MEDICAL COVERAGE POLICY	
SERVICE:	**Elivaldogene autotemcel (Skysona™)**
Policy Number:	**308**
Effective Date:	**04/01/2025**
Last Review:	**03/10/2025**
Next Review:	**03/10/2026**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Elivaldogene autotemcel (Skysona™)

PRIOR AUTHORIZATION:

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

BSWHP may consider **elivaldogene autotemcel (Skysona™)** medically necessary when the following criteria are met:

1. Male, age 4 years to 17 years; **AND**
2. Medication is prescribed by a neurologist, hematologist/oncologist, endocrinologist and or a stem cell transplant specialist; **AND**
3. Member has a documented diagnosis of early, active cerebral adrenoleukodystrophy (CALD) as defined by meeting all of the following:
    a. Elevated very long chain fatty acids (VLCFA) values; **AND**
    b. Confirmed human adenosine triphosphate binding cassette, sub family D, member 1 (ABCD1) mutation; **AND**
    c. Neurologic Function Score (NFS) less than or equal to 1; **AND**
    d. Active central nervous system (CNS) disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:
        i. Loes score between 0.5 and 9 on the 34-point scale; **AND**
        ii. Gadolinium enhancement (GdE+) on MRI of demyelinating lesions;
4. Member is a candidate for hematopoietic stem cell (HSC) mobilization; **AND**
5. Member has adequate cardiac function as evidenced by a left ventricular ejection fraction greater than 40%; **AND**
6. Member's screening result is negative for all of the following:
    a. Human immunodeficiency virus type 1 or 2 (HIV-1, HIV-2)
    b. Hepatitis B

c. Hepatitis C
d. Human T lymphotrophic virus 1 or 2 (HTLV-1, HTLV-2)

7. Request is for a one-time, single administration of treatment; **AND**
8. Member should NOT have ANY of the following:
    a. CALD secondary to head trauma; **AND**
    b. An immediate family member with a known or suspected Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, and familial adenomatous polyposis)
    c. Availability of a willing human leukocyte antigen (HLA)-matched family donor; **AND**
    d. An active bacterial, viral, fungal or parasitic infection; **AND**
    e. Prior gene therapy, including Skysona, for CALD; **AND**
    f. Prior allogenic hematopoietic stem cell transplant (HSCT); **AND**
    g. Prior or current malignancy or myeloproliferative disorder

BSWHP considers repeat administration of **elivaldogene autotemcel** experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers **elivaldogene autotemcel** for the treatment of all other indications to be experimental, investigational, and/or unproven.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:

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. The diagnosis of ALD can be established based on clinical findings and elevated VLCFAs and confirmed via genetic testing. Subtypes of ALD include adrenomyeloneuropathy (AMN), adult cerebral ALD, childhood cerebral ALD (cCALD; more commonly known as CALD), and Addison's-only ALD. CALD is the most severe and neurodegenerative form of ALD and the condition for which Skysona is indicated. The overall prevalence of adrenoleukodystrophy is approximately 1 in 17,000 newborns.

Boys with CALD typically present with neurologic symptoms between 3 and 10 years of age. After an initial period of normal development, symptoms typically include behavioral problems, such as attention-deficit/hyperactivity disorder (ADHD) and learning disabilities. Progressive symptoms include diminished visual acuity, hearing loss, gait instability, weakness and stiffness of limbs, and seizures. Within 2–3 years, symptoms progress to a loss of most neurologic function and total disability.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for early-stage CALD (no or mild signs and symptoms).

The U.S. Food and Drug Administration (FDA) granted approval of Skysona (elivaldogene autotemcel) to slow the progression of neurologic dysfunction in boys 4–17 years of age with early, active cerebral adrenoleukodystrophy (CALD), under the accelerated approval pathway.

Skysona is intended to be a one-time gene therapy and is designed to treat the underlying cause of CALD. The therapy uses ex vivo transduction with the Lenti-D LVV to add functional copies of the ABCD1 gene into a patient's own HSCs. The added gene allows patients to produce adrenoleukodystrophy protein (ALDP) to help break down very long chain fatty acids (VLCFAs) and slow or possibly prevent further inflammation and demyelination.

The safety and efficacy of elivaldogene autotemcel were assessed in two 24-month, open-label, single-arm studies, the Phase 2/3 study ALD-102 (n=32) and Phase 3 ALD-104 (n=35) study. Patients enrolled in these studies were diagnosed 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 less than or equal to 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. All patients had elevated very long chain fatty acid (VLCFA) levels and confirmed mutations in the ABCD1 gene. All patients were administered elivaldogene autotemcel as an intravenous infusion with a median (min, max) dose of 12 × 106 (5, 38.2) CD34+ cells/kg (N=67). The efficacy of elivaldogene autotemcel was compared to an external untreated natural history control. The Accelerated Approval of Skysona is based on 24-month Major Functional Disability (MFD)-free survival. 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). A post-hoc enrichment analysis in symptomatic patients assessed MFD-free survival from onset of symptoms (NFS ≥ 1) in elivaldogene autotemcel treated (N=11) and untreated patients (N=7). Elivaldogene autotemcel treated patients had an estimated 72 percent likelihood of MFD-free survival at 24 months from time of first NFS ≥ 1, compared to untreated patients who had only an estimated 43 percent likelihood of MFD-free survival. Study 1 (ALD-102) is complete and Study 2 (ALD-104) is ongoing at the time of product approval. There was insufficient duration of follow-up to assess efficacy in elivaldogene autotemcel treated patients who remained asymptomatic. All patients who completed the 24 months of follow-up in studies ALD-102 or ALD-104 were encouraged to participate in a long-term follow-up study (LTF-304) to continue monitoring safety and efficacy outcomes in boys treated with elivaldogene autotemcel through 15 years post-treatment.

There were insufficient data to compare relative efficacy of elivaldogene autotemcel 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 elivaldogene autotemcel with an external allo-HSCT control was performed for overall survival (OS) due to concerns about treatment-related toxicities. OS was analyzed as time-to-event Kaplan-Meier estimates comparing elivaldogene autotemcel (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 elivaldogene autotemcel and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of elivaldogene autotemcel, it does demonstrate a survival advantage of elivaldogene autotemcel 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 higher) or chronic graft versus host disease (GVHD) after elivaldogene autotemcel treatment.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	96365 – Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour 96366 – Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
HCPCS Codes:	C9399 - Unclassified drugs or biologicals (hospital outpatient use) J3590 - Unclassified biologics
ICD10 codes:	E71.520 Childhood cerebral X-linked adrenoleukodystrophy E71.521 Adolescent X-linked adrenoleukodystrophy
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	03/11/2024	New policy
Updated	03/10/2025	Minor formatting changes, ending note section updated to align with business entity changes.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Chiesa R, et al. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. Blood Adv. 2022;6(5):1512-1524. doi:10.1182/bloodadvances.2021005294
2. Bluebird bio. Skysona launch call. September 19, 2022. https://investor.bluebirdbio.com/events/event-details/skysonar-launch-call
3. Eichler F, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med. 2017;377(17):1630-1638. doi:10.1056/NEJMoa1700554
4. National Institute of Health National Institute of Neurological Disorders and Stroke. Adrenoleukodystrophy. Updated September 19, 2022. https://www.ninds.nih.gov/health-information/disorders/adrenoleukodystroph
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7. Raymond GV, et al. Survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2019;25(3):538-548. doi:10.1016/j.bbmt.2018.09.036
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9. U.S. Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee. June 9–10, 2022 Meeting Announcement. https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissueand-gene-therapies-advisory-committee-june-9-10-2022-meeting-announcement06092022
10. Skysona (elivaldogene autotemcel) [package insert]. U.S. Food and Drug Administration website. https://www.bluebirdbio.com/-/media/bluebirdbio/Corporate%20COM/Files/Skysona/SKYSONA_Prescribing_Information.pdf.
11. Bluebird bio. A study of the efficacy and safety of hematopoietic stem cells transduced with lenti-D lentiviral vector for the treatment of cerebral adrenoleukodystrophy (CALD) - full text view. NCT01896102. Full Text View - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/ NCT01896102?term=elivaldogene%2Bautotemcel&draw=2&rank=1
12. Bluebird bio. Observational study to evaluate allogeneic HSCT outcomes for cerebral adrenoleukodystrophy (CALD) - full text view. NCT02204904. Full Text View - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02204904?term=02204904&draw=2&rank=1
13. Bluebird bio. A clinical study to assess the efficacy and safety of gene therapy for the treatment of cerebral Adrenoleukodystrophy (CALD) - full text view. NCT03852498. Full Text View - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03852498?term=elivaldogene %2Bautotemcel&draw=2&rank=2
14. Bluebird bio. Long-term follow-up of participants with cerebral adrenoleukodystrophy who were treated with Lenti-D Drug Product - Full Text View. NCT02698579. Full Text View - ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT02698579?term=elivaldogene%2Bautotemcel&draw=2&rank=3

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***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid is offered through Scott and White Health Plan in the Central Texas Medicaid Rural Service Area (MRSA); FirstCare STAR is offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs; and FirstCare CHIP is offered through FirstCare in the Lubbock Service Area.