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ACMG THERAPEUTICS BULLETIN

Olipudase alfa approved for pediatric and adult patients with acid sphingomyelinase deficiency (ASMD): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Acid sphingomyelinase (ASM) deficiency (ASMD) is an autosomal recessive lysosomal storage disease resulting from deficiency of ASM, an enzyme encoded by the *SMPD1* gene.[1] Low or absent ASM activity results in sphingomyelin accumulation in the spleen, liver, lungs, bone marrow, lymph nodes, and/or the peripheral and central nervous systems. The phenotype of ASMD occurs as a

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continuum from a severe, rapidly progressive infantile neurovisceral disease (type A) to a later-onset chronic neurovisceral (type A/B) and visceral disease (type B).[2-4] Multisystemic clinical manifestations lead to significant morbidity and a shortened life span because of respiratory or liver disease.[1,5]

Management and Treatment

Recommendations for clinical management of individuals with ASMD have been published, including regular monitoring of growth and development and for neurologic, hematologic, and pulmonary symptoms.[1] These surveillance guidelines also include cardiac studies, liver function tests, and lipid profiling.[1]

There were no United States Food and Drug Administration (FDA)–approved targeted therapies for patients with ASMD before 2022. Treatment was supportive care or lifestyle modifications to address disease complications and improve quality of life.[1,5]

Newly Approved Therapy

Indication and approved treatment population

Olipudase alfa (Xenpozyme) is an enzyme replacement therapy and the first approved treatment for the non-central nervous system manifestations of ASMD in pediatric and adult patients. The approval is based on data from the ASCEND[2] and ASCEND-Peds[4] clinical trials. Olipudase alfa received orphan drug, fast track, breakthrough therapy, and priority review designations by the FDA, and it was issued a rare pediatric disease priority review voucher.[6] Therapeutic benefits have not been documented in infantile neurovisceral ASMD (type A), the most severe form that is rapidly progressive and uniformly fatal in early childhood.

Mechanism of action

Olipudase alfa is a recombinant human ASM administered via a biweekly intravenous infusion.[2,4,5,7] The drug catalyzes the hydrolysis of sphingomyelin, reducing accumulation in hepatocytes and mononuclear-macrophage cells in the lungs, liver, spleen, kidneys, and bone marrow.[5,8] This drug is not expected to cross the blood-brain barrier.[4]

Outcomes and efficacy

The ASCEND trial was a phase 2/3 study with 36 adult participants with ASMD type B or type A/B.[2] The ASCEND-Peds trial was a phase 1/2 trial with 20 pediatric participants with ASMD type B or type A/B.[4] These trials showed that treatment with olipudase alfa resulted in an improved predicted diffusing lung capacity for carbon monoxide and a reduction in splenic volume compared with placebo, which were the primary efficacy end points.[2-4] Other clinically relevant end points included decreased lyso-sphingomyelin accumulation, liver volume and transaminases, ground glass appearance on lung imaging, and improved platelet counts and lipid profiles.[3,4] In pediatric participants, there was also improvement in height z-score and lung function.[3-5]

Adverse effects and toxicity

The most common adverse events in adults (incidence $\geq$10%) are headache, nausea, cough, diarrhea, hypotension, and ocular hyperemia.[2,9] The most frequent adverse events in children (incidence $\geq$20%) are fever, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, and rash.[3-5,9] Serious treatment-related events in children include transient transaminitis, urticaria/rash, and anaphylaxis.[3-5,9] No adverse events led to the discontinuation of the drug.[2-4] Olipudase alfa has a box warning for hypersensitivity reactions, including anaphylaxis.[9]

Additional Considerations

At the time of this writing, there are ongoing clinical trials for olipudase alfa, including the open-label, extension phase 3 ASCEND trial and the long-term phase 2 study for enrolled pediatric participants who completed phase 1/2 in the ASCEND-Peds trial. There is a compassionate use program for patients with ASMD who could not participate in clinical trials (NCT04877132). There is also a national multicenter trial for data analysis of patients with early access to olipudase alfa (NCT05359276). Continued FDA approval for olipudase alfa may be reliant upon further demonstration of clinical benefit. Safety of olipudase alfa in pregnancy has not been established.

Conflict of Interest

All authors declare no conflicts of interest.

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