New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Skysona® (elivaldogene autotemcel) [bluebird bio]**
Dosage Formulations:	Intravenous (IV) infusion containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells.
FDA Approval Date: **FDB File Date:**	FDA: September 16, 2022 FDB: September 25, 2022
Indication:	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.
Mechanism 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 lentiviral vector (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 human adrenoleukodystrophy protein (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:	• Skysona is provided as a single dose for infusion containing a suspension of CD34+ cell in one or two infusion bags. The minimum recommended dose of Skysona is 5.0 × 10^6 CD34+ cells/kg. • Before mobilization, apheresis, and conditioning are initiated, confirm that hematopoietic stem cell (HSC) transplantation is appropriate for the patient. Perform screening for hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines before collection of cells for manufacturing. • Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. Collect a minimum target of 12 × 10^6 CD34+ cells/kg. A back-up collection of CD34+ cells of ≥ 1.5 × 10^6 CD34+ cells/kg (if collected by apheresis) or ≥ 1.0 × 10^8 TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. Back-up collection may be needed for rescue treatment in the case of compromise of Skysona after initiation of conditioning, primary engraftment failure, or loss of engraftment after infusion. • Full myeloablative and lymphodepleting conditioning must be administered before infusion of Skysona. Do not begin conditioning until Skysona has been received and stored at the treatment center and the availability of the back-up collection of CD34+ cells is confirmed. After completion of conditioning, allow a minimum of 48 hours of washout before Skysona infusion. • Skysona is shipped to the treatment center in a frozen state and must be stored according to product specifications. Coordinate the timing of Skysona thaw and infusion. Confirm the infusion time and adjust the start time of Skysona thaw such that it will be available for infusion when the patient and healthcare providers are ready. • Skysona is for autologous use only. The patient's identity must match the patient identifiers on the Skysona cassette(s) and infusion bag(s). Complete the infusion of Skysona as soon as possible, and no more than 4 hours after thawing. Administer each infusion bag of Skysona via intravenous infusion (drip) by gravity flow over a period of less than 60 minutes. After the entire content of the infusion bag is infused, flush all Skysona remaining in the infusion bag and any associated tubing with at least 50 mL of 0.9% sodium chloride solution to ensure that as many cells as possible are infused into the patient.

	• Standard procedures for patient management after HSC transplantation should be followed after Skysona infusion.
Disease State Clinical Highlights:	• Adrenoleukodystrophy (ALD), also known as X-linked adrenoleukodystrophy, is a rare genetic disorder that affects the white matter of the central nervous system (CNS) and the adrenal cortex. It is caused by pathogenic variants in the *ABCD1* gene located on the X chromosome which leads to males developing more serious complications compared to females. • The *ABCD1* gene encodes for the ALDP protein, a transporter protein, which helps facilitate transport of VLCFA molecules. In the absence of adequate ALDP protein, the breakdown of VLCFA is disrupted resulting in a buildup of these molecules in tissues throughout the body. Accumulation in the myelin of nerve cells and the adrenal cortex lead to the symptoms of ALD. • ALD is broken down into subtypes including adrenomyeloneuropathy (AMN), adult cerebral ALD, childhood cerebral ALD (cCALD, more commonly known as CALD), and Addison's-only ALD. CALD is the most severe form and typically presents between three and ten years of age. • The overall presence of all types of ALD is approximately 1 in 17,000 newborns. bluebird bio estimates about 40 patients are diagnosed with CALD in the United States every year. • Symptoms can vary widely, even among members of the same family. In CALD, 35% of affected males develop neurologic symptoms between three and ten years of age. Patients will develop normally and then start to show a loss of previously acquired skills. Many exhibit behavioral problems including attention deficit disorder and learning disabilities. Neurologic deterioration that includes increasing cognitive and behavioral abnormalities, blindness, and the development of quadriparesis may occur. • Without treatment, rapid progression is common leading to total disability in six months to two years and death within five to ten years of diagnosis. • Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the standard of care. It is given in pediatric patients with evidence of CNS involvement who have not progressed to neurological symptoms. • Diagnosis can be achieved by either genetic testing or attaining a VLCFA panel. In the United States, newborn screening for ALD was added to the Recommended Uniform Screening Panel in 2016. However, each state determines what disorders are included in their screening and as of 2019 only 12 states, including Missouri, screened for ALD. In practice, diagnosis is suspected upon identification of symptoms and confirmed via VLCFA and genetic testing.
Drug Clinical Highlights:	• Skysona is the first FDA-approved therapy shown to slow the progression of CALD. bluebird bio was granted Orphan Drug, Rare Pediatric Disease, and Breakthrough Therapy designations by the FDA. <u>Contraindications</u>: none <u>Warnings/Precautions:</u> • Hematologic Malignancy ○ Myelodysplastic syndrome (MDS), a hematologic malignancy, has developed in patients treated with Skysona in clinical studies. At the time of approval, three patients treated with Skysona had been diagnosed with MDS. Two patients who were diagnosed at 14 months and 2 years after treatment had preceding delayed platelet engraftment. The third patient had normal blood counts from 18 months to 5 years after treatment and presented 7.5 years after Skysona administration with symptomatic anemia and thrombocytopenia and was subsequently diagnosed with MDS with increased blasts. ○ Because of the risk of hematologic malignancy, carefully consider alternative therapies prior to the decision to treat a child with Skysona. Consultation with hematology experts is recommended.

- Serious Infections
  - Severe infections, including life-threatening or fatal infections, have occurred in patients after Skysona infusion. Grade 3 or higher infections occurred in 21% of all patients (12% bacterial, 3% viral, and 6% 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.
  - Monitor patients for signs and symptoms of infection before and after Skysona administration and treat appropriately. Administer prophylactic antimicrobials according to best clinical practices and clinical guidelines.
- Prolonged Cytopenias
  - Patients may exhibit cytopenias, including pancytopenia, for > 1 year following conditioning and Skysona infusion. Grade 3 or higher cytopenias on or after Day 60 following Skysona infusion occurred in 47% of patients and included low platelet count (14%), low neutrophil count (22%), low lymphocyte count (27%), and low hemoglobin (2%). Grade 3 cytopenias persisted beyond Day 100 in 15% of patients and included low platelet count (7%), low neutrophil count (9%), and low lymphocyte count (6%).
  - Monitor blood counts until normalization and assess patients for signs and symptoms of bleeding and/or infection prior to and after Skysona administration.
- Delayed Platelet Engraftment
  - Delayed platelet engraftment has been observed with Skysona. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 14% of patients had a platelet count ≤ 50×10^9/L beyond 60 days after treatment with Skysona.
  - Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved.
- Risk of Neutrophil Engraftment Failure
  - There is a potential risk of neutrophil engraftment failure after treatment with Skysona. Neutrophil engraftment failure was defined as failure to achieve 3 consecutive absolute neutrophil counts (ANC) ≥ 0.5×10^9 cells/L obtained on different days by Day 43 after infusion.
  - Monitor neutrophil counts until engraftment has been achieved, if neutrophil engraftment failure occurs in a patient treated with Skysona provide rescue treatment with back-up collection of CD34+ cells.
- Hypersensitivity Reactions
  - Allergic reactions may occur with the infusion of Skysona. The dimethyl sulfoxide in Skysona may have hypersensitivity reactions, including anaphylaxis which is potentially life-threatening and requires immediate intervention.
- Anti-retroviral Use
  - Patients should not take anti-retroviral medications for at least one month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed. Anti-retroviral medications may interfere with manufacturing of the apheresed cells.
  - If a patient requires anti-retrovirals for HIV prophylaxis, mobilization and apheresis of CD34+ cells should be delayed until HIV infection is adequately ruled out.
- Laboratory Test Interference
  - Skysona affected polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion. A PCR-based assay should not be used to screen for HIV infection in patients treated with Skysona as a false-positive test result is likely.

<u>Drug Interactions:</u>

- Vaccines: the safety and effectiveness of vaccination during or following Skysona treatment have not been studied. Vaccination is not recommended during the 6 weeks

preceding the start of myeloablative conditioning and until hematological recovery following treatment with Skysona.
- Anti-retrovirals: Patients should not take anti-retrovirals for at least one month prior to initiating medications for stem cell mobilization and for the expected during for elimination of the medications and until all cycles of apheresis are completed.

Clinical Studies:

- ALD-102 (NCT01896102) and ALD-104 (NCT03852498): open-label, single arm studies evaluating Skysona in male patients aged 4-17 years with early, active CALD, evidenced by elevated VLCFA values and confirmed *ABCD1* pathogenic variants.
- The following measurements were used to assess disease severity for study participants:
  - Loes score: measures the extent of disease severity on MRI, ranges from 0 to 35 with higher scores indicating more severe disease. A score of less than 0.5 is considered to be normal.
  - Gadolinium enhancement (GdE+) on MRI of demyelinating lesions: associated with an increased probability of progression and higher 5-year mortality.
  - Major functional disabilities (MFDs): includes loss of communication, cortical blindness, requirement of tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.
  - Neurologic function score (NFS): Used to rate clinical neurologic status. Scores range from 0 (asymptomatic) to 25 and assess hearing/auditory processing, communication, vision impairment, swallowing difficulty, and walking ability among others.

	Phase 2/3 ALD-102 N=32	**Phase 3 ALD-104 N=35**
Study Population (N = 67)	• 47% White/Caucasian, 38% Hispanic, 3% Asian, 3% Black or African American, 16% other races including mixed race*	• 60% White/Caucasian, 14% Hispanic, 6% Black or African American, 6% other races including mixed race*
Key Inclusion Criteria	• Males ≤ 17 years of age • Active CALD, as defined by elevated VLCFA values, active CNS disease established by central radiographic review of brain MRI demonstrating Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and GdE+ on MRI of demyelinating lesions • NFS ≤1	
Key Exclusion Criteria	• Receipt of an allogeneic transplant or gene therapy • Availability of a willing 10/10 HLA-matched sibling donor • Use of statins, Lorenzo's oil, or dietary regimens used to lower VLCFA levels after time of consent • Immediate family member with known or suspected familial cancer syndrome (FCS)	• Receipt of an allogeneic transplant or gene therapy • Use of statins, Lorenzo's oil, or dietary regimens used to lower VLCFA levels after time of consent • Immediate family member with known or suspected FCS

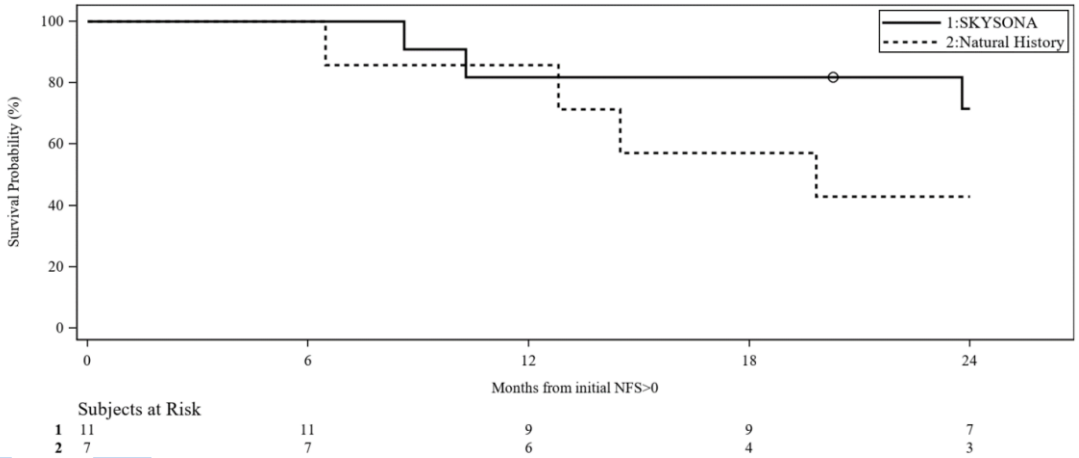
Interventions	Skysona administered by IV infusion following myeloablative conditioning with busulfan	
Primary Endpoints	• Percentage of patients who are alive and have none of the 6 MFDs at Month 24 and without allogenic hematopoietic stem cell transplantation (HSCT) or rescue cell administration • Proportion of patients who experienced either acute (≥ grade II) or chronic graft-versus-host disease by Month 24	• Percentage of patients who are alive and have none of the 6 MFDs at Month 24 • Percentage of patients with neutrophil engraftment after drug product infusion
Key Secondary Endpoints	• Percentage of patients who demonstrated resolution of GdE+ on MRI at Month 24 • Time to sustained resolution of GdE+ on MRI • Number of patients with change in total NFS from baseline to Month 24 • MFD-free survival rate • Overall survival rate at 24 months after Skysona drug infusion	• Percentage of patients without GdE+ on MRI at Month 24 • Change in total NFS from baseline to protocol scheduled visits • MFD-free survival over time • Overall survival

- Mobilization and Apheresis
  - Granulocyte-colony stimulating factor (G-CSF) 10 µg/kg (median) for a minimum of 4 days
  - Plerixafor 0.24 mg/kg for up to 3 days – optional in ALD-102 (administered to 34% of patients) and required in ALD-104.
  - 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 Conditioning
  - ALD-102: busulfan dose median (min, max) 14 (11.2 to 16.8) mg/kg over 4 days
  - ALD-104: busulfan dose median (min, max) 199 (151 to 213) mg/kg over 4 days
- Pre-treatment Lymphodepletion
  - ALD-102: cyclophosphamide dose median (min, max) 199 (151 to 213) mg/kg over 4 days
  - ALD-104: Fludarabine dose 180 mg/m^2 over 6 days for 11 patients; 160 mg/m^2 over 4 days (actual dose range 122 to 196 mg/m^2) for 24 patients
- Skysona Administration
  - All patients were administered Skysona as an intravenous infusion with a median (min, max) dose of 12 × 10^6 (5, 38.2) CD34+ cells/kg
- Efficacy Analysis
  - Skysona was compared to an external untreated natural history control (ALD-101). A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS ≥ 1) to time to first MFD or death in Skysona treated (n = 11) and natural history patients (n = 7). 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.

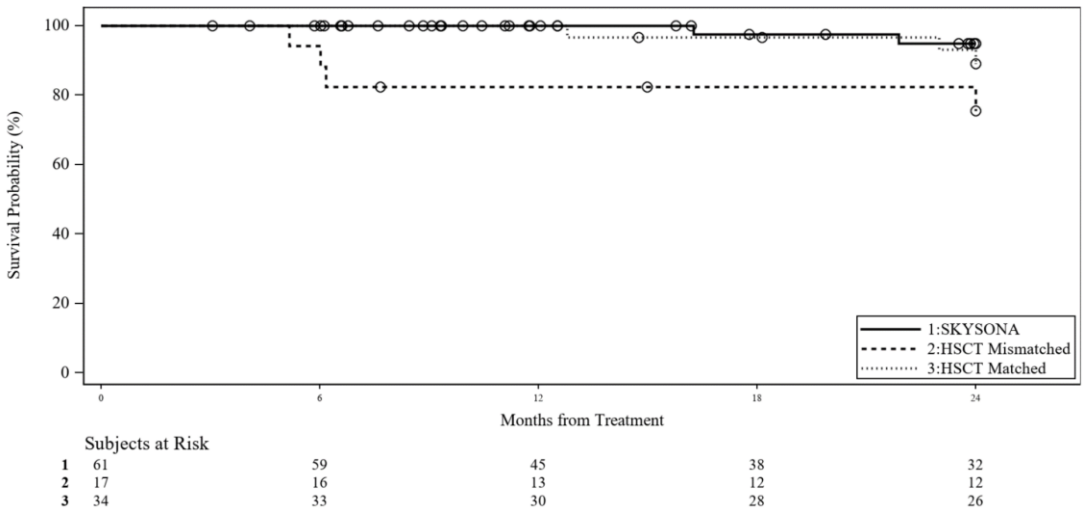
- The 7 patients in the natural history population were a median (min, max) 9 (5, 15) years old at time of CALD diagnosis, and 10 (5, 17) years at time of first NFS ≥ 1. The median Loes score at diagnosis was 5 (2, 9). Four (57%) had a baseline brain MRI pattern of disease inclusive of parieto-occipital involvement, 2 (29%) had frontal disease and 1 (14%) had isolated pyramidal tract disease. One (14%) had a baseline NFS=1 and the remainder were asymptomatic (NFS=0) prior to treatment.
- 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.
- Skysona-treated patients had an estimated 72% (95% CI: 35%, 90%) likelihood of MFD-free survival at 24 months from the time of first NFS ≥ 1, whereas untreated patients had an estimated 43% (95% CI: 10%, 73%) likelihood of MFD-free survival.

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



- Comparison with Allogenic HSCT Cohort
  - Clinical trial data were insufficient to compare the relative efficacy of Skysona to the standard of care allogenic hematopoietic stem cell transplant (allo-HSCT) in the treatment of CALD. Skysona was however compared with an external allo-HSCT control (data pooled from ALD-101, made into a prospective and retrospective observational study, ALD-103) to analyze overall survival (OS) due to concerns about treatment-related toxicities. OS was analyzed as time-to-event Kaplan-Meier estimates comparing Skysona (N=61) to early, active allo-HSCT subpopulation by donor type (HLA-matched N=34, HLA-mismatched N=17). There were insufficient long-term data to compare OS beyond Month 24, but there was a distinct difference in OS in the first 9 months between Skysona-treated patients and HLA-mismatched allo-HSCT patients. While this analysis does not provide evidence of efficacy of Skysona, it does demonstrate a survival advantage of Skysona compared to allo-HSCT from a HLA-mismatched donor.

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



- Adverse Events
  - The most common non-laboratory adverse reactions in patients treated with Skysona included mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, and rash (≥ 20%). The most common grade 3 or 4 laboratory abnormalities included leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, and hypokalemia (≥ 40%).

Price Per Unit (WAC):

$3 million per one-time infusion

Therapeutic Alternatives:

- Allogenic HSCT is the treatment of choice for boys with early-stage CALD. Observational studies have reported 5- and 8-year survival rates of 56%, with 5-year survival rates as high as 92% among patients treated at very early stages of the illness. There are risks associated with HSCT such as graft-versus-host disease, graft failure, and transplant-related mortality. These complications occur more frequently when matched unrelated donors or unmatched donors are used and when patients are older and have more advanced disease at the time of transplant. bluebird bio estimates that only 30% of patients with CALD are able to find a matched sibling donor. Of note, HSCT does not improve adrenal insufficiency. HSCT has also been associated with a 20% risk of morbidity and mortality in ALD.
- There are no other disease-modifying treatments available for CALD. Symptomatic and supportive care including physical therapy, psychological support, and special education should be made available to all applicable patients.

Prior Authorization Approval Criteria:

Must meet the following criteria:

<u>Initial Therapy:</u>

- Documented diagnosis of early, active CALD (E71.520, E71.521) including:
  - Elevated VLCFA values **AND**
  - Genetic testing confirmed pathogenic variants in *ABCD1* gene **AND**
  - Active CNS disease established by central radiographic review of brain MRI demonstrating:
    - Loes score between 0.5 and 9 (inclusive) on the 34-point scale **AND**
    - Gadolinium enhancement on MRI of demyelinating lesions **AND**
  - NFS ≤ 1 **AND**

	• Participant aged 4 to 17 years **AND** • Participant lacks history of HSCT **AND** • Participant lacks known or available HLA-matched family donor <u>Continuation of Therapy:</u> • None **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Skysona has not been studied in patients with a history of HIV infection, HBV infection, or HCV infection. • Patients are advised not to take antiretrovirals or hydroxyurea during Skysona mobilization and treatment. If a patient requires antiretrovirals for the prevention of HIV, confirm a negative HIV test before initiating treatment with Zynteglo. • Myelodysplastic syndrome has developed in patients treated with Skysona. Monitor with a complete blood count (with differential) at least twice in the first year and then annually thereafter.

Implication to State Medicaid Program:	• Skysona represents the most expensive therapy currently on the market. This list price does not include other treatment-related costs such as the apheresis procedure and approximately 2-month hospital stay required after infusion. Skysona is expected to be available by the end of 2022 through a network of qualified treatment centers (QTCs) in the United States. There are currently two QTCs listed by the manufacturer, located in Boston and Philadelphia, will the goal of having additional QTCs by the end of 2022.
	• Leriglitazone (Minoryx Therapeutics/Sperogenix) is currently in Phase 3 trials for ALD. Leriglitazone is an orally administered selective peroxisome proliferator-activated receptor (PPAR) agonist and metabolite of pioglitazone that aims to modify pathways leading to oxidative stress, neuroinflammation, mitochondrial dysfunction, demyelination, and axonal degeneration.
	  ○ Phase 2/3 Nexus study (NCT04528706): evaluating the use of leriglitazone in children with CALD. Currently in recruitment stage.
	  ○ Phase 2/3 Advance study (NCT03231878): includes adults with AMN. Preliminary data showed that six adult (15.4%) in the placebo group (n = 39) developed clinically progressive, adult cerebral ALD, compared to none in the leriglitazone group (n = 77).
	  ○ Minoryx anticipates approval could come at the end of 2023 at the earliest, with the anticipated price being $300,000-500,000 per year.

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