Skysona (elivaldogene autotemcel)
Clinical Coverage Criteria

Description

Skysona (elivaldogene autotemcel) is an autologous hematopoietic stem cell (HSC)-based gene therapy, indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD) without an available human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant.

Policy

This Policy applies to the following Fallon Health products:

☒ Fallon Medicare Plus

☒ MassHealth ACO

☒ NaviCare HMO SNP

☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)

☒ Community Care

Skysona (elivaldogene autotemcel) requires prior authorization by a Fallon Health Medical Director, except as noted below, for MassHealth ACO members effective April 1, 2025. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.

Effective April 1, 2025, MassHealth transitioned the review and management of all APAD and APEC carve-out drugs, including Skysona, to the MassHealth Drug Utilization Review (DUR) Program. Effective for dates of services on or after April 1, 2025, prior authorization requests for all APAD and APEC carve-out drugs, including Skysona must be submitted to the DUR Program for review and approval prior to administration. NOTE: Only the prior authorization request for Skysona and other APAD and APEC carve out drugs will be reviewed by the MassHealth DUR Program, Fallon Health is still responsible for reviewing prior authorization requests for the member's inpatient or outpatient hospital encounter.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria apply to Fallon Medicare Plus, NaviCare and Community Care members.

Skysona (elivaldogene autotemcel) is considered medically necessary to slow the progression of neurologic dysfunction in plan members with early, active cerebral adrenoleukodystrophy (CALD) without an available human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant when all of the following coverage criteria are met:

1. Age ≥ 4 years and ≤ 17 years at the time of treatment.
2. Diagnosis of adrenoleukodystrophy confirmed by both:
   a. Elevated plasma very long chain fatty acids (VLCFA) values according to the standard reference values of the performing laboratory, and
   b. The presence of a pathogenic variant in the adenosine triphosphate binding cassette, sub family D member 1 (ABCD1) gene detected by genetic testing.
3. Documentation of early, active CALD as defined by all of the following:
   a. Active CNS disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:

i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
ii. Gadolinium enhancement on MRI of demyelinating lesions.

b. Neurologic Function Score (NFS) ≤ 1.

4. The treating physician is a specialist in the treatment of CALD and Skysona will be administered at a Skysona Qualified Treatment Center.*
5. The plan member is without an human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant. Skysona should only be used in CALD patients without suitable alternative treatment options, given the increased risk of hematologic malignancy.[1]

* SKYSONA (elivaldogene autotemcel) Qualified Treatment Center Locator

Medicare Variation

Medicare statutes and regulations do not have coverage criteria for Skysona (elivaldogene autotemcel). Medicare does not have an NCD for Skysona (elivaldogene autotemcel). National Government Services, Inc. is the Medicare Administrative Contractor (MAC) with jurisdiction over Part A and B services in Fallon Health's service area. National Government Services, Inc. does not have an LCD for Skysona (elivaldogene autotemcel) (Medicare Coverage Database search 01/26/2026). Coverage criteria for Skysona (elivaldogene autotemcel) are not fully established by Medicare, therefore, the Plan's clinical coverage criteria are applicable.

MassHealth Variation

Effective April 1, 2025, MassHealth will transition the review and management of all APAD and APEC carve-out drugs, including Skysona, to the MassHealth Drug Utilization Review (DUR) Program. Effective for dates of services on or after April 1, 2025, prior authorization requests for all APAD and APEC carve-out drugs, including Skysona must be submitted to the DUR Program for review and approval before administration. Only prior authorization request for the APAD and APEC carve-out drugs will be reviewed by the MassHealth DUR Program, Fallon Health is still responsible for reviewing prior authorization requests for the member's inpatient or outpatient hospital encounter.

Additionally, also effective for dates of services on or after April 1, 2025, MassHealth will pay claims for APAD and APEC carve-out drugs for MassHealth ACO enrollees consistent with Sections 5.B.8.b and 5.C.9 of the current MassHealth Acute Hospital Request for Applications (Acute Hospital RFA) for in-state acute hospitals and regulations at 130 CMR 450.233(D) for out-of-state acute hospitals. Fallon Health will continue to pay claims for the member's inpatient or outpatient hospital encounter.

Refer to the following MassHealth Bulletins for additional information: MassHealth Managed Care Entity Bulletin 125 March 2025, MassHealth Acute Inpatient Hospital Bulletin 201 March 2025, and MassHealth Acute Outpatient Hospital Bulletin 41 March 2025, available at: https://www.mass.gov/masshealth-provider-bulletins.

The MassHealth Acute Hospital Carve-out Drugs List is available at: https://masshealthdruglist.ehs.state.ma.us/MHDL/.

Exclusions

- Retreatment with Skysona or use after failure of allogeneic hematopoietic stem cell transplant (HSCT).
- The safety and efficacy of Skysona in children less than 4 years of age have not been established.
- Use to treat or prevent adrenal insufficiency.
- Use in patients with CALD secondary to head trauma.
- There are no available data for Skysona administration in a geriatric population nor is it expected or intended to be used in this population.

[1] FDA Approves Required Labeling Changes for Increased Risk of Hematologic Malignancy Following Treatment with Skysona (elivaldogene autotemcel) August 7, 2025

- Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy.

Summary of Evidence

Background

Adrenoleukodystrophy (ALD) is a rare X-linked inborn error of metabolism caused by mutations in the adenosine triphosphate binding cassette, sub family D member 1 (ABCD1) gene (Zhu et al., 2020). Mutations in the ABCD1 gene prevent the production of the adrenoleukodystrophy protein (ALDP) in about 75% of people with this disorder. ALDP is located in the membranes of cell structures called peroxisomes. ALDP brings a group of fats called very long-chain fatty acids (VLCFAs) into peroxisomes, where they are broken down. With little or no functional ALDP, VLCFAs are not broken down and they build up in the body (NLM, 2013).

In males suspected of having ALD, the measurement of very long chain fatty acids (VCLFA) in blood is diagnostic, with nearly 100% sensitivity. However, this diagnostic marker can be normal in 15-20% of females (Huffnagel et al., 2019). Genetic testing should be performed to confirm the diagnosis of ALD. After genetic confirmation in the proband, targeted testing for the identified mutation in immediate and extended family members should be offered to those at risk of developing ALD. To date, over 900 unique disease-causing mutations have been catalogued with no correlation to phenotypes, and there is no identified means of determining which males with ALD will develop which clinical features of the disorder. Furthermore, all clinical phenotypes of X-linked ALD can occur within the same nuclear family (Zhu et al., 2020).

In affected males, the clinical spectrum ranges from isolated adrenal insufficiency and slowly progressive myelopathy to devastating cerebral unflammatory demyelination, termed cerebral ALD (CALD). As ALD is an X-linked disease, females were previously considered asymptomatic carriers. It is now known that even though adrenal insufficiency and CALD rarely occurs in females (less than 1%), more than half will develop signs and symptoms of progressive myelopathy with the frequency increasing sharply with age (from 18% in females <40 years to 88% in women >60 years of age) (Engelen et al., 2014).

CALD presents in males between 4 and 12 years of age, with a peak age at onset of around 7 years, affecting approximately one-third of boys with X-linked ALD. CALD is rare after 15 years of age and almost never occurs before 2 years of age. Early on, the disease is a purely radiographic finding, as lesions on brain MRI far precede clinical manifestations. Brain MRIs should be obtained annually starting at 12 months of age and obtained more frequently every 6 months from the ages of 3–10 years, when the risk of developing cerebral CALD is highest. Affected boys subsequently develop learning and behavior problems. This first stage is followed by neurologic deterioration that includes increasing cognitive and behavioral abnormalities, cortical blindness, central deafness, and the development of quadriparesis. Very rarely, visual function is relatively preserved despite advanced central nervous system involvement. Approximately 20% of affected boys have seizures, which may be the first manifestation. Although the rate of deterioration can be variable, rapid progression is common, with total disability developing by 6 months to 2 years and death within 5 to 10 years of diagnosis (Zhu et al., 2020).

As elevations in VLCFA were recognized to be present at birth, the potential to use newborn screening for ALD was appreciated (Gupta et al., 2022). As survival and clinical outcomes are superior if treatment is offered in the early stages of cerebral ALD, ALD was nominated to be added to the U.S. Recommended Uniform Screening Panel in 2012 (Zhu et al., 2020). Newborn screening is a state-based public health program in the United States. This means that each state or territory has its own newborn screening program. Also, state or territory level policies govern which conditions are included in their newborn screening program. Massachusetts and many other states conduct newborn screening for X-linked ALD (HRSA Newborn Screening, 2023). As newborn screening for ALD continues to expand in the United States, the reporting of mutations to variant databases and follow-up classification of variants based on phenotypic outcomes in affected families will be crucial to understanding the pathogenicity of new variants (Zhu et al., 2020).

Allogeneic hematopoietic stem cell transplant (allo-HSCT) has been the standard of care for the treatment of CALD since 2001. Retrospective studies have documented more favorable neurologic outcomes when allo-HSCT is performed early in the course of disease, prior to onset of significant neurologic dysfunction or radiographic disease burden. It has also been observed that allo-HSCT may increase rapidity of disease progression in patients with advanced cerebral disease (Loes score >9), and is no longer recommended for patients who meet this criterion. As such, allo-HSCT is performed in the early, active radiographic course of disease (Loes score 0.5-9 with gadolinium enhancement on brain MRI), which often corresponds to a time when patients are asymptomatic or mildly symptomatic (NFS 0 or 1).[2] The goal of treatment in this early, active phase of disease is to treat prior to the onset of significant neurologic dysfunction in an effort to prevent progression to disability and death, which is often rapid and more difficult to stabilize once disease is symptomatic.

In addition to the lack of efficacy in advanced disease, allo-HSCT does not reverse neurologic findings present at the time of transsplantation and does not stabilize cerebral disease for 3 to 24 months after stem cell infusion. Symptoms can progress during this time. This makes the early identification of potential allo-HSCT candidates essential. Transplant is ineffective for the adrenal manifestations of disease and is not felt to impact the development of adult onset adrenomyeloneuropathy. Transplantation requires the identification of a stem cell donor. If an acceptable human leukocyte antigen (HLA)-matched related donor is not available, then an unrelated donor or cord blood unit must be found. This process can take weeks and, in some circumstances, an acceptable unrelated stem cell donor may not be identified. Allo-HSCT comes with risks of acute mortality (~10% at day 100 from transplant) and late complications, a 5% risk failure of donor cell engraftment, and graft-versus-host disease (GVHD) (10–40% risk of acute GVHD and 20% risk of chronic GVHD). Patients with CALD must also meet institutional criteria for organ functioning, infectious disease status, and performance status. In summary, allo-HSCT is an effective therapy for patients who have early stage cerebral CALD, but it comes with significant short- and long-term risk (Zhu et al., 2020).

Transplantation of autologous, genetically modified hematopoietic stem cells (HSCs) is being extensively explored as an alternative to allo-HSCT for several conditions worldwide, with a large number of trials opened and patients being treated in the United States and Europe. This treatment strategy allows prompt identification of a stem cell source for transplant in every patient and overcomes the most severe immunological limitation of allo-HSCT represented by GVHD. In this setting, gene transfer is used to deliver a normal copy of the disease-causing gene (generally as cDNA) to the HSCs, thereby correcting their genetic defect (Shahryari et al., 2019).

Clinical Trials

Childhood CALD is one of the first neurologic disorders treated by the autologous gene therapy approach. Promising results reported in 2009 by Cartier and colleagues were obtained in 2 patients treated in the first clinical trial of hematopoietic stem cell gene therapy for CALD using autologous CD34+ transduced ex-vivo with Lenti-D lentiviral vector (also called elivaldogene autotemcel or eli-cel). Similar to what has been observed following allogeneic HSCT, clinical and

[2] The CALD–specific neurologic function scale (NFS) and the Loes MRI severity score are used to help determine the suitability of a patient for transplant. The NFS is a 25-point, ALD-specific tool that assesses the severity of neurologic dysfunction by assigning scores to 15 different disabilities. Lower scores indicate fewer symptoms and higher scores indicate a more significant disability. The NFS score can be used to guide the recommendation for allo-HSCT, but there is no score that absolutely determines the decision for allo-HSCT. The Loes MRI severity score is a 34-point scale that assigns a score to an MRI based on the extent of white matter lesions, with higher scores indicating more significant ALD involvement (Loes et al., 2003).

MRI gadolinium contrast enhancement is used to indicate the presence of the inflammatory process, and there is an association between the presence of contrast enhancement on T1-weighted MRI and cerebral ALD progression. To be considered for allo-HSCT, patients must have evidence of cerebral disease on brain MRI with the presence of gadolinium contrast enhancement around a consistent lesion, indicating a minimum Loes MRI score of 1. The upper limit of the Loes MRI score is debated and often depends on the clinical scenario (Melhem et al., 2000).

neuroradiological disease stabilization was observed in the 2 boys, who had progressive demyelination but no HLA-matched or cord blood donors (Cartier et al., 2009).

After these encouraging results, a larger, multicenter phase II/III clinical trial was launched in 2013 (ClinicalTrials.gov NCT01896102). Eligibility was restricted to patients who had gadolinium enhancement on MRI due to CALD and had the following signs of early-stage disease: a score on the CALD–specific neurologic function scale (which ranges from 0 to 25, with higher scores indicating more severe deficits) of 0 or 1, and a Loes score (which ranges from 0 to 34, with higher scores indicating an increased extent of lesions on MRI) of 0.5 to 9.0. Patients who had an HLA-matched sibling who could donate cells for transplantation were excluded from the study. CD34+ cells that were obtained from the enrolled patients by means of apheresis were transduced with the Lenti-D lentiviral vector. Interim results for 17 patients who were between 4 and 13 years of age at the time of enrollment were published by Eichler et al. (2017). At baseline, the median Loes score was 2.0 (range, 1.0 to 7.5), and all the patients had a score of 0 on the neurologic function scale. Data on the interim safety and efficacy assessments were available as of April 2017. At the time of the interim analysis, 15 of the 17 patients (88%) were alive and free of major functional disabilities; these 15 patients maintained a score on the neurologic function scale of 0 or 1. Two patients had neurologic disease progression. One of these patients (Patient 2016) withdrew from the study and later died from complications of allogeneic transplantation. In the other patient (Patient 2018), neurologic function deteriorated rapidly after treatment; a major functional disability (total incontinence) developed by month 9, and additional major functional disabilities continued to develop, including cortical blindness, loss of communication, and wheelchair dependence. Approximately 22 months after the infusion, the patient died from a viral infection complicated by rhabdomyolysis and acute kidney and liver failure; these complications and the immediate cause of death were judged to be not directly related to the investigational therapy. Mean follow-up was 29.4 months (range, 21.6 to 42.0). This study has since met its target accrual of 32 subjects and has been closed to additional accruals.

Final results for the phase II/III study (ClinicalTrials.gov NCT01896102) were published by Eicher and colleagues in 2024. A total of 32 patients received Skysona and 29 patients (91%) completed the 24-month study and are being monitored in the long-term follow-up study (NCT03852498). Two patients were withdrawn and referred for alloHSCT before their month 24 visit; another experienced early and rapid disease progression while on-study resulting in major functional disabilities (MFDs) and death. For the primary efficacy endpoint, 24-month MFD-free survical, 90.6% (95% CI 75.0 to 98.0) of participants were alive and had none of the 6 major functional disabilities (MFDs) at month 24. For the primary safey endpoint, 0% (95% CI 0.0 to 10.9) of participants experienced either acute (≥ Grade II) or chronic GVHD by month 24, At 24 months, none of these 29 patients had major functional disabilities, and the overall survival was 96.7% (95% CI 78.6 to 99.5). Insertional oncogenesis is an ongoing risk associated with the integration of viral vectors. At 24 months, no patients developed insertional oncogenesis, however, myelodysplastic syndrome (MDS) with excess blasts developed in one patient at month 92; the patient underwent allogeneic hematopoietic stem-cell transplantation and did not have MDS at the most recent follow-up.

A phase III trial was opened in January 2019 (ClinicalTrials.gov NCT03852498) and 35 patients are enrolled. This study was completed in July 2023, results are posted on ClinicalTrials.gov but not yet published.

After completing either the phase II/III study or the phase III study, participants were enrolled in a long-term safety and efficacy follow-up study NCT02698579). Participants will be followed for an additional 13 years for a total of 15 years post Skysona infusion.

Duncan et al., 2024 performed an integration analysis of genetic studies, flow cytometry, and morphologic studies in peripheral-blood and bone marrow samples from patients who received Skysona in the completed phase II/III study (NCT01896102 and phase III study (NCT03852498) and the ongoing long-term safety and efficacy follow-up study NCT02698579). Hematologic cancer developed in 7 of 67 patients after the receipt of Skysona 1 of 32 patients in the ALD-102 study (NCT01896102) and 6 of 35 patients in the ALD-104 study (NCT03852498)]:

myelodysplastic syndrome (MDS) with unilineage dysplasia in 2 patients at 14 and 26 months; MDS with excess blasts in 3 patients at 28, 42, and 92 months; MDS in 1 patient at 36 months; and acute myeloid leukemia (AML) in 1 patient at 57 months. Of the 5 patients with MDS with excess blasts or MDS with unilineage dysplasia who underwent allogeneic hematopoietic stem-cell transplantation (HSCT), 4 patients remain free of MDS without recurrence of symptoms of cerebral adrenoleukodystrophy, and 1 patient died from presumed graft-versus-host disease 20 months after HSCT (49 months after receiving eli-cel). The patient with AML is alive and had full donor chimerism after HSCT; the patient with the most recent case of MDS is alive and awaiting HSCT. Hematologic cancer developed in a subgroup of patients who were treated with Skysona. The authors state that these cases are associated with clonal vector insertions within oncogenes and clonal evolution with acquisition of somatic genetic defects.Lund et al., 2024 reported on a 9-year-old boy with adrenoleukodystrophy due to ABCD1 whole-gene deletion who was diagnosed with active cerebral adrenoleukodystrophy characterized by demyelination and gadolinium enhancement on brain MRI. The boy underwent hematopoietic stem cell gene therapy with autologous $CD34^+$ cells transduced with an ABCD1-expressing lentiviral vector (Skysona) as part of the ALD-104 (NCT03852498) clinical trial. Fifty days after infusion, the patient's MRI showed gadolinium resolution; the whole-blood vector copy number (VCN) was 0.666 copies/mL. Six months following infusion, an MRI showed re-emergence of gadolinium enhancement; the VCN had decreased to 0.029 copies/mL.

U.S. Food and Drug Administration (FDA)
On October 18, 2021, bluebird bio, Inc. submitted a Biologics License Application to the FDA for licensure of elivaldogene autotemcel (eli-cel) with the proprietary name of Skysona. Bluebird bio, Inc. proposed the indication, “for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy (CALD) who do not have an available and willing human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor.” Results from two studies ALD-102 (NCT 01896102) and ALD-104 (NCT03852498) were submitted. Studies ALD-102 and ALD-104 enrolled subjects ages 4-17 years of age with early, active CALD, defined by a Neurologic Function Score (NFS) ≤1 and brain magnetic resonance imaging (MRI) with gadolinium enhancement (GdE+) and a Loes Score 0.5-9. Patients who had an HLA-matched sibling who could donate cells for transplantation were excluded from the studies.

The prespecified primary efficacy endpoint in ALD-102 was the percentage of subjects who had none of the 6 major functional disabilities (MFDs), were alive, did not receive a rescue allo-HSCT or rescue cell administration, and had not withdrawn or been lost to follow-up at Month 24 (i.e., Month 24 MFD-free survival). The 6 MFDs consisted of loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, complete loss of voluntary movement. Month 24 MFD-Free survival criteria was defined as: alive at 24 months post-infusion; had not developed any of the MFDs by 24 months post-infusion; had not received rescue cell administration or allo-HSCT by 24 months post-infusion; and had not withdrawn from the study or had not been lost to follow-up by 24 months post-infusion. Percentage of participants who were alive and have none of the 6 major functional disabilities (MFDs) at Month 24 were reported.

As none of the study subjects in ALD-104 had reached 24 months of follow-up after treatment with Skysona at the time of BLA submission, so only the 32 ALD-102 subjects were evaluated for the primary efficacy endpoint. The study success criterion was superiority compared to a clinical benchmark of 50%. This benchmark was derived from 2 subpopulations from Study ALD-101 (a historical, retrospective study that included untreated CALD subjects). The 50% benchmark was chosen to demonstrate that Skysona was better than no treatment on MFD-free survival at 24 months. Twenty-three out of 26 (88%) subjects achieved Month 24 MFD-free survival (95% CI: 70%, 98%). ALD-102 was thus successful on the primary efficacy endpoint.

Athough ALD-102 met the success criterion for the primary efficacy endpoint, the FDA reviewers had concerns about the results. The main challenges were that few events (MFDs and deaths) occurred in the allo-HSCT and Skysona populations, and subjects treated with allo-HSCT and Skysona were generally diagnosed and treated at very early stages of disease. In comparison, event rates were high in the untreated natural history population, but the natural history population was older, with more advanced cerebral disease on MRI, and more likely to present

with symptomatic disease at time of diagnosis or shortly after diagnosis. As a result, it was difficult to determine if the lower numbers of MFDs and deaths in the treated populations were due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. It is unclear what the clinical course would have been in subjects with very early stages of disease had they not been treated. The reviewers conducted additional analyses to assess the clinical benefit.

In an analysis of MFD-free survival at 24 months, the reveiwers conducted a Kaplan-Meier (KM) time-to-event analysis that compared estimated time to progression to MFD or death from first NFS ≥ 1 among the untreated and treated subpopulations. The KM curves showed a striking difference between treatment groups (Skysona, allo-HSCT) and untreated natural history group. MFD-free survival KM estimates at the 24-month time point were 43% (95% CI: 10%, 73%), 69% (95% CI: 41%, 86%), and 72% (95% CI: 35%, 90%) for the untreated, allo-HSCT treated and Skysona-treated symptomatic subpopulations, respectively. It is notable that 28% of Skysona-treated symptomatic subjects experienced an MFD or death within 24 months of first NFS ≥ 1, as compared to 57% of the untreated natural history subpopulation. In essence, twice as many symptomatic natural history subjects progressed to MFD or death within 24 months of symptom onset as compared to a similar SKYSONA subpopulation.

The analysis of MFD-free survival at 24 months following first NFS ≥ 1 establishes an effect of Skysona on an intermediate clinical endpoint that is reasonably likely to predict long-term clinical benefit on MFD-free survival and slowing of progression of neurologic dysfunction as compared to the natural history of disease in symptomatic subpopulations. Success on this intermediate clinical endpoint forms the basis of accelerated approval, and confirmatory post-marketing review (PMR) studies will be required to assess long-term efficacy.

The primary evidence of efficacy lies in the outcomes of patients with parieto-occipital disease, as this pattern was the most common across studies, presents the earliest (in childhood) and is one of the most rapidly progressive if left untreated. Although numbers of subjects are small, there is evidence for efficacy in frontal patterns of disease, as well.

There are two populations for whom there is greater uncertainty regarding a favorable benefit-risk determination given the uncertainty of durability of effect and the magnitude of hematologic malignancy risk. Specifically, boys with isolated pyramidal tract pattern of disease on brain MRI and asymptomatic boys with very early radiographic findings (i.e., Loes score 1-2). Boys with the isolated pyramidal tract MRI pattern are known to have a slower progression of radiographic and clinical disease, typically with stable Loes score over time and prolonged duration between radiographic diagnosis and the onset of symptomatic disease (usually adulthood). Boys with very early radiographic and asymptomatic disease are poorly represented in the natural history of disease due to frequent delayed diagnosis at the time the natural history subjects were diagnosed, and thus the time course of expected clinical progression of disease is relatively unknown. Therefore, relative long-term efficacy and benefit-risk assessment in these populations with isolated pyramidal tract disease or very early radiographic and asymptomatic disease could only be determined with a longer duration of follow-up.

The prespecified primary safety endpoint was proportion of participants who had experienced either acute ([>or=] grade ii) or chronic graft versus host disease (GVHD) by month 24. Acute GVHD graded on the Acute GVHD Grading Scale (I-IV): Grade I is characterized as mild disease, Grade II as moderate, Grade III as severe (involvement of any organ system), and Grade IV as life-threatening; chronic GVHD was determined by the Investigator. Percentage of participants who experienced with either acute (>= Grade II) or chronic GVHD at Month 24 were reported.

The safety population included 67 subjects treated in the Phase 3 studies, ALD-102 and ALD-104.

Subjects were followed for a median of 23.5 months (range 1.4 months to 7.3 years). Safety data with a data cutoff of Aug. 18, 2021, were systematically reviewed, and cases of concern for malignancy or diagnosed malignancy that occurred at any time after the data cutoff date were reviewed on an ad hoc basis.

Insertional oncogenesis is the major safety concern with Skysona. Insertional oncogenesis is the primary safety concern with lentiviral vectors (LVVs). Insertional oncogenesis is the consequence of permanent alteration of the host genome by the vector. LVV integration into the DNA of target cells has the potential to affect the expression of nearby genes and may provide those cells with a growth advantage. Cells with a growth advantage may undergo preferential expansion and transform into a hematologic malignancy. At the time of FDA approval, three subjects had been diagnosed with hematologic malignancy (myelodysplastic syndromes, MDS). MDS is a rare hematologic malignancy in pediatric patients with no predisposition to development in children with CALD. However, it has been diagnosed in three subjects after treatment with Skyson. For all three subjects, the malignancy appears to have been caused by integration of the lentiviral vector into a proto-oncogene. In addition to the three subjects with MDS, the clinical review team has a specific concern for the possible development of malignancy in at least nine other subjects.

Two subjects died after treatment with Skysona. One underwent allo-HSCT due to CALD progression and subsequently died from HSCT complications. The second subject died from multisystem organ failure that was a complication of an adenovirus infection. He also had rapid progression of his CALD. It cannot be ruled out with certainty that his treatment with Slysona less than two years earlier may have contributed to the florid adenovirus infection.

There were many serious adverse reactions in the trials, having occurred in in 57% of subjects. The most common non-laboratory, non-cancer serious adverse reactions (≥ 3% incidence) that occurred after treatment with Skysona were febrile neutropenia (18%), pyrexia (18%), seizure (7%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%). No subjects were diagnosed with graft versus host disease.

FDA Update August 7, 2025
On August 7, 2025, the FDA Approves Required Labeling Changes for Increased Risk of Hematologic Malignancy Following Treatment with Skysona (elivaldogene autotemcel).

At the time of initial approval of Skysona in 2022, hematologic malignancy was identified as a serious risk, with MDS reported in 3 of 67 patients (4%) across clinical studies. Since initial approval, FDA has received seven additional reports from clinical trial participants, and as of July 2025, hematologic malignancies have been diagnosed in 10/67 (15%) clinical trial participants, more than tripling the previously reported incidence.

FDA has completed a review of the clinical trial data and has required updates to the Boxed Warning, Indications and Usage, Warnings and Precautions, and Adverse Reactions – Clinical Trials Experience sections of the prescribing information and Medication Guide to include new safety information on the increased risk of hematologic malignancy. Notably, the revised Indications and Usage restricts the indication to patients without an available human leukocyte antigen (HLA)-matched allogeneic hematopoietic stem cell (allo-HSC) donor. Therefore, Skysona should only be used in CALD patients without suitable alternative treatment options, given the increased risk of hematologic malignancy. The Limitations of Use section retains language emphasizing careful consideration of appropriateness and timing of treatment.

The Boxed Warning recommendation for closely monitoring patients for evidence of malignancy through complete blood counts was increased from every 6 months to every 3 months.

Early diagnosis of hematologic malignancy can be critically important. Therefore, patients should be closely monitored with complete blood counts at least every 3 months and through assessments for evidence of clonal expansion or predominance at least twice in the first year after Skysona administration and annually thereafter, and bone marrow evaluations should be considered as clinically indicated. If hematologic malignancy is detected in a patient who received Skysona, the event should be reported to the manufacturer and instructions will be provided on collection of samples for further testing.

The approval for Skysona included a postmarketing requirement (PMR) under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to conduct a 15-year long-term follow-up prospective, observational safety study to assess the long-term safety and the risk of secondary

malignancies occurring after treatment with Skysona. The study includes monitoring (at pre-specified intervals) for clonal expansion.

Analysis of Evidence (Rationale for Determination)

The recommendation for accelerated approval is based primarily on the Kaplan-Meyer time to event analysis in a symptomatic subset of Skysona-treated subjects and similar untreated controls. Skysona slowed the progression of neurologic dysfunction (NFS ≥ 1) assessed by major functional disabilities (MFDs) or death at 24 months from time of symptom onset compared to an untreated natural history population. Confirmatory post-marketing review (PMR) studies will be required to assess long-term efficacy.

Hematologic cancer developed in 7 of 67 patients treated with Skysona; the cases are associated with clonal vector insertions within oncogenes and clonal evolution with acquisition of somatic genetic defects. Insertional oncogenesis is an ongoing risk associated with the integration of viral vectors.

Since initial approval, FDA has received seven additional reports from clinical trial participants, and as of July 2025, hematologic malignancies have been diagnosed in 10/67 (15%) clinical trial participants, more than tripling the previously reported incidence. This resulted in labeling changes, limiting Skysona to boys 4- 17 years of age with early, active cerebral adrenoleukodystrophy (CALD) without an available human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant.

References

1. National Library of Medicine (NLM). Medline Plus. ABCD1 Gene. Last updated July 1, 2013. Available at: https://medlineplus.gov/genetics/gene/abcd1/. Accessed 07/24/2023.
2. Gupta AO, Raymond G, Pierpont EI, et al. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. *Expert Opin Biol Ther*. 2022 Sep;22(9):1151-1162.
3. Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. *Orphanet J Rare Dis*. 2019 Feb 7;14(1):30.
4. Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain*. 2014 Mar;137(Pt 3):693-706
5. Moser AB, Jones RO, Hubbard WC, et al. Newborn Screening for X-Linked Adrenoleukodystrophy. *Int J Neonatal Screen*. 2016 Dec;2(4):15.
6. Health Resources & Services Administration (HRSA). Newborn Screening in Your State. Date Last Reviewed: June 2023. Available at: https://newbornscreening.hrsa.gov/your-state. Accessed July 24, 2023.
7. Zhu J, Eichler F, Biffi A, Duncan CN, Williams DA, Majzoub JA. The Changing Face of Adrenoleukodystrophy. *Endocr Rev*. 2020 Aug 1;41(4):577–9.
8. Mahmood A, Raymond GV, Dubey P, et al.. Survival analysis of haematopoietic cell transplantation for childhoodcerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol.* 2007;6(8):687–692.
9. Loes DJ, Fatemi A, Melhem ER, et al.. Analysis of MRI patterns aids prediction of progression in X-linkedadrenoleukodystrophy. *Neurology*. 2003;61(3):369–374.
10. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging inpredicting disease progression. *AJNR Am J Neuroradiol*. 2000; 21(5):839–844.
11. Orchard PJ, Blazar BR, Wagner J, et al.. Hematopoietic cell therapy for metabolic disease. *J Pediatr.* 2007;151(4):340–436.
12. Peters C, Charnas LR, Tan Y, et al.. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic celltransplantation experience from 1982 to 1999. *Blood.* 2004;104(3):881–888.
13. Raymond GV, Aubourg P, Paker A, et al.. Survival and functional outcomes in boys with cerebral adrenoleukodystrophywith and without hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(3):538–548.

14. Shahryari A, Saghaeian Jazi M, Mohammadi S, et al. Development and clinical translation of approved gene therapyproducts for geneticdisorders. *Front Genet*. 2019; 10:868.
15. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al.. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science.* 2009;326(5954):818–823.
16. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *NEngl J Med*. 2017; 377(17):1630–1638.
17. Yengi L, Parsons G, Pasackow E, et al.. Evidence that prevalent SMG6 insertions are not associated with abnormalclinical findings in patients treated with lenti-D autologous hematopoietic stem cell gene therapy for cerebraladrenoleukodystrophy. Paper presented at: Program of the 27th Annual Congress of the European Society for Gene and CellTherapy; 2019; Barcelona, Spain, 164. (Abstract P264).
18. Eichler F, Duncan CN, Musolino PL, et al. Lentiviral Gene Therapy for Cerebral Adrenoleukodystrophy. *N Engl J Med*. 2024 Oct 10;391(14):1302-1312.
19. Rattay TW, Rautenberg M, Söhn AS, et al. Defining diagnostic cutoffs in neurological patients for serum very long chain fatty acids (VLCFA) in genetically confirmed X-Adrenoleukodystrophy. *Sci Rep*. 2020 Sep 15;10(1):15093.
20. Duncan CN, Bledsoe JR, Grzywacz B, et al. Hematologic Cancer after Gene Therapy for Cerebral Adrenoleukodystrophy. *N Engl J Med*. 2024 Oct 10;391(14):1287-1301.
21. Orchard PJ, Eichler F, Duncan C, et al. Lenti-D Hematopoietic Stem Cell Gene Therapy Stabilizes Neurologic Function in Boys with Cerebral Adrenoleukodystrophy. Abstracts. *Biol Blood Marrow Transplant* 2020;26: S8-S74.
22. Lund TC, Orchard PJ, Nascene DR, et al. Secondary failure of lentiviral vector gene therapy in a cerebral adrenoleukodystrophy patient with an ABCD1 whole-gene deletion. *Mol Ther*. 2024 Oct 2;32(10):3313-3317.
23. bluebird bio, Inc. Skysona [package insert]. U.S. Food and Drug Administration website. https://www.fda.gov/vaccines-blood-biologics/skysona. Revised 09/2022. Accessed 01/23/2025.
24. bluebird bio, Inc. Summary Basis for Regulatory Action – Skysona. U.S. Food and Drug Administration website: https://www.fda.gov/vaccines-blood-biologics/skysona. Accessed 01/23/2025.
25. Bluebird bio, Inc. Clinical Study Protocol ALD-102. Protocol Version: 10.0. Protocol Date: 23 September 2020. National Library of Medicine ClinicalTrials.gov website. https://clinicaltrials.gov/study/NCT01896102#publications. Accessed 01/23/2024.
26. Skysona – Find a Qualified Treatment Center [website]. Somerville (MA): bluebird bio, Inc. Available at: https://www.skysona.com/find-a-qualified-treatment-center. Accessed 01/26/2026.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

At this time, no product-specific ICD-10-PCS, CPT or HCPCS codes have been assigned to Skysona (elivaldogene autotemcel) and its administration.

Code	Description
J3387	Injection, elivaldogene autotemcel, per treatment

ICD-10-CM Diagnosis Code	Description
E71.520	Childhood cerebral X-linked adrenoleukodystrophy

Policy history

Origination date:	03/01/2024
Review/Approval(s):	Technology Assessment Committee: 07/25/2023 (policy origination), 01/28/2025 (annual review; updated coverage criteria to indicate that the

treating physician is a specialist in the treatment of CALD; updated Summary of Evidence and References; updated Coding section to include documentation that payment will only be made for Skysona for MassHealth ACO members when non-340B stock is used), 01/27/2026 (annual review, updated criteria, clarifying that Skysona is covered only when the plan member is without a human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant given the FDA warning of an increased risk of hematologic malignancy; updated coding).
Utilization Management Committee 02/18/2025: (annual review and approval), 02/17/2026 (annual review, approved for updated criteria).

Instructions for Use

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Fallon Health follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

For plan members enrolled in NaviCare, Fallon Health first follow's CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.