Long-Term Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency (ASMD)

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Objective

All completion of the Phase 1b trial, all 5 patients were enrolled in an ongoing extension study (ClinicalTrials.gov identifier NCT02029656 clinicaltrials.gob/EudraCT number: 2015–00001–490) to evaluate the long-term safety and efficacy of olipudase alfa.

Safety Findings

Olipudase alfa was well tolerated, with no deaths, serious adverse events, or adverse events that led to discontinuation reported through 18 months.

Study Design

This is a multinational, multicenter, nonrandomized, open-label, long-term extension trial of patients who have previously completed a study with olipudase alfa. Currently only the 5 patients from the Phase 1b trial participate in the US. Patients enrolled the 18-month timepoint they were receiving at the end of the original study. Intravenous infusions of olipudase alfa were administered every 2 weeks.

Main outcome measures are safety, efficacy, pharmacodynamics, and pharmacokinetics.

Background

Acid sphingomyelinase deficiency (ASMD), historically referred to as Niemann-Pick disease types A and B (NPD A and B), is an autosomal recessive disorder caused by mutations in the SMPD1 gene which encodes the lysosomal enzyme acid sphingomyelinase (ASM). ASM deficiency results in accumulation of sphingomyelin within hepatocytes, mononuclear macrophages, and in severe cases, neurons, causing a progressive multisystem disease. Clinical hallmarks of ASMD include hepatosplenomegaly, infiltrative lung disease, pro-atherogenic lipid profile, anemia, and thrombocytopenia. Symptoms in patients with ASMD manifest in a broad clinical spectrum ranging from an infantile neurovisceral form (NPD A), an intermediate chronic neurovisceral form (NPD B variant), to a chronic visceral form (NPD B).

Olipudase alfa (recombinant human ASM) is an investigational enzyme replacement therapy developed for the treatment of the non-neurological manifestations of ASMD in adult clinical trials; five adults received olipudase alfa every two weeks for 28 weeks. The treatment was well-tolerated, with no serious or severe adverse events or deaths reported for the duration of the study. Treatment with olipudase alfa resulted in decreased sphingomyelin content in the liver, decreased plasma ceramide, and improvements in inflammatory liver disease, spleen and liver volumes, lipid profiles, and quality of life measures.

Results

Ceramide Levels in Plasma and DBS

Figure 1. Mean ceramide levels in plasma (A) and dried blood spots (DBS) (B). Plasma ceramide levels remained normal and stable in the US; in dried blood spots (DBS), mean ceramide concentrations were in the normal range at baseline. Changes over time are shown relative to baseline, with data represented as mean ± SEM. Values are above normal, suggesting dynamics of substrate concentrations were in the normal range at the LTS. In dried blood spots (DBS), mean ceramide levels remained normal and stable in all patients relative to baseline. Values are above normal, suggesting dynamics of substrate concentrations were in the normal range at the LTS.

Figure 4. Effect of olipudase alfa on infiltrative lung disease. High-resolution CT images (level 2) of the lung of Patient 1 (A) at Week 6 (B), and Week 24 (C). The straight arrow in each image refers to vascular changes best seen at the periphery. The black arrow refers to ground glass opacity. D Quantitative assessment of infiltrative lung disease showing mean scores for ground glass appearance, interstitial, and reticulonodular components at baseline, Week 26, and Week 78. Areas of both lungs for each patient were evaluated at 4 anatomic levels: 1 level of the aortic arch; 2 levels of the carina; 3/4 levels between the aortic arch and carina 1 level above the hemidiaphragm (5 cm above the hemidiaphragm), based on a 4-point scale: 0=normal disease; 1=mild disease affecting 1–25% of lung volume (green); 2=moderate, affecting 26–50% of lung volume (yellow); 3=severe, affecting 51–100% of lung volume. The data show progressive decrease in the septal lines and ground glass opacity, particularly in the latter, which has nearly completely resolved.

Conclusions

These are the final data on long-term effects of olipudase alfa in adult patients with ASMD.

The majority of patients (4/5) remained at the 3 mg/kg dose of olipudase alfa; one patient had a reduction in dose but maintained a stable safety profile, continues to show response in efficacy, and remains on treatment with olipudase alfa. Hepatosplenomegaly, infiltrative lung disease, and atherogenic lipid profile, prominent features of ASMD, continued to show improvement over time.

Mean percent predicted DLCO increased from 58.3% at baseline to 76.4% at 18 months (p<0.05), improving the mean for the group to mildly reduced DLCO values. The most prominent change was in the 3 patients with the lowest DLCO at baseline; suggesting the pulmonary response to enzyme replacement therapy with olipudase alfa. Importantly, statistically significant improvements in liver and spleen volumes, and in DLCO were noted at 18 months following initiation of olipudase alfa treatment.

In conclusion, this long-term extension study suggests that olipudase alfa treatment has a sustained favorable safety profile in adult patients with ASMD and leads to clinically relevant improvements in liver and spleen volumes, DLCO, and lipid parameters.

The safety and tolerability of olipudase alfa are currently being investigated in pediatric patients; in the ASCEND-Peds trial (ClinicalTrials.gov identifier NCT02029656 clinicaltrials.gob/EudraCT number: 2014–00198–01).

The efficacy and safety of olipudase alfa in adults with chronic visceral ASMD are also being currently confirmed in a phase 2/3 trial, ASCEND (ClinicalTrials.gov identifier NCT02029656 clinicaltrials.gob/EudraCT number: 2014–00071–76).

Fasting Lipid Parameters

Figure 5. Pre-infusion fasting levels of total cholesterol (A), triglycerides (B), HDL cholesterol (C), and LDL cholesterol (D). Mean baseline levels were elevated for triglycerides, total cholesterol, LDL-C, and low for HDL-C. By Week 78, triglycerides decreased by 42%, total cholesterol by 12.6%, LDL-C by 15.4%, and HDL-C increased by 7.9%. Data represent mean ± SEM.

Main outcome measures are safety, efficacy, pharmacodynamics, and pharmacokinetics.

Disclosures

MPW has served as a consultant to Sanofi Genzyme. BS has received honoraria and research grants from Sanofi Genzyme. BS was employed by Sanofi Genzyme at the time this work was completed. All other authors were employees of Sanofi Genzyme. Medical writing support was provided by Sanofi Genzyme. The trial was sponsored by Sanofi Genzyme.

References