Sponsor: Sanofi **Drug substance(s):** olipudase alfa	**Study Identifiers:** NCT02004691; EudraCT number 2015-000371-26; U1111-1142-5963 **Study code:** DFI12712

Title of the study:

A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency

Study center(s):

16

Study period:

Date first patient enrolled: 18 December 2015

Date last patient completed: 19 October 2023

Study Status: Completed

Phase of development: 2/3

Objectives:

Primary

The primary objective of this ASCEND Phase 2/3 study is to evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with Acid Sphingomyelinase Deficiency (ASMD) by assessing changes in:

1. spleen volume as measured by abdominal magnetic resonance imaging (MRI) (and for the United States [US] only, in association with patient perception related to spleen volume as measured by splenomegaly-related score [SRS]); and,
2. infiltrative lung disease as measured by the pulmonary function test (PFT), diffusing capacity of the lung for carbon monoxide (DL_{CO}).

Secondary

- To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks
- To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration (For the US, the effect of olipudase alfa on SRS was a part of the primary objective)
- To characterize the effect of olipudase alfa on the following endpoints assessed sequentially:

1. The effect of olipudase alfa on liver volume after 52 weeks of study drug administration
2. The effect of olipudase alfa on platelet count after 52 weeks of study drug administration
3. The effect of olipudase alfa after 52 weeks of study drug administration on fatigue
4. The effect of olipudase alfa after 52 weeks of study drug administration on pain
5. The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea

Methodology:

The DFI12712 study is a Phase 2/3, multicenter, repeat-dose, clinical trial and was divided into 2 consecutive major periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52 to be followed by 2) an extension treatment period (ETP). Initially, the ETP was double-blind as patients in the placebo group crossed over to active treatment.

The PAP assessed the difference between patients treated with olipudase alfa or placebo primarily in percent change from baseline to Week 52 in spleen volume MN (for US only, in combination with SRS) and % predicted DL_{CO}. All secondary and other end points were analyzed.

Number of study participants:

Planned: 36
Randomized: 36

Treated: 36

Evaluated:

Efficacy: 36

Safety: 36

Diagnosis and criteria for inclusion:

A male or female patient, aged 18 years or older, with documented deficiency of ASM as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes; a clinical diagnosis consistent with NPD B and the following additional criterion:

- DL_{CO} ≤70% of the predicted normal value
- Spleen volume ≥6 multiples of normal (MN) measured by MRI
- Splenomegaly related score (SRS) ≥5

Study products:

Investigational medicinal product(s):
Placebo (0.9% sodium chloride), olipudase alfa
Formulation:
Olipudase alfa is a sterile, non-pyrogenic white to off-white lyophilized cake supplied in single use, 20 cc Type 1 glass vials. Each vial contained 20 mg of extractable olipudase alfa.
The lyophilized powder was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL olipudase alfa, which was further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered.
Route(s) of administration: Intravenous

Dose regimen: Once every 2 weeks

Duration of study intervention:

This study was divided into 2 consecutive major periods: PAP and ETP. The PAP treatment period was for 52 weeks. After 52 weeks in the PAP, participants were entered and remained in the ETP for up to 4 years. A participant was considered 'ETP completed' when the participant completed the end of study visit (within 2 weeks after the last treatment) or responded to the final safety follow up phone call from the study site made 30 to 37 days after the participant's final administration of study intervention (as applicable).

Criteria for evaluation:

Efficacy:
Primary efficacy endpoints
- Percentage change in spleen volume (in MN) from baseline to Week 52 (combined with change in SRS from baseline to Week 52 in the US only, and referred to as the "combination spleen endpoint")
- Percentage change in % predicted DL_{CO} adjusted for hemoglobin and ambient barometric pressure, (throughout this document, referred to as "% predicted DL_{CO}") from baseline to Week 52

Secondary efficacy endpoints:

- Percentage change in liver volume (in MN) from baseline to Week 52
- Percentage change in platelet counts from baseline to Week 52
- Week 52 change from baseline in fatigue severity as measured by Item 3 of the BFI scale
- Week 52 change from baseline in pain severity as measured by Item 3 of the BPI-SF scale
- Week 52 change from baseline in dyspnea severity as measured by the FACIT dyspnea tool
- Change in SRS from baseline to Week 52 (except US, where it was part of the primary "combination spleen endpoint")

Safety: Assessment of adverse events (AEs), including SAEs, infusion-associated reactions (eg, cytokine release syndrome [CRS], acute phase reactions) and adverse events of special interest (AESIs).

Statistical methods:

Analysis of efficacy

The 2 primary efficacy endpoints (percentage change in spleen volume in MN from baseline to 52 weeks and percentage change in % predicted DL_{CO} from baseline to 52 weeks) and secondary efficacy endpoints were analyzed in the modified intent to treat (mITT) population (defined as all randomized patients who received at least 1 infusion (partial or total)) using the mixed model for repeated measures (MMRM). For US only, spleen volume was combined with change in SRS from baseline to Week 52 and was referred to as the "combination spleen endpoint".

The primary and secondary endpoints were tested using a 2 stage gatekeeping strategy to maintain the 5% familywise error rate. Hochberg method was used to test the 2 primary endpoints. Thus, for all countries except US, the study is declared positive if at least one of the two primary efficacy endpoints is statistically significant. For US only where combination spleen endpoint was considered a primary endpoint, the component of SRS change from baseline to Week 52 was sequentially tested at α=0.15 after spleen volume showed a statistical significance. Thus, for US only, the study was declared positive if either DL_{CO} or combination spleen endpoint was significant. When both primary endpoints were met, the secondary endpoints were tested by a pre-specified testing order.

Analysis of safety

For safety population (defined similarly to mITT), all treatment-emergent AEs (TEAEs), all TEAEs potentially related to study drug, all TEAEs leading to treatment discontinuation and/or study discontinuation, all TEAEs that were IARs, all treatment-emergent SAEs (including treatment-related SAEs), and all AEs with fatal outcome were summarized by actual treatment groups. The TEAE observation period was defined as the time from the first infusion of study drug through the end of study visit or 30 to 37 days after the last infusion of study drug, whichever occurred later. Additional summaries were also provided using the most recent dose the patient received before the event of interest.

Summary Results:

Population characteristics

- 36 adult patients were randomized.
- Patients' demographics and baseline disease characteristics were generally balanced in both treatment groups, except for gender (50% males and 50% females in the olipudase alfa group; 28% males and 72% females in the placebo group).

The mean age at randomization was 34.81 years. Overall, the mean (standard deviation [SD]) age at ASMD diagnosis was 18.0 (18.4) years (14.6 [16.1] years in placebo group and 21.4 [20.3] years in olipudase alfa group, respectively.

One participant in the placebo group did not complete the PAP. Four participants in the placebo/olipudase alfa group and 2 participants in the olipudase alfa/olipudase alfa group did not complete the ETP.

Primary reasons for permanent treatment/study discontinuation were as follows:

- In the placebo/olipudase alfa group: AE, withdrawal of consent, poor compliance to protocol, pregnancy, and other reason related to COVID-19 (impossibility to travel to and from the infusion site due to COVID-19 pandemic) (1 participant each).
- In the olipudase alfa/olipudase alfa group: withdrawal of consent and other reason not related to COVID-19 (participant's decision) (1 participant each).

Summary Results:

Efficacy results

Primary

• % predicted DL_{CO}: Primary efficacy endpoint measured by percentage change in % predicted DL_{CO} from baseline to Week 52 was 21.97% for the olipudase alfa group and 2.96% for the placebo group. The difference between the 2 treatment groups (19.01%) was statistically significant after the multiplicity adjustment (p = 0.0004). During the ETP, at Week 104, the LS mean in percentage change from baseline in % predicted DL_{CO} improved by 28.04% and 28.49% in the placebo/olipudase alfa group (n = 10) and the olipudase alfa/olipudase alfa group (n = 10), respectively.

• Spleen volume MN: The LS mean percentage change in spleen volume MN from baseline to Week 52 demonstrated a reduction in the olipudase alfa group (39.45%) compared to an increase in the placebo group (0.48%); resulting in a difference of -39.93% that was statistically significant after the multiplicity adjustment (p <0.0001). During the ETP, at Week 104, the LS mean percentage change in spleen volume from baseline in the placebo/olipudase alfa group patients (n = 11) was reduced by 35.93% and by 46.95% in the olipudase alfa/olipudase alfa group (n = 14).

• Combination spleen endpoint for US only: The primary efficacy endpoint measured by percentage change in spleen volume in MN from baseline to Week 52 is combined with change in SRS score from baseline to Week 52. The change in SRS score from baseline to Week 52 was -7.66 for the olipudase alfa group and -9.28 for the placebo group. The difference between the 2 treatment groups was not statistically significant after the multiplicity adjustment (p = 0.6364). Thus, for the US only, the primary efficacy "combination spleen endpoint" is not considered statistically significant. During the ETP, the LS mean percentage change in SRS score from baseline to Week 104 in the placebo/olipudase alfa group (n= 16) reduced by 10.86, and in the olipudase alfa/olipudase alfa group (n = 11), the reduction was 13.47; a mean difference of -2.60 was observed in reduction of SRS scores across the treatment groups.

Secondary

For all countries except US, sequential testing of the secondary endpoints proceeded:

• The following parameters are considered statistically significant after the multiplicity adjustment:

- Liver volume: The percentage reduction in liver volume in MN from baseline to Week 52 was 28.06% for the olipudase alfa group and 1.47% for the placebo group. The difference between the 2 treatment groups (-26.60%) was statistically significant after multiplicity adjustment (p <0.0001). Furthermore, during the ETP, at Week 104, the LS mean percentage change in liver volume from baseline reduced by 30.66% in the placebo/olipudase alfa group patients (n = 11), and by 33.42% in the olipudase alfa/olipudase alfa group (n = 14), a further reduction relative to the 27.80% reduction observed in the olipudase alfa group at Week 52.

- Platelet count: The LS mean percentage change in pre-infusion platelet count from baseline to Week 52 was 16.82% for the olipudase alfa group and 2.49% for the placebo group. Difference between the 2 treatment groups (14.33%) was statistically significant after multiplicity adjustment (p = 0.0185). Furthermore, during the ETP, the LS mean percentage change in pre-infusion platelet counts from baseline at Week 104 was 21.73% in the placebo/olipudase alfa group (n = 15) and 24.94% in the olipudase alfa/olipudase alfa group (n = 13).

• BFI scale –Item 3: The difference of change in BFI scale –Item 3 from baseline to Week 52 was not statistically significant between olipudase alfa and placebo groups. Thus, sequential testing of the secondary endpoints stopped.
• Other PROs: There was no significant difference between olipudase alfa and placebo in the other PROs questionnaires (BPI-SF scale Item 3, FACIT dyspnea symptom score, and SRS) measuring change from baseline to Week 52 or the ETP as all the nominal p-values were >0.05.

For US only:

Since SRS was not statistically significant, the combination spleen endpoint was not considered statistically significant. Thus, secondary endpoints were not tested for statistical significance under multiplicity adjustment; however, nominal p-values are provided for all the results.

Safety results

PAP

All patients in the placebo and the olipudase alfa groups experienced at least 1 TEAE. The total number of events was lower in the olipudase alfa group (242) compared to the placebo group (270). The percentage of patients with TEAEs related to the study drug was greater in the olipudase alfa group (66.7%, n=12) compared to the placebo group (33.3%, n=6). The number of patients with serious TEAEs was similar between the placebo (n=4) and the olipudase alfa groups (n=3). None of the serious TEAEs led to treatment discontinuation or were considered potentially related to olipudase alfa.

There were no TEAEs that led to treatment discontinuation or study withdrawal. The percentage of patients with TEAEs that led to study treatment interruption was identical in both groups (16.7% each).

No deaths were reported. The percentage of patients with protocol-defined IARs was greater in the olipudase alfa group (44.4%) compared to the placebo group (27.8%). One patient (5.6%) in the olipudase alfa group experienced a TEAE (one event) that met criteria for dose limiting toxicity (DLT1) compared to 5 patients in the placebo group (4 patients [22.2%] with 6 events met DLT2, and 1 patient [5.6%] with 1 event that met the laboratory criteria for DLT3 but did not exhibit the clinical symptom component).

Regarding immunogenicity, treatment emergent ADAs occurred in 4/18 (22.2%) of olipudase alfa and 1/18 (5.6%) placebo treated patients. Of these, 2 olipudase alfa and 2 placebo treated patients were positive for in-vitro assay of neutralizing antibodies directed against catalytic activity; however, none of the patients developed NAb that interfered with enzyme uptake into cells.

PAP+ETP

During PAP+ETP, all participants experienced at least 1 TEAE, the large majority of TEAEs were mild or moderate in severity. Overall, protocol-defined IARs were similar in the placebo/olipudase alfa group and the olipudase alfa/olipudase alfa group. The most common IARs in the overall population were from the SOC Nervous system disorders (headache) followed by Skin and subcutaneous tissue disorders (urticaria). The number of participants with SAEs were similar in the placebo/olipudase alfa and the olipudase alfa/olipudase alfa groups. The most common SAE in the placebo/olipudase alfa group was in the SOC of Nervous systems disorders and Cardiac disorders, and in the olipudase alfa/olipudase alfa group, the most common SAEs were in the SOC of Infections and infestations and Hepatobiliary disorders. There were no cases of APR or CRS. There were 2 participants with TEAEs (rash, pregnancy) that led to treatment withdrawal during the ETP. The participant who became pregnant had an uneventful pregnancy and delivered a healthy baby. No deaths were reported during the PAP+ETP.

Laboratory findings, vital signs, and ECGs did not raise any new safety concerns. Abdominal examination showed improvement over time, consistent with decrease in spleen volume, and there were no other potentially clinically meaningful changes in physical examination or neurological function associated with olipudase alfa treatment. Additionally, olipudase alfa was overall well tolerated in participants receiving infusions in the at-home setting.

Olipudase alfa showed a favorable safety profile in adults with ASMD.

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