start to show a loss (regression) of previously acquired skills. Before the loss of skills, affected males may exhibit behavioral problems including attention deficit and hyperactivity disorder (ADHD) and learning disabilities. Affected individuals usually develop cognitive deficits which means that they may have impairment of their mental processes and have difficulty acquiring information and knowledge.

Later on, they will develop additional symptoms including diminished clarity of vision (diminished visual acuity), hearing loss, gait difficulty, and eventually weakness and stiffness of limbs, convulsions or seizures. Eventually, affected children loose most neurological function and become totally disabled with blindness, deafness, and inability to move voluntarily.

The prevalence of ALD is estimated to be between 1 in 10,000 and 1 in 17,000 individuals in the general population. Prevalence refers to the number of people in the general population who have a disorder at any given time. Rare disorders like ALD often go undiagnosed or misdiagnosed making it difficult to determine the true frequency of the disorder in the general population. The condition occurs throughout the world in all ethnic groups.

Efficacy

The safety and efficacy of Skysona® were assessed in two 24-month, open-label, single-arm studies in patients with early, active CALD as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement (GdE+) on MRI, as well as a neurologic function score (NFS) of ≤ 1, indicating limited changes in neurologic

function. The NFS was used to evaluate 15 domains of neurological function with a maximum score of 25. A total NFS=0 indicates absence of neurologic dysfunction or asymptomatic disease. The patients enrolled and treated with Skysona® (Study 1, N=32; Study 2, N=35) all had elevated very long chain fatty acid (VLCFA) levels and confirmed mutations in the ABCD1 gene. Following completion of Study 1 and Study 2, patients enroll in a subsequent and ongoing long-term follow-up study. The efficacy of Skysona® was compared to an external untreated natural history control. Data for the Natural History Population in the retrospective natural history study (Study 3) was collected from existing medical records for patients with CALD. The Natural History Population had early, active disease at diagnosis, though gadolinium status was defined by either having a GdE+ MRI during the study or unknown GdE status and clinical course that suggested active disease.

Skysona® Studies Study 1 is complete, and Study 2 is ongoing at the time of product approval. In Study 1, patients were 47% White/Caucasian, 38% Hispanic, 3% Asian, 3% Black or African American, and 16% other races including mixed race. In Study 2, patients were 60% White/Caucasian, 14% Hispanic, 6% Black or African American, 6% other races including mixed race.

Mobilization and Apheresis:

- G-CSF 10 µg/kg (median) for a minimum of 4 days.
- Plerixafor 0.24 mg/kg for up to 3 days – optional in Study 1 (administered to 34% of patients) and required in Study 2.

For all patients, one cycle of mobilization and apheresis and one to two apheresis collection days were sufficient to obtain the requisite number of cells needed for manufacturing.

Pre-treatment Myeloablative Conditioning:

- Study 1: Busulfan dose median (min, max) 14 (11.2 to 16.8) mg/kg over 4 days.
- Study 2: Busulfan dose median (min, max) 16.8 (12 to 21.2) mg/kg over 4 days.

Pre-treatment Lymphodepletion:

- Study 1: Cyclophosphamide dose median (min, max) 199 (151 to 213) mg/kg over 4 days.
- Study 2: Fludarabine dose 180 mg/m2 over 6 days for 11 patients; 160 mg/m2 over 4 days (actual dose range 122 to 196 mg/m2) for 24 patients; (fludarabine dose decreased due to viral infections in the initial cohort).

Patients received seizure, hepatic veno-occlusive disease, anti-fungal, and antibiotic prophylaxis in accordance with institutional guidelines. Skysona® Administration:

- All patients were administered Skysona® as an intravenous infusion with a median (min, max) dose of 12 × 106 (5, 38.2) CD34+ cells/kg (N=67).

After Skysona® Administration:

- G-CSF – optional in Study 1 (administered to 75% of patients) and required in Study 2 (beginning on Day 5).

Comparison of Skysona® with the Natural History of CALD

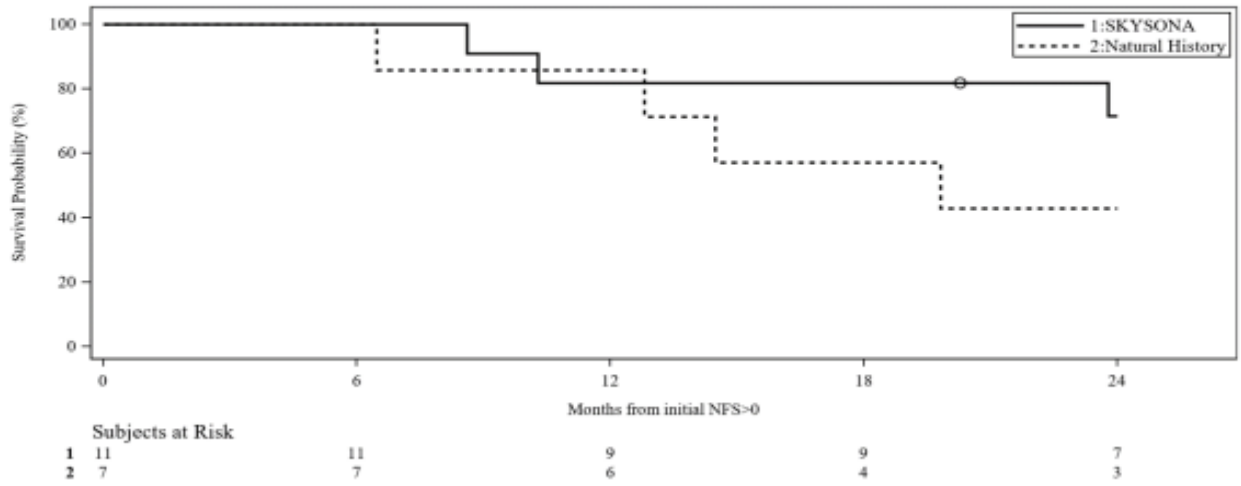
A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS ≥ 1) to time to first Major Functional Disability (MFD) or death (i.e., MFD-free survival) in Skysona® treated and Natural History patients. The MFDs are defined as: loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. To be included in the analysis, patients had to have symptoms at baseline (NFS=1) or be asymptomatic (NFS=0) at baseline and have developed symptoms (NFS ≥ 1) during the course of follow-up in the study. Additionally, they had to have at least 24 months of follow-up after initial NFS ≥ 1 or have had an event (MFD or death).

The 7 patients in the Natural History Population were a median (min, max) 9 (5, 15) years old at time of CALD diagnosis, and 10 (5, 17) years at time of first NFS ≥ 1. The median Loes score at diagnosis was 5 (2, 9). Four (57%) had a baseline brain MRI pattern of disease inclusive of parieto-occipital involvement, 2 (29%) had frontal disease (without parieto-occipital involvement) and 1 (14%) had isolated pyramidal tract disease. One (14%) had a baseline NFS=1 at diagnosis, and the remainder were asymptomatic (NFS=0) at diagnosis.

The symptomatic Skysona® subpopulation (N=11) had baseline median (min, max) age at treatment of 6 (4, 10) years, age at first NFS ≥ 1 of 7 (4, 10) years, and a baseline Loes score of 2.5 (1, 9). Ten (91%) patients had a parieto-occipital pattern of disease on brain MRI and 1 (9%) had isolated pyramidal tract disease. At baseline, 2 (18%) patients had an NFS=1 and the remainder were asymptomatic (NFS=0) prior to treatment.

Slower progression to MFD or death from time of symptom onset (first NFS ≥ 1) was seen for early, active CALD patients treated with Skysona® compared to a similar natural history of disease. Kaplan Meier (KM) estimated MFD-free survival at Month 24 from time of first NFS ≥ 1 were 72% (95% CI: 35%, 90%) for the symptomatic Skysona® subpopulation and 43% (95% CI: 10%, 73%) for the Natural History Population. There were insufficient data beyond 24 months for the symptomatic Skysona® subpopulation to assess long-term MFD-free survival as compared to the natural history of disease. There was insufficient duration of follow-up to assess efficacy in Skysona® treated patients who remained asymptomatic.

Figure 1 Kaplan-Meier Curve of MFD-free Survival in Symptomatic Patients of SKYSONA and Natural History Populations



Isolated Pyramidal Tract Disease:

Two untreated patients in Study 3 had early CALD with isolated pyramidal tract disease on brain MRI. Both remained asymptomatic for approximately 10 years following CALD diagnosis with first symptoms documented at 19 and 20 years of age. Ten patients with early, active pyramidal tract disease were treated with Skysona® in Studies 1 and 2 and have only been followed a maximum of 77 months following treatment and to a maximum age at last follow-up of 15 years. Two (20%) Skysona®-treated patients were diagnosed with myelodysplastic syndrome (MDS) and received allo-HSCT as treatment of the hematologic malignancy. One (10%) patient developed symptoms and worsening lesions on brain MRI approximately 6 months following treatment with Skysona® and was withdrawn from the study to receive allo-HSCT at the investigator's discretion. He subsequently died of transplant-related causes.

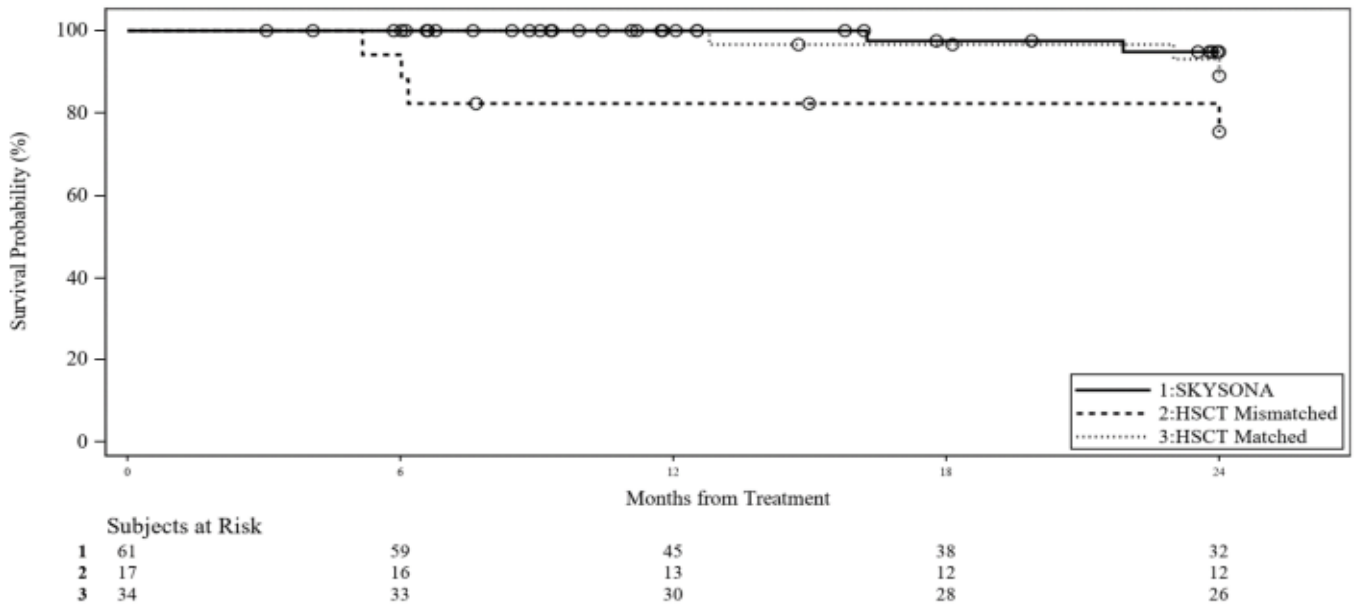
Comparison of Skysona® with Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT):

There were insufficient data to compare relative efficacy of Skysona® to the standard of care, allogeneic hematopoietic stem cell transplant (allo-HSCT) in the treatment of CALD. However, while it does not inform the efficacy analysis, comparison of Skysona® with an external allo-HSCT control (pooled from Study 3 and from a mixed perspective and retrospective allo-HSCT data collection study, Study 4) was performed for overall survival (OS) due to concerns about treatment-related toxicities. OS was analyzed as time-to-event Kaplan-Meier estimates comparing Skysona® (entire efficacy population, N=61) to early, active allo-HSCT subpopulations by donor type: human leukocyte antigen (HLA)-Matched allo-HSCT Subpopulation (N=34) and HLA-Mismatched allo-HSCT Subpopulation (N=17). There were insufficient long-term data to compare OS beyond Month 24.

However, a distinct difference in OS in the first 9 months following treatment was seen for the subpopulation who received allo-HSCT from an HLA-mismatched donor as compared to Skysona® and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of Skysona®, it does demonstrate a survival advantage of Skysona® as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT Subpopulation largely attributed to allo-HSCT-related toxicities.

No patient experienced acute (≥ Grade II) or chronic graft versus host disease (GVHD) after Skysona® treatment.

Figure 2 Kaplan-Meier Curve of Overall Survival Between SKYSONA and Allo-HSCT Treated Populations



Post-treatment Brain MRI at Month 24 following treatment with Skysona®, 7/36 (19%) evaluable patients had a cerebral MRI Loes score increase of ≥ 6 points; 3/30 (10%) evaluable allo-HSCT patients had a cerebral MRI Loes score increase of ≥ 6 points.

- Most common non-laboratory adverse reactions (≥ 20%): mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, rash.
- Most common Grade 3 or 4 laboratory abnormalities (≥40%): leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, hypokalemia.

Safety

ADVERSE EVENTS

In the two trials, serious adverse reactions from Day 1 (Skysona® infusion) to last follow-up occurred in 54% of patients. The most common non-laboratory, serious adverse reactions (≥ 3% incidence) that occurred after treatment with Skysona® were febrile neutropenia (18%), pyrexia (fever) (18%), seizure (7%), myelodysplastic syndrome (4%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%).

Table 1: Non-Laboratory Adverse Reactions Reported in ≥ 10% of Patients Between the Start of Conditioning and 24 Months Following Treatment with Skysona®

Adverse Reaction	Any Grade N (%)	Grade 3 or Higher N (%)
Blood and lymphatic system disorders	--	--
Febrile neutropenia[a]	49 (73%)	49 (73%)
Cardiac disorders	--	--
Tachycardia[b]	10 (15%)	0
Eye disorders	--	--
Vision blurred	7 (10%)	0
Gastrointestinal disorders	--	--
Mucositis[c]#	62 (92%)	34 (51%)
Nausea	56 (84%)	17 (25%)
Vomiting	51 (76%)	12 (18%)
Abdominal pain[d]	30 (45%)	2 (3%)
Constipation	28 (42%)	0
Diarrhea	19 (28%)	1 (1%)
General disorders and administration site conditions	--	--
Pyrexia	24 (36%)	3 (4%)
Injury, poisoning and procedural complications	--	--
Transfusion reaction[e]	8 (12%)	2 (3%)
Metabolism and nutrition disorders	--	--
Decreased appetite	43 (64%)	27 (40%)
Nervous system disorders	--	--
Headache	19 (28%)	0
Anxiety[f]#	10 (15%)	0
Respiratory, thoracic, and mediastinal disorders	--	--
Epistaxis	13 (19%)	5 (7%)
Adverse Reaction	**Any Grade N (%)**	**Grade 3 or Higher N (%)**
Oropharyngeal pain[g]#	12 (18%)	3 (4%)
Cough	7 (10%)	0
Skin and subcutaneous tissue disorders	--	--
Alopecia	48 (72%)	1 (1%)
Rash[h]	14 (21%)	0
Pruritus[i]#	13 (19%)	0
Skin hyperpigmentation	12 (18%)	0
Vascular disorders	--	--

Hypertension	8 (12%)	1 (1%)

* Includes adverse events associated with conditioning.
[a] Febrile neutropenia includes febrile bone marrow aplasia and febrile neutropenia. [b] Tachycardia includes sinus tachycardia and tachycardia. [c] Mucositis includes anal inflammation, colitis, gastrointestinal inflammation, mucosal inflammation, proctitis, and stomatitis. [d] Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain upper.
[e] Transfusion reaction includes allergic transfusion reaction and anaphylactic transfusion reaction. [f] Anxiety includes akathisia, agitation, anxiety, and irritability.
[g] Oropharyngeal pain includes mouth ulceration, oral pain, and oropharyngeal pain. [h] Pruritus includes anal pruritus, pruritus, and pruritus allergic.
[i] Rash includes rash, rash erythematous, rash maculo-papular, and urticaria. # Encompasses more than one system organ class.

Table 2: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 40% of Patients Between the Start of Conditioning and 24 Months Following Treatment with Skysona®

Laboratory Abnormality	Grade 3 or 4 N (%)
Leukopenia	67 (100%)
Lymphopenia	67 (100%)
Thrombocytopenia	67 (100%)
Neutropenia	64 (96%)
Anemia	56 (84%)
Hypokalemia	28 (42%)

* Includes laboratory abnormalities associated with conditioning.

Pancytopenia:
Two patients had serious adverse reactions of pancytopenia for >1 year after treatment with Skysona® and required prolonged support with blood and platelet transfusions as well as growth factors (G-CSF and eltrombopag). One patient had intercurrent parvovirus infection. Pancytopenia in the second patient never resolved, and he was diagnosed with myelodysplastic syndrome approximately 2 years after Skysona® administration.

Platelet Engraftment Delay:
Platelet engraftment was defined as 3 consecutive platelet values ≥ 20 × 109/L on different days and no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. Platelet engraftment was not achieved by Day 43 after Skysona® administration in 13 of 63 patients (21%). Patients treated with Skysona® achieved platelet engraftment at median (min, max) Day 29 (14, 108) in clinical studies, including two patients treated with a thrombopoietin receptor agonist at the time engraftment criteria were met until 10 or 14 months after treatment with Skysona®. One of the two had persistence of mild thrombocytopenia after discontinuation of the eltrombopag, and the other remained severely thrombocytopenic (platelet count < 50 × 10^9/L) until he was diagnosed with myelodysplastic syndrome approximately 2 years after Skysona® administration.

Neutrophil Engraftment:
Neutrophil engraftment was defined as achieving 3 consecutive absolute neutrophil counts (ANC) ≥ 0.5 × 10^9 cells/L (after initial post-infusion nadir) obtained on different days by Day 43 after Skysona® infusion. While all patients met criteria for neutrophil engraftment following treatment with Skysona® in clinical trials, 7 of 67

patients (10%) required G-CSF beyond Day 43, including 3 patients who required G-CSF more than 3 months after treatment with Skysona®. In three other patients, G-CSF discontinuation was followed by a decrease in neutrophil count to < 0.5 × 10^9 cells/L occurring within 3 days and lasting for two to five weeks.

Infusion-Related Reactions:
Nausea and vomiting have occurred on the day of infusion. Premedication with anti-emetic, anti-pyretics and/or antihistamines may be considered.

WARNINGS & PRECAUTIONS

- Serious Infections: Life-threatening bacterial and viral infections may occur. Monitor patients for signs and symptoms of infection.
- Prolonged Cytopenias: Patients may exhibit cytopenias >1 year after treatment with Skysona®. Monitor patients for bleeding and infection.
- Delayed Platelet Engraftment: Monitor patients for thrombocytopenia and bleeding until platelet engraftment and count recovery.
- Risk of Neutrophil Engraftment Failure: Monitor absolute neutrophil counts and if neutrophil engraftment does not occur, give rescue cells.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Skysona® adds functional copies of the ABCD1 cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with Lenti-D LVV. After Skysona® infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP. Functional ALDP can then participate in the local degradation of very long chain fatty acids (VLCFAs), which is believed to slow or possibly prevent further inflammation and demyelination.

Dose & Administration

ADULTS

N/A

PEDIATRICS

- Dosing of Skysona® is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight.
- The minimum recommended dose is 5.0 × 106 CD34+ cells/kg.
- Full myeloablative and lymphodepleting conditioning must be administered before infusion of Skysona®.

GERIATRICS

N/A

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Skysona® is a cell suspension for intravenous infusion.
- A single dose of Skysona® contains a minimum of 5.0 × 106 CD34+ cells/kg of body weight, suspended in a solution containing 5% dimethyl sulfoxide (DMSO).