Skysona® (elivaldogene autotemcel) – New orphan drug approval

- On September 16, 2022, bluebird bio announced the FDA approval of Skysona (elivaldogene autotemcel), to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active cerebral adrenoleukodystrophy 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 to 9.
    - This indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)- free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
    - Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy.
    - 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 human adenosine triphosphate binding cassette, sub family D, member 1 *(ABCD1)* transgene.
    - Skysona has not been studied in patients with CALD secondary to head trauma.
    - Given the risk of hematologic malignancy with Skysona, and unclear long-term durability of Skysona and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the appropriateness and timing of treatment for each boy, especially for boys with isolated pyramidal tract disease based on available treatment options since their clinical symptoms do not usually occur until adulthood.
- CALD is an ultra-rare, progressive and irreversible neurodegenerative disease that primarily affects young boys. The disorder is caused by mutations in the *ABCD1* gene that affect the production of ALDP and subsequently leads to accumulation of very long-chain fatty acids. This accumulation leads to the breakdown of myelin, the protective sheath that nerve cells need to function effectively, especially for thinking and muscle control.
    - Nearly half of patients who do not receive treatment die within five years of symptom onset.
- Skysona is a one-time gene therapy that uses *ex-vivo* transduction with a lentiviral vector to add functional copies of the *ABCD1* gene into a patient's own hematopoietic stem cells.
- The efficacy of Skysona was established in two 24-month, open-label, single-arm studies in patients with early, active CALD (Study 1, N = 32; Study 2, N = 35). The efficacy of Skysona was compared to an external untreated natural history control. A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms to time to first MFD or death (ie, MFD-free survival) in Skysona treated and natural history patients.
    - Kaplan-Meier estimated MFD-free survival at month 24 from time of first NFS ≥ 1 were 72% (95% CI: 35, 90) for the symptomatic Skysona subpopulation and 43% (95% CI: 10, 73) for the natural history population.
    - There were insufficient data beyond 24 months for the symptomatic Skysona subpopulation to assess long-term MFD-free survival as compared to the natural history of disease. There was insufficient duration of follow-up to assess efficacy in Skysona treated patients who remained asymptomatic.
- Skysona carries a boxed warning for hematologic malignancy.

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- Additional warnings and precautions for Skysona include serious infections; prolonged cytopenias; delayed platelet engraftment; risk of neutrophil engraftment failure; hypersensitivity reactions; anti-retroviral use; and laboratory test interference.

- The most common non-laboratory adverse reactions (≥ 20%) with Skysona use were mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, and rash.

- The most common Grade 3 or 4 laboratory abnormalities (≥ 40%) with Skysona use were leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, and hypokalemia.

- Skysona is provided as a single dose for infusion containing a suspension of CD34+ cells in one or two infusion bags. The minimum recommended dose of Skysona is 5.0×10^6 CD34+ cells/kg.

    — Skysona is designed to be administered to the patient once, but the treatment process is comprised of several steps.
    — Refer to the Skysona drug label for complete dosing and administration recommendations.

- Skysona will be priced at $3.0 million for a one-time dose.

- Bluebird bio anticipates that product will be available by the end of 2022 through a limited number of Qualified Treatment Centers, including Boston Children's Hospital and Children's Hospital of Philadelphia.

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