Press Release

Xenpozyme® (olipudase alfa) approved by European Commission as first and only treatment for ASMD

Paris, June 28, 2022. The European Commission (EC) has approved Xenpozyme® (olipudase alfa) as the first and only enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in pediatric and adult patients with ASMD type A/B or ASMD type B. The approval is based on positive data from the ASCEND and ASCEND-Peds clinical trials, in which Xenpozyme showed substantial and clinically relevant improvement in lung function (as measured by diffusing capacity of the lung for carbon monoxide, or DLco) and reduction of spleen and liver volumes, with a well-tolerated safety profile. Given the urgent unmet medical needs of the ASMD community, the European Medicines Agency (EMA) granted Xenpozyme PRIority MEdicines (PRIME) designation. Xenpozyme has also received special breakthrough designations from several other regulatory agencies around the world.

> ***John Reed, M.D., Ph.D***
> Executive Vice President, Global Head of Research and Development, Sanofi
> *"The ASMD community has waited many years for a treatment for this rare and debilitating genetic disease. The approval of Xenpozyme by the European Commission represents a transformational shift in what we can offer to patients, demonstrated by the clinically important improvements across major manifestations of ASMD and the sustained effects noted over longer term treatment."*

ASMD is an extremely rare, progressive genetic disease with significant morbidity and mortality, especially among infants and children, as many pediatric patients will not survive to adulthood. Signs and symptoms of ASMD may include enlarged spleen or liver, difficulty breathing, lung infections, and unusual bruising or bleeding, among other disease manifestations. Current management of the disease includes palliative and supportive care to manage the symptoms.

Xenpozyme is an enzyme replacement therapy designed to replace deficient or defective acid sphingomyelinase (ASM), an enzyme that allows for the breakdown of the lipid sphingomyelin. In individuals with ASMD, the insufficient amount of the ASM enzyme means sphingomyelin is poorly metabolized, potentially leading to lifelong accumulation in and damage to multiple organs.

> ***Maurizio Scarpa, M.D., Ph.D***
> University Hospital of Udine, Italy
> *"We welcome the European Union approval of Xenpozyme as the first and only disease-specific therapy for ASMD with a potential to oppose disease progression. This is a significant milestone for individuals living with ASMD, a disease associated with substantial morbidity and risk of premature death."*

Approval based on positive results from two clinical trials in children and adults

ASCEND

The ASCEND trial randomized 36 adult patients with ASMD type A/B or type B to receive Xenpozyme or placebo for 52 weeks (primary analysis), to evaluate the efficacy and safety of the drug. The study demonstrated that Xenpozyme improved lung function, assessed as the percent change from baseline to week 52 in predicted diffusing capacity of the lung

for carbon monoxide (DLco), and reduced spleen size, evaluated as percent change from baseline in multiples of normal (MN) spleen volume.

- Patients treated with Xenpozyme had improvement in DLco from baseline to week 52 of 22% compared to 3% for the patients in the placebo group. The difference between the two treatment arms (19%) was statistically significant (p=0.0004).
- Patients treated with Xenpozyme had reduction in spleen size by 39.5% at week 52 compared to increase by 0.5% for the patients in the placebo group. The difference between the two treatment arms (40%) was statistically significant (p<0.0001).
- All ASCEND patients treated with Xenpozyme showed improvement in one or both primary endpoints (DLco and spleen size reduction).

The incidence of adverse events (AEs) was similar in patients receiving Xenpozyme to that in patients receiving placebo. There were five serious AEs in the Xenpozyme arm and 11 in the placebo arm, none of which was treatment-related. There were no AEs that led to treatment discontinuation or study withdrawal. The most common AEs in the ASCEND trial were headache, nasopharyngitis, upper respiratory tract infection, cough, and arthralgia.

ASCEND-Peds

The single-arm ASCEND-Peds trial studied 20 pediatric patients with ASMD type A/B or type B who all received Xenpozyme, with a primary objective of evaluating the safety and tolerability of Xenpozyme for 64 weeks. All patients completed the study and continued in an extension trial. The ASCEND-Peds study also explored efficacy endpoints of progressive lung disease and of spleen and liver enlargement. After one year of treatment (52 weeks), the percent predicted DLco mean increase from baseline was 33% in nine patients who were able to perform the test at baseline (children over the age of five were assessed if they were able to perform the test). Additionally, the spleen volume mean decrease was 49% compared to baseline.

Over the 64-week treatment period, all ASCEND-Peds patients experienced at least one AE, which were mostly mild and moderate. Five treatment-related serious AEs were observed in three patients: two cases of transient, asymptomatic alanine aminotransferase (ALT) increase in one patient, one case each of urticaria and rash in one patient, and one anaphylactic reaction in one patient. No patients had to permanently discontinue treatment due to an AE. The most common AEs in the ASCEND-Peds trial were pyrexia, cough, vomiting, nasopharyngitis, diarrhea, headache, upper respiratory tract infection, contusion, abdominal pain, nasal congestion, rash, urticaria, scratch, and epistaxis.

About Xenpozyme

Xenpozyme® (olipudase alfa) is an enzyme replacement therapy designed to replace deficient or defective acid sphingomyelinase (ASM), an enzyme that allows for the breakdown of sphingomyelin. Accumulation of sphingomyelin in cells can cause harm to the lungs, spleen, and liver, as well as other organs, potentially leading to early death. Xenpozyme has been evaluated in pediatric and adult patients to treat non-CNS manifestations of ASMD type A/B and ASMD type B. Xenpozyme has not been studied in patients with ASMD type A.

In March 2022, Xenpozyme was approved in Japan under the SAKIGAKE (or "pioneer") designation, marking the first approval for olipudase alfa anywhere in the world. In the United States, where olipudase alfa received Breakthrough Therapy designation, the Food and Drug Administration (FDA) is currently reviewing olipudase alfa's Biologics License Application (BLA), with a target action date for the FDA decision (PDUFA date) anticipated for October 2022.

About ASMD

Historically known as Niemann-Pick disease types A, A/B, and B, ASMD is a rare, progressive, and potentially life-threatening genetic disease. ASMD represents a spectrum of disease, with two types that may represent opposite ends of a continuum referred to as ASMD type A and ASMD type B. ASMD type A/B is an intermediate form that includes varying degrees of central nervous system (CNS) involvement.

About Sanofi

We are an innovative global healthcare company, driven by one purpose: we chase the miracles of science to improve people's lives. Our team, across some 100 countries, is dedicated to transforming the practice of medicine by working to turn the impossible into the possible. We provide potentially life-changing treatment options and life-saving vaccine protection to millions of people globally, while putting sustainability and social responsibility at the center of our ambitions.
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