Sponsor: Sanofi **Drug substance(s):** olipudase alfa	**Study Identifiers:** IND: 12757; EudraCT/EU trial number: 2013-000051-40; NCT02004704; U1111-1141-65868 **Study code:** LTS13632

Title of the study:

A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency

Study center(s):

This study was conducted at 8 centers that enrolled participants in Brazil, France, Germany, Italy, United Kingdom, Belgium, and the United States of America.

Study period:

Date first patient enrolled: 04 December 2013

Date last patient data entered as per cut off date: 06 September 2023

Study Status: Completed

Phase of development: Phase 2

Objectives:

Primary

- The primary objective of this study is to obtain data regarding the safety of olipudase alfa in participants with acid sphingomyelinase deficiency (ASMD) who are exposed to long term treatment with olipudase alfa.

Secondary

- The secondary objectives of this study are to obtain data regarding the efficacy of olipudase alfa and to characterize olipudase alfa pharmacodynamics (PD) and pharmacokinetics (PK) following long-term administration.

Methodology:

This phase 2, multinational, multicenter, nonrandomized, open-label, long-term study was designed to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency who already participated in studies with olipudase alfa (DFI13412 or DFI13803-Peds study). Patients continued to receive the dose of olipudase alfa they were receiving at the end of their original study provided they had not missed more than 1 biweekly dose before entry into this study.

Number of study participants:

25

Diagnosis and criteria for inclusion:

The patient completed the treatment period of a previous study of olipudase alfa (adult study DFI13412 and pediatric study DFI13803) with an acceptable individual safety profile in the opinion of the investigator and sponsor. The patient has no new condition or worsening of an existing condition which in the opinion of the investigator which would preclude the enrollment of patients or interfere with the patient participating or completing the study. In the opinion of the investigator, the patient is able to adhere to the requirements of the study.

Study products

Investigational medicinal product(s): olipudase alfa

The study drug, olipudase alfa, is a sterile, white to off-white lyophilized cake supplied in single-use, 20 cc Type 1 glass vials. Each vial contains 20 milligrams of extractable olipudase alfa. The study drug was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL of olipudase alfa. The study drug was further diluted in 0.9% sodium chloride for injection solution to a specific volume based on dose and body and weight. Patients received an IV infusion of olipudase alfa every 2 weeks. Home infusion was possible. Patients must have met specific eligibility requirements. In addition, the Investigator and the Sponsor must have agreed that home infusion was appropriate. Patients continued their current dose if they did not miss more than 1 dose between studies. Dose reintroduction regimens were required for patients who missed more than 1 dose before the entry into this study or during this study (LTS13632), depending on their usual dose. For patients who received home infusions and missed 2 or fewer doses, the investigator decided whether reintroduction was to occur at the hospital/study site or via home infusion. For patients who missed 3 or more doses ≥0.6 mg/kg, reintroduction of olipudase alfa occurred at the hospital/study site. If the study site visit was not possible due to site closure or extenuating circumstances that prevented an in-person site visit (eg, during the COVID-19 pandemic), reintroduction was done via home infusion if the patient had previously been approved for home infusion.

Duration of study intervention:

Up to 9 years or until olipudase alfa became commercially accessible, whichever comes first unless the participant decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible.

Criteria for evaluation:

Primary

- Assessment of adverse events (AEs)/treatment-emergent adverse events (TEAEs), including infusion-associated reactions (IARs) and Adverse Events of Special Interest (AESI).
- Complete Physical examinations.
- Extended Neurologic examinations.
- Abbreviated Physical Exam
- Weight.
- Height (pediatric participants only).
- Vital sign measurements.
- Clinical laboratory tests.
- Electrocardiograms (ECGs).
- Doppler echocardiography.
- Safety biomarkers.
- Liver biopsy (only participants who previously participated in the DFI13412 study).
- Liver ultrasound with Doppler (only participants who previously participated in DFI13803).
- Immune response assessments.

Secondary

- Abdominal magnetic resonance imaging (MRI) to evaluate improvements in spleen and liver volume.
- Pulmonary imaging (high-resolution computed tomography [HRCT]. and chest X-ray [at selected sites]).
- Pulmonary function test.
- Hematology (hemoglobin and platelet count).
- Lipid profile.
- Health outcome questionnaires (adult and Pediatric).
- Hand X ray for bone age and bone maturation (pediatric participants).
- Linear participant growth by height Z score (pediatric participants).

Statistical methods:

Safety Analysis: Adverse events continuing from the original study into this extension study were identified and reported as one AE avoiding duplication of the same AE in two databases. Adverse event summaries included the number of events, number, and percentage of patients experiencing an adverse event. The denominator for computation of percentages is the safety population. Sorting order followed the internationally agreed MedDRA system organ class (SOC) order, and further by decreasing number of events overall in preferred terms (PTs) within SOCs. Unless specified otherwise, the displays included the original study data along with data collected in this study. The AEs were classified into treatment-emergent adverse events (TEAEs): AEs that started during the on-treatment period – either in this study or in the original study.
Analysis of efficacy variables: All efficacy analyses to assess changes in organomegaly (spleen and liver), infiltrative lung disease, pulmonary function, cycle ergometry endpoints, physician's global assessment, hemoglobin/platelet, efficacy biomarkers, lipid profile, bone biomarkers, health outcome questionnaires, were performed using the safety population.

Additional endpoints for pediatric patients included: linear growth (Height z-score), bone age, and tanner staging. Baseline for most efficacy parameters was defined as the last non-missing value before the first infusion in the original study. Selected efficacy measures were analyzed with analysis of covariance adjusting for baseline.

Summary Results:

Demographic and other baseline characteristics:

Population characteristics: Mean age in years at screening was 32.0 in adult patients and 7.6 in pediatric participants. Majority of participants were categorized as White (100% of adults and 85% of pediatric populations). The ratio of male to female participants was ~ 1:1. Participants who completed the DFI13412 (adult study) had a mean age at ASMD diagnosis of 6.96 years and participants who completed DFI13803 Peds had a mean age at ASMD diagnosis of 2.48 years. The mean age at ASMD diagnosis for all participants enrolled in the LTS13632 study was 3.38 years and the diagnosis of ASMD was confirmed for all participants who previously completed either the DFI13412 or DFI13803 Peds studies. Assessment of UGT1A1 revealed none of the participants had Gilbert syndrome.

Exposure:

For all participants the mean exposure to study intervention was 352.35 weeks, and the minimum and maximum exposures were 226.1 weeks and 501.7 weeks. The mean total year exposure [standard deviation (SD)] of all participants was 6.75 years (1.86 years) with a minimum of 4.3 years and a maximum of 9.6 years.

Of note: to comply with the requirements of the Pediatric Investigational Plan (PIP) every pediatric participant was treated with olipudase alfa in the LTS13632 study for at least 3 years.

Safety results:

Olipudase alfa showed a favorable long-term safety profile and infusions were well-tolerated by both adults and pediatric participants in the clinical and at-home settings.

The safety population was comprised of 5 adult and 20 pediatric participants. All participants reported at least 1 TEAE, were mostly mild or moderate. One adult and 10 pediatric participants experienced SAEs; in 4 of the pediatric participants the SAEs were considered related to treatment. The events included anaphylactic reaction, hypersensitivity (2 events), urticaria, rash, and alanine aminotransferase increased (2 events). No TEAE led to permanent treatment discontinuation and there were no deaths. In the overall safety population, the number of participants and number of events in the Infections and Infestations SOC gradually declined.

Protocol-defined infusion associated reactions (IARs) occurred in 17 (68.0%) participants, including 1 participant with anaphylactic reaction. IARs in both adults and pediatric participants were more frequently reported between the start of an infusion and 72 hours after the end of the infusion. The proportion of patients experiencing protocol-defined IARs was highest during the first year of exposure to olipudase (which includes the dose-escalation phase) and gradually declined through the interval 4-to-<5 years. There were no APR or CRS events. The proportion of participants experiencing hypersensitivity related TEAEs declined each year from 60.0% during the time period <1 year to 25.0% during year 4 to <5.

In the overall safety population during the time interval from <1 year of exposure to 9 to <10◦years of exposure the number of participants and number of events in the Infections and Infestations SOC gradually declined.

Olipudase alfa showed a favorable long-term safety profile and was well tolerated in participants in the LTS13632 study, including those receiving olipudase alfa infusions in the at-home setting. Based on these data, olipudase alfa infusion by a qualified health care professional at home is a reasonable option for physicians to consider for participants who have demonstrated a tolerability of the maximum maintenance dose in the at-site (ie, clinical) setting.

Immunogenicity:

There were 18 participants (3 adults and 15 pediatric) who developed treatment-emergent anti-drug antibody (ADA). Seventeen participants were treatment-induced, and 1 was treatment boosted.

Fifteen participants had a persistent ADA response, 1 was transient, and 1 was indeterminate (only the last timepoint was ADA positive with a titer of 50). The median titer for ADA positive participants was 200.

Among the ADA positive participants, no participant tested positive for NAb that inhibited cellular uptake and 11 participants (2 adults and 9 pediatric participants) tested transiently or intermittently positive for NAb that inhibited enzyme catalytic activity. The clinical relevance of NAb positivity in the in vitro assays is not known.

The effect of olipudase alfa on spleen volume (MN) was analyzed according to response to ADA (ie, treatment emergent ADA positive and negative). Positive response includes 15 pediatric participants and negative response includes 5 pediatric participants. By Month 84 for 4 pediatric participants in the positive group and 3 pediatric participants in the negative group, the mean percent change (reflecting improvement) in spleen volume (MN) was similar (-79.0 [SD=5.0, range, -83% to -72%] and -71.0 [SD=7.9, range -79% to -63%] in the positive and negative response groups respectively) (p=0.0012 and 0.0261, respectively).

The effect of olipudase alfa on mean platelet count was analyzed according to ADA status (positive or negative). Positive ADA response included 15 pediatric participants and negative included 5 pediatric participants. By Month 78, for 3 of the participants in the positive group, and 2 participants in the negative group, the mean percent change in mean platelet count was, 62.2%% (SD=37.9) and 66.7% (SD=37.2), respectively.

Efficacy:

In this long-term extension study, efficacy was assessed as a secondary endpoint in all 5 adult and all 20 pediatric participants, who rolled over at the end of their original study. Data collected corresponds to a maximum observation period of >9 years for adult and >7 years for the pediatric population (participants who completed the original study later have less data). Participants treated with olipudase alfa in LTS13632 showed an improvement over time that was sustained in most parameters. All

comparisons are presented as percent change from baseline of original study.

Spleen volume reduced over time:
- In the 5 adults, by Month 102, mean (SD) spleen volume (MN) decreased 63.60% (6.34).
- In the pediatric participants, by Month 84, mean (SD) spleen volume (MN) decreased by 75.56% (7.15) (n=7).

Liver volume reduced over time:
- In the 5 adults, by Month 102, mean (SD) liver volume (MN) decreased by 46.71% (14.40).
- In the pediatric participants, by Month 84, mean (SD) liver volume (MN) decreased by 59.55% (14.26) (n=7).

Mean pre-infusion platelet count improved over time by varying degrees:
- By Month 90, the mean (SD) platelet count increased by 21.83% (17.89) in 4 adult participants with available assessment.
- In the pediatric participants, at Month 84, mean (SD) platelet count increased by 63.97% (32.67) (n=5).

Mean pre-infusion hemoglobin improved over time by varying degrees:
- By Month 90, the mean (SD) hemoglobin increased by 15.2% (6.2) for 4 adult participants with available assessment.
- In the pediatric participants, by Month 78, mean (SD) hemoglobin increased by 13.1% (22.6) (n=5).

Lipid profile improved favorably over time in adults and pediatric participants:
- Decreased proatherogenic (total cholesterol, LDL-cholesterol, VLDL-cholesterol, Apolipoprotein B, lipoprotein (a), and triglycerides)
- Increased antiatherogenic (HDL-cholesterol and apolipoprotein A1) lipid parameters

Parameters to measure infiltrative lung disease impact were improved with improved function in both populations.
- Derived percent predicted DLco (adjusted for Hemoglobin) improved over time in most participants:
- In the 5 adults, by Month 78, the mean (SD) percent improvement from baseline was 55.29% (48.08)
- In the pediatric participants, by Month 84, the mean (SD) percent improvement from baseline was 46.20% (48.46) (n=5).
- Over time, derived percent predicted DLco (adjusted for Hemoglobin) improved in most participants. In particular, one adolescent participant had a decrease in DLco over time that is possibly due to multiple factors including fluctuations in hemoglobin, normalization of height, missed infusions and/or COVID-19 infection.
- Pulmonary function test results of FVC, FEV1 and TLC had varying degrees of improvement over time.
- Both lungs ground glass appearance and reticulo-nodular score (by HRCT and X-ray) improved over time until no disease was observed during the study in both adult and pediatric populations

Some pediatric growth parameters showed sustained improvement over time:

- Mean Height Z-score showed improvements of 2.31 at Month 72, out of 5 participants, 5 participants improved (1 in adolescent, 3 in child, and 1 in the infant cohort).

- By Month 72, meaningful bone age (by hand X-Ray) improvement of 28.345 months (n=5) was observed, indicating that bone age was getting closer to actual age over time. Four out of 5 participants who became adults during the course of the LTS13632 study reached complete skeletal maturity.

Overall, olipudase alfa treatment demonstrated benefit in efficacy endpoints achieved at the end of the original studies and these were maintained for a maximum observation period of >9 years in the adult participants and >7 years in the pediatric population.

Health Economics:

For PRO assessments:
- Improvements in some of the symptoms and functioning, as measured by child and parent reported assessments, were observed at certain follow up timepoints among pediatric participants. Nominally significant improvements in multidimensional fatigue, present pain and general core total – related quality of life were observed in pediatric participants, as measured by the PedsQL questionnaire. Nominally statistically significant changes were not observed at all of the follow-up intervals. This could be due to small sample size to detect any meaningful change.
- In adults, nominally statistically significant improvements were only noted on the pain severity score scale of BPI and the role emotional score of the SF-36 by Month 18. There was no significant reductions in fatigue, pain or dyspnea at Month 78.
- Small sample size (five adult and twenty pediatric participants) for the PRO analysis in the LTS13632 study and lack of comparator arm made the results generally difficult to interpret.

Issue date: 29-Aug-2024