CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Gene Therapy – Skysona Utilization Management Medical Policy
- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 12/11/2024; selected revision 01/08/2025

OVERVIEW

Skysona, an autologous hematopoietic stem cell-based gene therapy, is indicated to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active **cerebral adrenoleukodystrophy**.[1] Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5 to 9 points.[1] This indication was approved under accelerated approval based on 24-month Major Functional Disability-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Skysona is given as a single dose by intravenous infusion; the minimum recommended dose is 5.0 x 10^6 $CD34^+$ cells/kg.

Disease Overview

Cerebral adrenoleukodystrophy is a rare, neurodegenerative X-linked genetic disease in young boys that mainly affects the nervous system and adrenal glands.[2-6] The estimated incidence of adrenoleukodystrophy is 1:20,000 to 1:30,000 males. It is caused by a defect in the adenosine triphosphate-binding cassette, subfamily D, member 1 (*ABCD1*) gene. Very long chain fatty acids accumulate, which causes inflammation and damage to the brain; other tissue types are also impacted. Among patients diagnosed with adrenoleukodystrophy, cerebral adrenoleukodystrophy developed in around 35% of boys before 12 years of age; a small percentage of impacted patients are ≥ 12 years of age. The conditions leads to progressive destruction of white matter, loss of cognitive and neurologic function, and early death if not treated.[2] Early stages of cerebral adrenoleukodystrophy are clinically asymptomatic and are only detected by performing an MRI of the brain.[2-4] Irreversible, devastating neurologic decline can result which include major functional disabilities such as loss of communication, cortical blindness, difficulty swallowing, total incontinence, use of a wheelchair for ambulation, or complete loss of voluntary movement. As the disease progresses, patients often develop profound disability.[2-4] If an allogeneic hematopoietic stem cell transplantation (HSCT) is not performed, almost one-half of impacted patients will likely die within a decade after symptom onset.[2] Reviews provide additional information regarding monitoring and diagnosis (e.g., Loes and Neurologic Function scores).[10-13]

Clinical Efficacy

The efficacy of Skysona was evaluated in two 24-month, open-label, single-arm, single-dose, multicenter, multinational pivotal trials involving male patients ≤ 17 years of age with early, active cerebral adrenoleukodystrophy as defined by its FDA-approved indication.[1,2] STARBEAM (ALD-102) was a Phase II/III investigation which is completed and involved 32 patients who did not have a matched sibling donor for allogeneic HSCT.[1,2] Study 2 (ALD-104) is an ongoing trial that included 35 patients.[1] Skysona was compared with a natural history population, as well as patients who underwent allogeneic HSCT. Patients in both studies could enroll in a long-term follow-up study (LTF-304).[1,2] It should be noted that patients involved in these two studies had elevated very long chain fatty acid levels and confirmed mutations in the *ABCD1* gene. In the STARBEAM study, 91% of patients (n = 29/32) completed the 24-month study and are being followed long-term. At Month 24, none of these patients had major functional disabilities and overall survival was 94%. At a median of 6 years of follow-up, the neurologic function score was stable compared with the baseline score in most patients; 81% of patients had no major functional disabilities.

Guidelines

Skysona has not been addressed in guidelines following approval by the FDA. In September 2022, international recommendations for the diagnosis and management of patients with adrenoleukodystrophy (a consensus-based approach) were published.[7] It was noted that allogeneic HSCT is the standard treatment for cerebral adrenoleukodystrophy and can halt progression. Genetically transduced autologous stem cell transplantation (gene therapy [Skysona]) should be considered (if available) in boys if allogeneic donor options are poor. Outcome is poor in patients with advance disease (Loes score > 9 and/or a neurologic function score > 1). Regarding gene therapy (Skysona), it states that this therapy is not available for routine care; long-term safety data are not yet available. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful assessment in experienced centers.

Safety

Skysona has a Boxed Warning regarding hematologic malignancy.[1] Hematologic malignancies, including life-threatening cases of myelodysplastic syndrome and acute myeloid leukemia, have developed in patients who received Skysona. Patients have been diagnosed between 14 months and 7.5 years of age following receipt of Skysona, and the cancers appear to be due to the Skysona lentiviral vector, Lenti-D, integration in proto-oncogenes. Due to the risk of hematologic malignancy, consider alternative therapies, including allogeneic HSCT for patients who have a suitable, willing, and available matched sibling donor before treating a child with Skysona.[1] As of April 2024, hematologic cancer developed in 10% of patients (n = 7/67) who received Skysona in STARBEAM and Study ALD-104.[8] At diagnosis, all patients had high-frequency integrations in oncogenes, most of which were *MECOM*.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Skysona. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skysona as well as the specialized training required for administration of Skysona, approval requires Skysona to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 6 months to allow for an adequate time frame to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria, as noted by **[verification in claims history required]**. For dosing criteria verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. In the criteria for Skysona, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Skysona as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skysona is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cerebral Adrenoleukodystrophy.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, and S):
   - **A)** Patient is a male*; AND
   - **B)** Patient is ≥ 4 and < 18 years of age; AND
   - **C)** Patient has not received Skysona in the past **[verification in claims history required]**; AND
     Note: If no claims for Skysona is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Skysona.
   - **D)** Patient has early, active cerebral adrenoleukodystrophy as demonstrated by meeting ALL of the following (i, ii, and iii):
     - **i.** Patient has a neurologic function score ≤ 1 **[documentation required]**; AND
     - **ii.** Patient has gadolinium enhancement on brain magnetic resonance imaging (MRI) **[documentation required]**; AND
     - **iii.** Patient has a Loes score between 0.5 and 9 **[documentation required]**; AND
   - **E)** Patient has a pathogenic variant in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene **[documentation required]**; AND
   - **F)** Patient has elevated very long chain fatty acid levels according to the standard reference values of the laboratory **[documentation required]**; AND
   - **G)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
     - **ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
   - **H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
   - **I)** Patient does not have any of the following (i and ii):
     - **i.** Prior or current hematologic malignancy or myeloproliferative disorder; AND
     - **ii.** Familial cancer syndrome or a history of such in his immediate family; AND
   - **J)** According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **K)** Patient has undergone liver function testing within the past 30 days and meets ALL of the following (i, ii, and iii):
     - **i.** Aspartate aminotransferase level is ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **ii.** Alanine aminotransferase level is ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **iii.** Total bilirubin level is ≤ 3.0 mg/dL **[documentation required]**; AND
   - **L)** Within the past 30 days, the patient meets ONE of the following (i or ii):
     - **i.** Estimated creatinine clearance is ≥ 50 mL/minute **[documentation required]**; OR
     - **ii.** Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2 **[documentation required]**; AND
   - **M)** According to the prescribing physician, patient does not have evidence of cardiac compromise; AND

N) Prior to collection of cells for manufacturing, screening is negative for ALL of the following (i, ii, iii, and iv):
- **i.** Hepatitis B virus **[documentation required]**; AND
- **ii.** Hepatitis C virus **[documentation required]**; AND
- **iii.** Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND
- **iv.** Human immunodeficiency virus 1 and 2 **[documentation required]**; AND

O) Within the past 30 days, patient meets ALL of the following (i, ii, and iii):
- **i.** Peripheral blood absolute neutrophil count ≥ 1,500 cells/mm^3 **[documentation required]**; AND
- **ii.** Platelet count ≥ 100,000 cells/mm^3 **[documentation required]**; AND
- **iii.** Hemoglobin ≥ 10 g/dL **[documentation required]**; AND

P) Patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, myeloablative conditioning, and lymphodepletion; AND
- **ii.** A granulocyte-colony stimulating factor product will be used for mobilization; AND
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Cyclophosphamide or fludarabine will be used for lymphodepletion; AND

Q) The medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist physician; AND

R) Current patient body weight has been obtained within the past 30 days **[documentation required]**; AND

S) If criteria A through R are met, approve one dose of Skysona by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight **[verification required]**.

* Refer to the Policy Statement.

Dosing. The recommended dose of Skysona is a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight administered by intravenous infusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skysona is not recommended in the following situations:

1. **Patient has a Full *ABCD1* Gene Deletion.** In one patient involved in the Skysona clinical trials who had a full *ABCD1* gene deletion, disease progression occurred.[1,9] The patient experienced radiologic disease progression, along with declining peripheral blood vector copy number, suggesting a loss of product efficacy which may have been immune mediated. The patient eventually underwent allogeneic HSCT for treatment. A noted limitation of use is that an immune response to Skysona may limit the persistence of descendent cells of Skysona, causing rapid loss of efficacy of Skysona in patients with full deletions of the *ABCD1* transgene.

2. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Prior allogeneic hematopoietic stem cell transplant was an exclusion criterion in the pivotal studies.

3. **Prior Receipt of Gene Therapy.** This was an exclusion criterion in the pivotal studies.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Skysona® intravenous infusion [prescribing information]. Sommerville, MA: Bluebird Bio; April 2024.
2. Eichler F, Duncan CN, Musolino PL, et al. Lentiviral gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2024;391(14):1302-1312.
3. Raymond GV, Moser AB, Fatemi A. X-Linked Adrenoleukodystrophy. 1999 Mar 26 [Updated 2023 Apr 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1315/pdf/Bookshelf_NBK1315.pdf. Accessed on December 1, 2024.
4. X-linked cerebral adrenoleukodystrophy. National Institute of Health: Genetic and Rare Disease Information Center Website. Available at: https://rarediseases.info.nih.gov/diseases/9412/x-linked-cerebral-adrenoleukodystrophy. Last updated September 2024. Accessed on December 1, 2024.
5. Kornbluh AB, Baldwin A, Fatemi A, et al. Practical approach to longitudinal neurologic care of adults with X-linked adrenoleukodystrophy and adrenomyeloneuropathy. *Neurol Genet*. 2024;10:e200192.
6. Engelen M, Kemp S, Eichler F. Adrenoleukodystrophy. *Handb Clin Neurol*. 2024;204:133-138.
7. Engelen M, Van Ballegoij WJ, Mallack EJ, et al. International recommendations for the diagnosis and management of patients with adrenoleukodystrophy: a consensus-based approach. *Neurology*. 2022;99(21):940-951.
8. Duncan CN, Bledsoe JR, Grzywacz B, et al. Hematologic cancer after gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2024;391:1287-1301.
9. 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;32(10):3313-3317.
10. Kumar S, Sait H, Polipalli SK, et al. 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.
11. Loes DJ, Site S, Moser H, et al. Adrenoleukodystrophy: a score method of brain MR observations. *AJNR Am J Neuroradiol*. 1994;15:1761-1766.
12. Thibert KA, Raymond GV, Nascene DR, et al. Cerebrospinal fluid matrix metalloproteinases are elevated in cerebral adrenoleukodystrophy and correlated with MRI severity and neurologic dysfunction. *PLoS One*. 2012;7(11):e50430.
13. Moser HW, Loes DJ, Melhem ER, et al. X-linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. *Neuropediatrics*. 2000;31(5):227-239.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	In the Policy Statement "attestation required by physician" was removed from selected criteria. It was added that for certain criteria, verification is required as noted by "verification in claims history required". In addition, the following changes were made: **Cerebral Adrenoleukodystrophy:** The phrase "as determined by the prescribing physician" was removed from the requirement regarding that the patient is without an active infection (bacterial, viral, fungal, or parasitic). The phrase "plans to" was changed to "will" to be more directive in the requirement that the patient undergoes mobilization, apheresis, myeloablative conditioning, and lymphodepletion. "Documentation required" was added regarding the laboratory parameters that the estimated creatinine clearance is ≥ 50 mL/minute or estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2. It was added that the patient has not received Skysona in the past, with "verification in claims history required". Regarding the specialist requirement, the word "physician" was added after "stem cell transplant specialist". Dosing was added in an additional section with the other standard requirements for alignment with similar policies; dosing requirements were always present with Skysona for this policy. **Conditions Not Recommended for Approval:** For the Exclusion regarding patients with a Prior Hematopoietic Stem Cell Transplantation, the "attestation required by physician" was removed. A Note was added that the prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.	11/15/2023

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Annual Revision	In the Policy Statement, the phrase "if claims history is available" was added regarding that verification in claims history is required for certain criteria. Statements regarding	12/11/2024

	dosing were slightly altered to align with standard wording. Regarding Documentation, "medical test results" was added and the word "prescription" was removed before the phrase "claims records". In addition, the following changes were made: **Cerebral Adrenoleukodystrophy:** • For approval, the descriptor of "per" was added before the word "lifetime". Also, "single" was added before the word "dose" for clarification. • Regarding the Note in the criteria which addresses that the patient has not received Skysona in the past (with verification in claims history required), a phrase was added to include situations in which claims history is not available. • The phase "pathogenic variant" replaced the wording of "confirmed mutation". • The requirement that the patient does not have a Human Leukocyte Antigen (HLA) matched family donor (with documentation) was revised. The new criteria states that the patient does not have an HLA-matched donor or the patient has an HLA-matched donor, but the individual is not able or is not willing to donate. The Documentation requirement was removed. • The requirement was removed that according to the prescribing physician, the patient is able to undergo monitoring by magnetic resonance imaging. • Regarding the requirement that the patient has "adequate hepatic function" this wording was changed to state that the patient has "undergone liver function testing". Also, the requirement that this information be obtained "within the past 30 days" was added. For these laboratory requirements, the phrase "values are normal or" was changed to "level is". • Regarding the requirement that the patient has "adequate renal function", this phrase was removed before the cited estimated creatinine clearance and estimated glomerular filtration rate. Also, the requirement that this information be obtained "within the past 30 days" was added. • Prior to collection of cells for manufacturing, the phrase "cellular screening" replaced the phrase "patient screening". • The phrase "patient does not have evidence of hematological compromise" was removed before the cited hematologic laboratory requirements. Also, the requirement that this information be obtained "within the past 30 days" was added. The requirement that the patient does not have an uncorrected bleeding disorder was removed. • The requirement was removed that the patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before conditioning. Also, the medication examples in the Note were removed. • The requirement was removed that the prescribing physician confirms that the patient or his partner of childbearing potential will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Skysona. • A specific individual criterion was added that current patient body weight has been obtained within the past 30 days with documentation required. Previously, body weight was obtained without documentation required. • Dosing criteria were rephrased to emphasize that Skysona is provided as a "one-time (per lifetime)" single dose. The requirement that the body weight be obtained based on patient weight prior to the first apheresis was removed. It was added that verification is required.	
Selected Revision	**For Cerebral Adrenoleukodystrophy**, the word "cellular" was removed from the criterion which stated that prior to collection of cells for manufacturing, cellular screening is negative.	01/08/2025