Amsterdam, 30 May 2024
EMA/223166/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xenpozyme

Olipudase alfa

Procedure no: EMEA/H/C/004850/P46/006

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 29th of February 2024, the MAH submitted a completed paediatric study for Xenpozyme, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has been provided.

Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study LTS13632 is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing the final CSR of study LTS13632) is expected to be submitted in August 2024.

Study LTS13632 has been conducted as part of an agreed paediatric investigation plan (PIP).

2.2. Information on the pharmaceutical formulation used in the study

Patients have received olipudase alfa via IV infusions. Each vial contained 20 milligrams of extractable olipudase alfa and was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL of olipudase alfa. Olipudase alfa was further diluted in 0.9% sodium chloride for injection solution to a specific volume based on dose to be administered. The length of the infusion time were adjusted based on the patient's tolerance of the infusion. Eligible patients could receive home infusions.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the paediatric data of:

LTS13632 study is a Phase 2, multinational, multicentre, nonrandomized, open label, long-term treatment study of patients who previously participated in a study with olipudase alfa.

2.3.2. Clinical study

LTS13632 study

Description

LTS13632, a Phase 2, multinational, multicentre, nonrandomized, open label, long-term study was designed to assess the safety and efficacy of olipudase alfa in participants with acid sphingomyelinase deficiency (ASMD) who already participated in studies with olipudase alfa.

Assessor's comment

This study included 5 adult and 20 paediatric patients. Only data of paediatric patients is assessed in this procedure, therefore the five adult patients of DFI13412 study are not further discussed.

Methods

Study participants

Inclusion criteria were:

- The patient completed the treatment period of a previous study of olipudase alfa with an acceptable safety profile in the opinion of the investigator and sponsor.
- The patient and the patient's parent(s)/legal guardian(s) is willing and able to provide signed written informed consent.
- The patient who is female and of childbearing potential must have a negative urine pregnancy test for beta-human chorionic gonadotropin (β-HCG).
- Female patients of childbearing potential and sexually mature male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle or use 2 acceptable effective methods of contraception up to 15 days following their last dose of study drug.

Exclusion criteria were:

- The patient has any new condition or worsening of an existing condition which in the opinion of the investigator would make the patient unsuitable for enrolment, or could interfere with the patient participating in or completing the study.
- The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study.
- The patient is unwilling or unable to abstain from the use of alcohol for 1 day prior to and 3 days after each olipudase alfa infusion for the duration of the treatment period.
- The patient is unwilling or unable to avoid, for 10 days before and 3 days after liver biopsies, medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, erythromycin, valproic acid, antidepressants, kava, echinacea) or may cause or prolong bleeding (eg, anticoagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng) (only patients who previously participated in the DFI13412 study).
- The patient requires medication(s) that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, desipramine]).

Assessor's comment

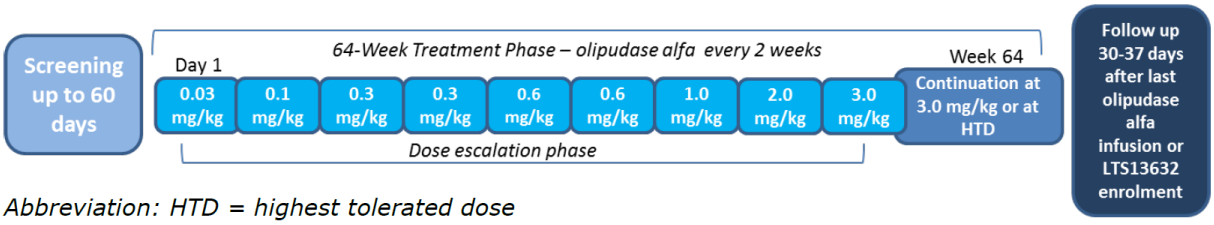
Patients who completed a previous study of olipudase alfa, study DFI13803 for paediatric patients, were included in the long-term follow-up LTS13632 study. Thus no new patients were treated with olipudase alfa in this study. The original inclusion (male/female <18 yoa, ASM deficiency documented, spleen volume ≥5 MN and Z-score of -1 or lower) and exclusion criteria for study DFI13803 are not assessed here as they were considered acceptable at MAA.

Treatments

Participants received an intravenous infusion of olipudase alfa every 2 weeks for up to 9 years, or until olipudase alfa became commercially accessible, whichever came 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. To comply with the requirements of the Paediatric Investigational Plan (PIP) every paediatric participant was treated with olipudase alfa in the LTS13632 study for at least 3 years.

Patients will start this study at the same dose they were receiving at the end of the primary study (DFI13803), provided that they have not missed more than 1 biweekly dose between studies. See Figure 1 for a schematic representation of the study schedule of DFI13803 after which paediatric patients enrolled into LTS13632 study.

Figure 1 Trial DFI13803 Study Schema and Dose Escalation Plan.



Abbreviation: HTD = highest tolerated dose

Home infusions were possible. Eligibility criteria for home infusions are listed in the SmPC.

Assessor's comment

In the primary study (DFI13803), patients were up-titrated with olipudase alpha via a dose escalation regimen from 0.03 mg/kg to a target dose of 3 mg/kg. Treatment was administered as an intravenous infusion once every 2 weeks. This is conform the SmPC.
For this long-term extension, patients continued on the same dose as they were receiving at the end of the primary study.

Eligible patients could receive home infusion conform the SmPC.

The study participants were treated in the LTS13632 for at least 3 years, which is defined as time from the first infusion of the investigational medicinal product IMP (included) from original study to the end of LTS13632. End of the LTS study was defined as a study duration up to 9 years, or until olipudase alfa became commercially accessible, whichever came 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. Thus, long-term data up of at least three years is available of all treated patients.

Objectives

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

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

Assessor's comment

The study objectives are acceptable.

As this is an uncontrolled long-term study, it is impossible to draw robust conclusions on the efficacy and safety effects of the treatment. The study will enable to determine whether there is a maintenance of pharmacodynamic effects while maintaining a tolerable safety profile.

Outcomes/endpoints

The primary endpoints of this study were data pertaining to the safety and tolerability of olipudase alfa:

- Assessment of adverse events (AEs)/treatment-emergent AEs including infusion associated reactions (IARs), and adverse event of special interest (AESI).
- Complete Physical examinations.
- Extended Neurologic examinations.
- Abbreviated Physical Exam.
- Weight.
- Height (paediatric patients only).
- Vital sign measurements.
- Clinical laboratory tests.
- Electrocardiograms (ECGs).
- Doppler echocardiography.
- Safety biomarkers.
- Liver ultrasound with Doppler (only patients who previously participated in DFI13803).
- Immune response assessments.

The secondary endpoints of this study included:

- 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.
- Haematology (haemoglobin and platelet count).
- Lipid profile.

- Health outcome questionnaires.
- Hand X-ray for bone age and bone maturation.
- Linear patient growth by height Z-score.

Assessor's comment

The primary endpoint focusses on safety. Endpoints are considered adequate to assess safety and tolerability of olipudase alfa in paediatric patients.

The efficacy endpoints are secondary endpoints in this study. Splenomegaly and hepatomegaly are the most commonly shared symptoms of ASMD and were studied in previous studies. Spleen and liver volumes enable serial assessment over prolonged period of time. Besides, pulmonary function and imaging, haematology, lipid profiles, bone age and bone maturation were assessed. Impaired lung function, low haemoglobin levels and platelet counts, dyslipidaemia and skeletal abnormalities are common features of ASMD. Efficacy endpoints are acceptable.

Sample size

Sample size was determined by the number of patients who completed the treatment phase of a previous clinical study of olipudase alfa, signed the informed consent form for the LTS13632 study, and met the eligibility criteria. It was expected that the sample size for this study was approximately 25.

Assessor's comment

The sample size of 25 consists of 20 paediatric and 5 adult patients of previous studies.

Randomisation and blinding (masking)

This was a non-randomized, open-label study. No randomisation or blinding procedures were in place.

Statistical Methods

For efficacy and safety endpoints, baseline is defined as the last available non-missing value before the first infusion in the original study.

Every paediatric patient was treated in the LTS13632 study for at least 3 years. The treatment period was defined as time from the first infusion of the investigational medicinal product IMP (included) from original study to the end of LTS13632. Therefore, all the summaries in this assessment report contain data from the original study and LTS13632 study.

The safety set will include all enrolled patients who received at least 1 infusion (partial or total) of olipudase alfa in the current study. All analysis will be done on the safety set unless specified otherwise.

The term "paediatric patients" means patients coming from the original paediatric trial, DFI13803. Some of these patients will reach adult age (18 years old) while in this study. These patients will be adults by age, but they will remain part of the "paediatric patient" cohort.

This study had a first interim database lock for with a data cut-off of 10 December 2019, to write a first interim CSR for regulatory submissions in 2020. The second interim database lock with a cut-off

date of 01 March 2021 was done for global regulatory submissions in 2021. The data presented in this final CSR comprises all the data up to the last participant last visit on 06 September 2023.

Analysis of efficacy variables

Spleen and liver volumes will be assessed by abdominal MRI to quantify the degree of splenomegaly and hepatomegaly. Pulmonary function tests (PFT) will be performed in patients ≥5 years old at screening in the original study to measure lung volumes, air flow, and gas exchange for evidence of interstitial lung disease (ILD) at approximately every 6 months for first 2 years in this study (starting at 3 months in this study for paediatric patients), and every 12 months thereafter. High-resolution computed tomography scans of the chest and chest X-ray (posterior-anterior and lateral views) will be obtained at approximately every 12 months (starting at 9 months in this study for paediatric patients). This evaluation is meant to quantify the degree of possible interstitial lung disease (ILD).

Blood samples are collected for the evaluation of platelets and haemoglobin at each scheduled clinic visit every 6 months (in addition to haematology sample of complete blood count).

A hand X-ray is performed at Screening and Week 52 in the original study, and will continue every 6 months of exposure to olipudase alfa. Bone age will be provided by the central vendor - BioClinica; they will use calculations based on the Greulich & Pyle Atlas.

Patient height is collected at screening and within 24 hours prior to every infusion visit in the original study, then every 6 months in the extension study. Z-score is the normalized value when compared to mean and standard deviation of height of children considered to have normal growth, based on gender and age (World Health Organization list from 2007).

For efficacy analysis: All comparisons were presented in change or percent change from baseline of original study at various timepoints. As participants entered the LTS13632 study at different times, the timepoint chosen for analysis was the latest assessment with at least 5 participants in paediatric population, which was the number of participants deemed necessary for a meaningful analysis. For most outcome measures this timepoint was Month 84 in paediatric participants. In a few cases, an earlier timepoint was used to obtain the minimum of 5 participants for analysis.

For more details see the provided Protocol and SAP.

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.

Assessor's comment

The original paediatric study had a duration of 64 weeks. After that, patients were eligible to enrol in the long-term study LTS13632 to continue receiving olipudase alfa. The end of the DFI13803 study was defined as the day that the last patient entered in the LTS13632.
Baseline values and values up to week 52 (at MAA data was available of all 20 paediatric patients up

to week 52) in this AR, are thus the values of study DFI13803 which were assessed at MAA and summarised in the EPAR and SmPC. There was data available of some participants (n=5-7) up to month 48 at MAA, which is also included in the SmPC.

The MAH has used the latest time point of the long-term extension study at which the data of five patients was available for analysis. Five patients is a small number for analysis however, this approach is understandable to be able to analyse long-term data. Nevertheless, it would be of value to have a comprehensive analysis at the 3 years timepoint for all 20 included patients, as this was the minimal required follow-up requested by the PDCO. For this procedure, the Assessor has compiled these data from the response data. For the upcoming variation procedure when submitting the final CSR (expected in august 2024), the MAH is requested to include the 3 year timepoint in the overview for both adult and paediatric patients.

Results

Participant flow

Twenty paediatric participants were enrolled in the LTS13632 study. All 20 paediatric participants received the study intervention and completed the study treatment as well as the study.

Of note, study completion was reached earlier than anticipated due to the earlier than anticipated regulatory approval. However, there was no consequence for the participants. In some countries, where olipudase alfa was still not commercially available at the time of study completion, participants were further offered treatment in either a local study (eg, in France) or in the olipudase alfa Post Access Program.

Recruitment

The study was conducted in the United States, Brazil, United Kingdom, France, Germany, Belgium, and Italy. This study was conducted from 04 December 2013 (first patient enrolled) through 06 September 2023 (last patient last visit).

Baseline data

Of the 20 paediatric participants, seventeen (85%) participants were Caucasian/White, 1 (5%) participant reported race as Other, and 2 (10%) participants were South East Asian. The mean age (standard deviation [SD]) in years at screening was 7.6 (4.43; 1 to 17) and 10 (50%) participants were male. There were 4 adolescents, 9 children and 7 infants. The mean weight (SD) in kg at baseline was 23.38 (10.80; 9.9 to 51.5).

The mean age (SD) in years at ASMD diagnosis was 2.5 and the diagnosis of ASMD was confirmed for all participants. See Table 1 for an overview of the baseline disease characteristics. Assessment of UGT1A1 revealed that no participant had Gilbert syndrome.

Table 1 Summary of baseline disease characteristics - Safety Population

	Patients from DFI13803 (Pediatrics) (N = 20)
Age at symptom onset (years)	
Number of patients with value	18
Mean (SD)	1.420 (1.017)

Median	1.027
Min : Max	0.16 : 3.92
Age at diagnosis (years)	
Number of patients with value	20
Mean (SD)	2.478 (2.449)
Median	1.932
Min : Max	0.02 : 11.09
ASM activity (peripheral leukocytes), nmol/h/mg	
Number of patients with value	19
Mean (SD)	0.135 (0.078)
Median	0.120
Min : Max	0.00 : 0.30
Spleen status, n (%)	
Number of patients with value	20
Partial Splenectomy	0
Fully Intact	20 (100%)
Symptoms present at disease onset, n (%)	
Number of patients with value	20
Excessive Bleeding/Bruising	2 (10%)
Other Symptoms	5 (25%)
None	1 (5%)
Splenomegaly	20 (100%)
Hepatomegaly	20 (100%)
Respiratory Disease	7 (35%)
Thrombocytopenia	11 (55%)
Failure To Thrive	11 (55%)
Short Stature	18 (90%)
Pain	10 (50%)

Note: Percentages are calculated using the number of participants who have available data at each age cohort as the denominator.
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Number analysed

All 20 participants from the DFI13803 Peds Phase 1/2 paediatric study were enrolled in the LTS13632 Phase 2 study. Participants were enrolled directly into this study from their previous study.

There were no participants who withdrew from the study, nor participants who discontinued treatment from any cohort. All participants completed follow up, eg. concluded with a safety follow up phone call.

Assessor's comment

This study included 20 ASMD paediatric patients. From the original study; neurologic manifestations were seen in 8 out of 20 paediatric patients (40%) at baseline consistent with a clinical diagnosis of ASMD Type A/B. The remaining 12 patients had a clinical diagnosis consistent with ASMD Type B. There were 4 adolescents, 9 children and 7 infants.

From the Participants disposition (16.2.1) it is clear that all 20 paediatric patients were followed up to week 156 (36 months). However, not all study visits up to week 156 were (entirely) performed for each participant due to Covid-19 or for other reasons. From week 162 onwards, participant numbers dropped. The following is deduced from the Participants disposition:

N=20 up to week 156
N=17 up to week 162
N=16 up to week 170
N=15 up to week 176
N=14 up to week 188
N=13 up to week 194
N=12 up to week 208
N=11 up to week 234
N=10 up to week 248
N=9 up to week 274
N=6 up to week 286
N=3 up to week 316

However, it remains somewhat unclear of how many patients data is available at which timepoint and the MAH is requested to clearly state this when the full CSR is submitted in the variation procedure. For example, from the Participant disposition (16.2.1) is stated that data is available of n=12 participants at week 208 (= month 48), while spleen volume available for n=13 at month 48.

Efficacy results

The efficacy parameters were assessed as secondary endpoints. Data collected corresponds to a maximum observation period of >7 years for the paediatric population.

Assessor's comment

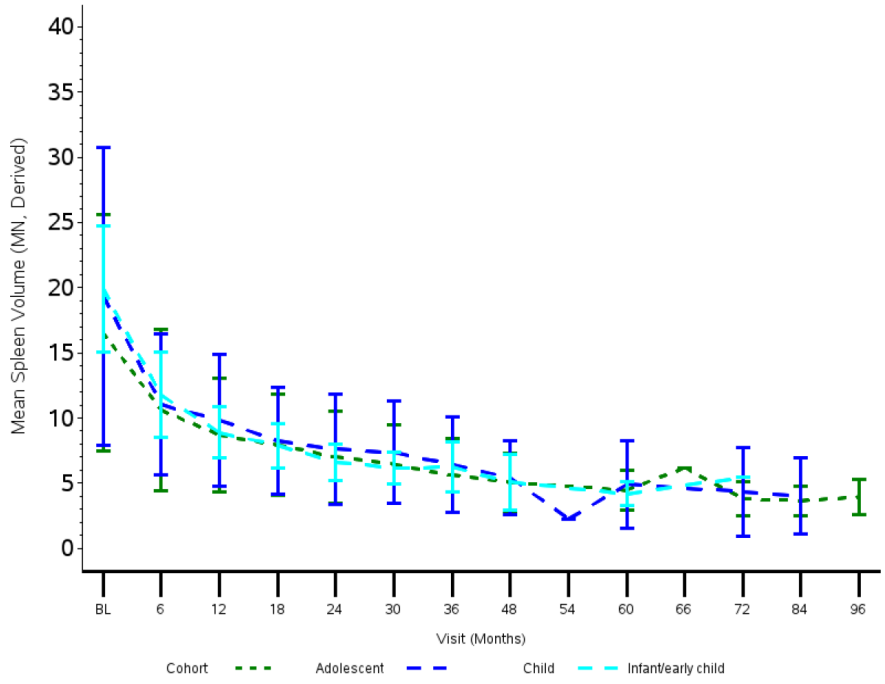
It should be noted that presented data of baseline up to 12 months was already available at MAA and presented in the SmPC, as this is data from the original study DFI13803. Preliminary data of the paediatric patients in the extension study up to Month 48 was available for 5 to 7 patients (depending on the variable) and presented in the SmPC.

In the current procedure, data is presented of up to month 84. Primary focus of assessment is on the newly presented data, especially on the data up to 3 years of treatment since this is available for all treated paediatric patients. After this timepoint, number of patients per timepoint decreases.

Spleen volume

A reduction of spleen volume (multiple of normal [MN]) was observed at all timepoints starting as early as Month 6 and was sustained up to the latest time point (Figure 2).

Figure 2 Summary plot of mean spleen volume (MN) over time by age cohort (Paediatrics Only) - Safety Population



Note: The vertical bars represent standard deviation
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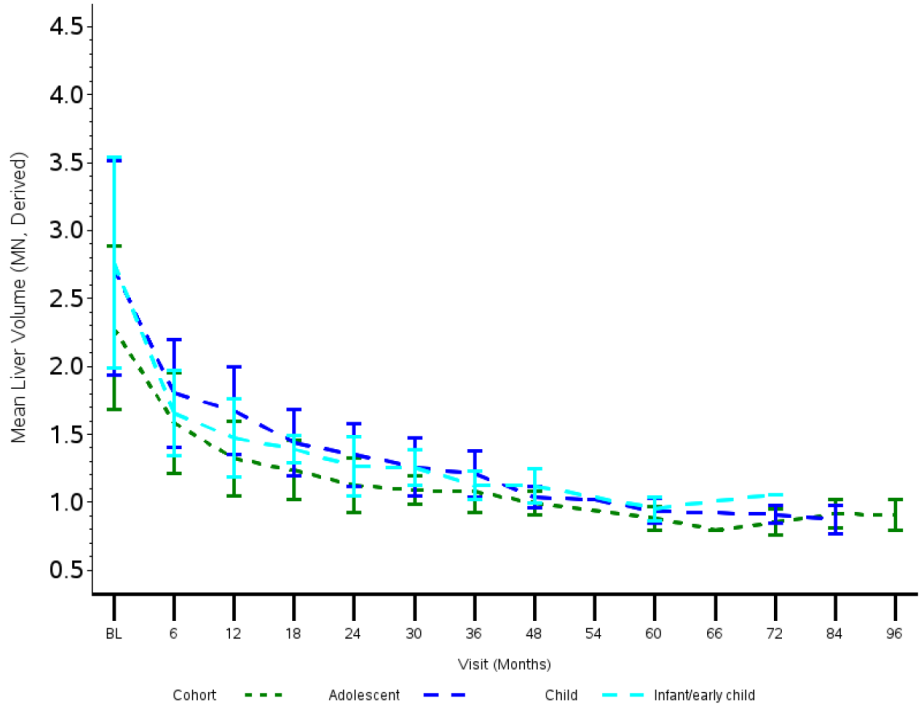
- At baseline, mean spleen volume was 18.98 (MN) (SD = 8.77, n = 20) reflecting moderate splenomegaly. By Month 36, the mean percent reduction was 67.37% (SD= 6.30) ($p<0.0001$, n=17).
- By Month 84, the mean (SD) spleen volume (MN) decreased by 75.56% (SD = 7.15) ($p<0.0001$, n = 7). Mean spleen volume for these 7 paediatric patients was 17.30 (MN, SD = 11.20) at baseline and 3.82 (MN, SD = 1.89) at Month 84.

Liver volume

A reduction of liver volume (MN) was observed at all timepoints starting as early as Month 6 and was sustained throughout the time period (Figure 3).

Figure 3 Summary plot of mean liver volume (MN) over time by age cohort (Paediatrics Only) -Safety Population



Note: The vertical bars represent standard deviation
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- At baseline, mean liver volume (MN) was 2.65 (SD = 0.74) reflecting moderate hepatomegaly. By Month 36, the mean percent reduction from baseline was 53.73% (SD= 10.25) ($p<0.0001$, n=17).
- By Month 84, mean liver volume (MN) decreased by 59.55% (SD = 14.26) ($p<0.0001$, n = 7). Mean liver volume for these 7 paediatric patients was 2.43 (MN, SD=0.74) at baseline and 0.90 (MN, SD=0.10) at Month 84.

Assessor's comment

At baseline, the mean spleen volume of all paediatric patients was 18.98 MN and 12/20 participants were categorized in the severe splenomegaly category (spleen volume >15 MN). Spleen size decreased upon olipudase alpha, the decrease was most prominent in the first few months. At 36 months the reduction from baseline was -67.37% (based on n=17) which further decreased to -75.6% (based on n=7) to a spleen volume of 3.82 MN by month 84, confirming long term maintenance of efficacy.

Liver volume was also enlarged at baseline; mean liver volume was 2.65 MN. Liver volume also decreased in the months after treatment. At month 36 levels decreased by -53.73%, reaching normal liver volumes (mean liver volume of 1.16 MN, n=17). This sustained in the 7 patients who were followed up to 84 months, confirming long term maintenance of efficacy. Data up to month 48 (of n=7, reduction of -55.4%) is presented in the SmPC.

In conclusion, the presented data show a maintenance of the effect on spleen and liver volume.

For future submissions (e.g. filing the full CSR of the long-term extensions study), it would be informative to have the patient numbers contributing data per timepoint more clearly displayed in the graph as parts of the X-axis.

Pulmonary function tests

Derived percent predicted diffusing capacity of the lung for carbon monoxide (DLco) (adjusted for haemoglobin) improved over time in most participants. The pulmonary function results of forced vital capacity (FVC), Forced Expiratory Volume in the First 1 Second (FEV1), and total lung capacity (TLC) had varying degrees of improvement over time. A summary is presented in Table 2.

Table 2. Summary of Pulmonary function test results (Paediatrics Only) -Safety Population

	Baseline Mean (SD)	**Month 36** Mean (SD) percent change from baseline	**Month 84** Mean (SD) percent change from baseline
Dlco	54.79% (14.23) N=9	60.14% (51.17) N=8	46.20% (48.46)* N=5
FVC	77.44% (16.26) N=13	25.63% (21.83) N=12	37.08% (34.56) N=6
FEV1	76.51% (16.08) N=13	22.04% (17.83) N=12	28.85% (33.40) N=6
TLC	86.76% (23.26) N=10	40.46% (34.13) N=8	*At 72 months:* 33.97% (24.55) N=7

* one adolescent participant had a decrease in Dlco over time that was most likely due to multiple factors including anaemia, normalization of height, missed infusions and/or COVID-19.
Abbreviations: Dlco, Derived percent predicted diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; FEV1, Forced Expiratory Volume in the First 1 Second; TLC, total lung capacity.

Assessor's comment

Progression of respiratory disease in ASMD is slow, but inevitable, due to the accumulation of Niemann-Pick cells in the lung tissues, potentially leading to a progressively worsening of pulmonary function.

Pulmonary function tests suggest an improvement of interstitial lung disease upon olipudase alpha treatment; increased Dlco was observed in most patients. Other pulmonary functionality tests show varying degrees of improvement.

These findings are in line with the presented data in the SmPC. The SmPC states a mean % predicted Dlco (SD) of 54.8 (14.2, n=9) at baseline and a mean percent change (SD) from baseline of 32.9% (8.3, n=9) and 60.3% (58.5, n=5) at 12 and 48 months, respectively.

The data show maintenance of efficacy on pulmonary function.

Haematology

Mean pre-infusion platelet count improved over time:

- At baseline, mean platelet count was 137.74 x 10^9/L (SD = 62.32; range, 67.3 to 329.5) in the 20 paediatric participants, reflecting mild thrombocytopenia.
- The mean (SD) platelet count increased by 29.29% (31.80, n=15) and by 63.97% (32.67, n = 5) by Month 36 and Month 78, respectively.

Mean haemoglobin improved over time:

- At baseline, mean haemoglobin was 122.8 g/L (SD =16.8; range 86 to 151) (n = 20).
- Mean (SD) haemoglobin increased by 5.1% (12.4, n=16) and 13.1% (22.6, n = 5) by Month 36 and 78, respectively.

Lipid profile

Lipid profile improved over time. Baseline mean values of pro-atherogenic lipoproteins (total cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, apolipoprotein B, lipoprotein (a) and triglycerides) were within or slightly elevated over the average upper limit of normal (ULN). Sustained reduction was observed over time. Baseline mean values for antiatherogenic lipoproteins (HDL-cholesterol and apolipoprotein A1) were below normal ranges. Sustained improvement was observed at most timepoints.

Health outcome questionnaires

The following questionnaires were evaluated:

- The PedsQL Generic Core Scales: The PedsQL Generic Core Scales consists of multidimensional scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning), and two summary scores (Psychosocial Health Summary Score, and a Generic Core Total Score).
- PedsQL Multidimensional Fatigue Scale: The PedsQL Multidimensional Fatigue Scale encompasses three domains and scores (General Fatigue, Sleep/Rest, and Cognitive), and a Total Scale Score is computed.
- PedsQL Pediatric Pain Questionnaire.

Improvements in some of the symptoms and functioning, as measured by child and parent reported assessments, were observed at certain follow up timepoints among paediatric participants. Nominally significant improvements in multidimensional fatigue, present pain and general core total - related quality of life were observed in paediatric 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.

Bone age

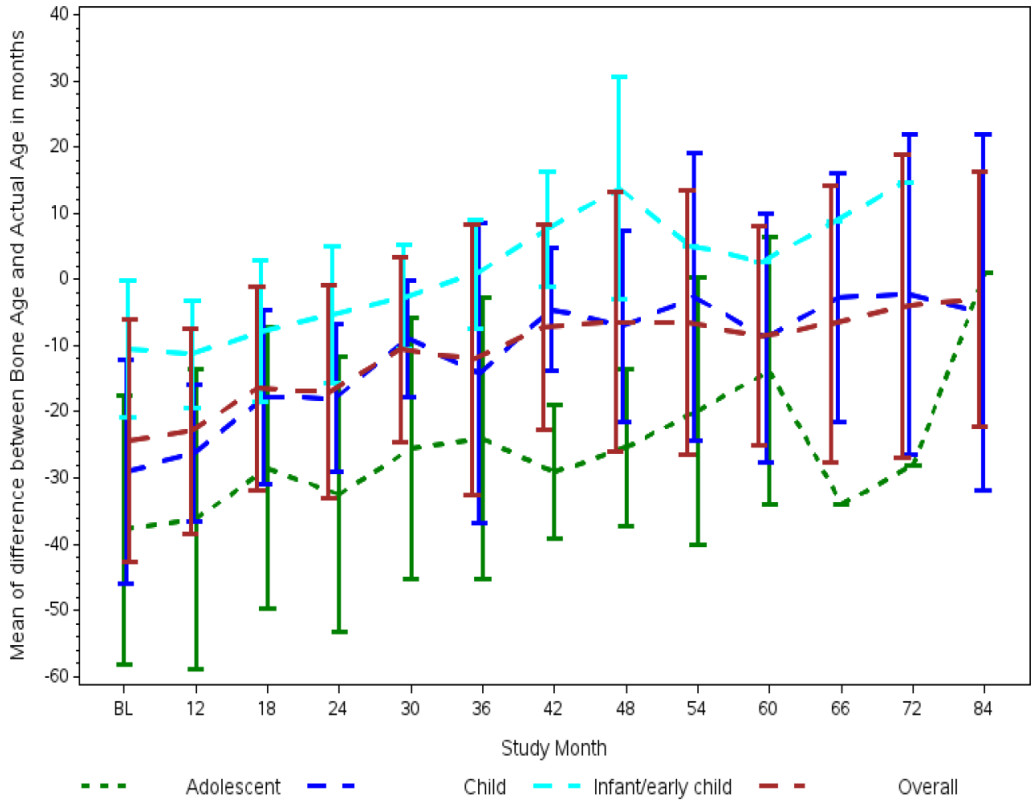
The age of complete skeletal maturity (ie, bone age by hand X-ray) is 18 years for females and 19 years for males, and after reaching skeletal maturity there is no advancement in bone maturity, thereafter. For paediatric participants who became adults during the course of LTS13632 study and

reached skeletal maturity threshold the first timepoint when skeletal maturity was reached was their last timepoint included in the study analysis and their subsequent assessments were not included in the study analysis.

Four out of 5 participants who became adults during the course of the LTS13632 study reached complete skeletal maturity.

- At baseline, overall, 20 paediatric participants had a mean delay in bone age of 24.3 months compared to their actual age (delay in months per cohort was 37.8 in adolescent, 29.1 in child and 10.5 in infant).
- By Month 36, meaningful bone age improvement of 13.649 months (n = 17) was observed, indicating that bone age was getting closer to actual age over time (Figure 4). The mean delay in bone age for these 17 patients at baseline was -25.7 months compared to their actual age.
- By Month 72, meaningful bone age improvement of 28.345 months (p = 0.0828, n = 5) was observed (Figure 4). The mean delay in bone age for these five patients at baseline was -32.4 months compared to their actual age.

Figure 4 Summary plot of difference between bone age and actual age in months (Paediatrics Only) by age group - Safety Population



Note: The vertical bars represent standard deviation
The age of complete skeletal maturity is 18 years for females and 19 years for males, and the subsequent timepoints after reaching skeletal maturity were excluded from the bone age analysis in the participants who became adults during the study.
PGM=PRODOPS/GZ402665/LTS13632/CSR_03/REPORT/PGM/mo_boneage_g.sas OUT=REPORT/OUTPUT/mo_boneage_g_diff_i.rtf (13DEC2023 - 13:36)

Linear patient growth by height Z-score

- Overall mean (SD) Height Z-score was -2.14 (0.84) at baseline.
- By Month 36, overall mean Height Z-score (SD) improved by 1.57 (0.68, n = 15). Height Z-score was -2.14 at baseline for these 15 paediatric patients
- By Month 72, overall mean Height Z-score (SD) improved by 2.31 (1.34), (p = 0.0013; n = 5). Height Z-score was -2.79 at baseline for these 5 paediatric patients
  (*NB. Assessor calculated the baseline values of these patients based on the observed value and change from baseline value at Month 36 and 72*).

Assessor's comment

Platelet levels at baseline were 137.7 10^9/L (n=20), which improved during olipudase alpha treatment with a percentual increase of 29.29% and 63.97% in platelet count at month 36 (n=15) and month 78 (n=5), respectively. An increase of +35.8% was reported in n=5 patients up to month 48 in the SmPC. Data indicate a maintenance of effect.

The treatment had a less pronounced effect on haemoglobin levels, after 36 and 78 months of treatment haemoglobin levels increased 5.1% (n=16) and 13.1% (n=5) respectively. Haemoglobin levels were analysed and presented in g/dL however, mmol/L is the more common unit used in the EU. The MAH is requested to present all information and data on haemoglobin levels in mmol/dL instead of g/dL in upcoming procedures. At the next regulatory opportunity, the MAH is also requested to implement these editorial changes in the SmPC.

Also the lipid profile and quality of life and some of the symptom scores (slightly) improved over the course of olipudase alpha treatment.

Bone age delay improved upon olipudase alpha treatment; after 36 and 72 month of treatment, bone age delay improved by 13.65 months (n=17) and 28.35 months (n=5), respectively. Normalized bone age is only of benefit to the patient in case also growth is normalized. It can be concluded that these five patient had delayed bone age and growth at baseline and that after 72 months of treatment these patients had normalized growth and Z-scores.

Safety results

Exposure

For all paediatric participants the mean exposure to study intervention was 315.79 weeks, and the minimum and maximum exposures were 226.1 weeks and 425.6 weeks. The mean total year exposure [standard deviation (SD)] of all participants was 6.05 years (1.34 years) with a minimum of 4.3 years and a maximum of 8.2 years.

All paediatric participants achieved the maximum 3.0 mg/kg maintenance dose during DFI13803 and have continued on this dose during LTS13632. Seven paediatric participants in the predecessor study and 2 paediatric participants in LTS13632 had dose reductions due to Dose Limiting Toxicity (DLTs), Infusion-associated reactions (IARs) and/or missed doses.

Adverse Events (AEs)/Treatment-Emergent AEs

All 20 paediatric participants experienced TEAEs while participating in LTS13632. The most commonly reported TEAEs were pyrexia (90%), cough (80%), diarrhoea (75%), vomiting (75%), nasopharyngitis

(70%), and headache (65%). Ten paediatric participants experienced overall 29 treatment-emergent serious adverse events (SAEs) including 4 paediatric participants who experienced 7 treatment-related SAEs. In 3 of these paediatric participants the treatment related SAEs were reported in the predecessor study; they were comprised of alanine aminotransferase increased (2 events), urticaria and rash, and anaphylactic reaction during dose escalation. The fourth paediatric participant experienced hypersensitivity (2 events) while in LTS13632. All SAEs considered related to study treatment occurred during infusion at the clinical site; none occurred during at-home infusion. No TEAE led to permanent treatment discontinuation/study withdrawal and all participants recovered.

Algorithmically defined IARs

Algorithmic definition of IARs included all events reported between the infusion start and 24 hours after the end of the infusion, regardless of investigator opinion assessment of IMP relatedness. All participants experienced an algorithm-defined IAR. The most frequently reported events were headache, urticaria, pyrexia, and upper respiratory tract infection.

Protocol-defined IARs

Protocol-defined IARs were any TEAE that occurred within 24 hours and considered related or possibly drug-related by the Investigator. There were also separate algorithm defined to identify hypersensitivity reactions and anaphylactic reactions.

Thirteen of 20 (65%) paediatric participants experienced a total of 130 IAR events. The proportion of participants 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 . While enrolled in LTS13632, protocol defined IARs were reported by 40% of paediatric participants.

Adverse Events of Special Interest

AESIs included IARs, pregnancy, symptomatic overdose (serious or nonserious) of study drug, certain laboratory values and other significant events, as defined in the protocol. IARs have been discussed in above.

There was no paediatric pregnancy or pregnancy in a paediatric partner of a participant in the study. There were no symptomatic overdoses in paediatric participants the study.

The definition of Dose Limiting Toxicity (DLT) evolved over time for the product based on available data; the definitions were based on changes in specific liver function tests relative to baseline and/or the upper limit of normal, and included symptoms of DLT3. Specifically, DLT1 (any increase in AST, ALT, total bilirubin, or AP >3 x baseline [prior to rhASM therapy]), DLT2 (any increase in total bilirubin or AP >1.5 x baseline, in the presence of AST or ALT above the normal range) and DLT3 (any increase in ALT or AST >3 x the ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]) are defined in protocol and eCRF. Among paediatric participants, there were 4 participants who experienced 5 DLT1 events; 5 participants who experienced 6 DLT2 events; and 1 participant who experienced 2 DLT3 events; except for 2 DLT1 occurrence in LTS13632, all other DLTs occurred during dose escalation in the original study. None of the events led to permanent treatment discontinuation/study withdrawal.

Assessor's comment

All paediatric patients reported TEAEs. Pyrexia, vomiting, headache and diarrhoea are known ADRs which are listed in the SmPC. Nasopharyngitis (70%) and cough (80%) are not listed in the SmPC,

but were also observed in the original study (EPAR) and most likely reflect common cold symptoms frequently observed in paediatric patients.

It is unclear whether the reported TEAEs are only from the period of the long-term extension study or whether these numbers also include the observations from the original study. For example, the reported percentages of events of cough (80%) and nasopharyngitis (70%) are the same as the percentages reported in the EPAR. The MAH should clarify at the upcoming variation procedure; it is preferred to clearly state which reported events were from the original study (and thus already covered in the SmPC) and which events occurred in the long-term extension phase of the study.

Four paediatric participants experienced 7 SAEs that were labelled as treatment related, which were hypersensitivity (2 events), increased alanine aminotransferase (2 events), urticaria (1 event), rash (1 event), and anaphylactic reaction (1 event). The hypersensitivity events occurred during the long-term extension phase, the other SAEs in the previous study. Hypersensitivity reactions are known to occur more often in paediatric patients than in adult patients. All participants recovered from their SAEs. All SAEs are labelled in the SmPC and it is clearly stated that patients treated with olipudase alpha should be monitored for hypersensitivity reactions. No additions are considered necessary.

SAEs that the investigator assessed as not related to treatment were peripheral oedema after the infusion, poor venous access, craniofacial injury caused by a car accident, skull fractured base, moderate nuchal rigidity and pyrexia, lethargy, pyrexia (suspected otitis media) and one confirmed otitis media. One participant had food allergy which was an SAE on day 752, with the last administration of treatment at day 731. The patient was discharged on the same day. All events were assessed as not related to the treatment which is agreed with.

The reported 130 IARs events included 102 events from the original study and 28 events in LTS. Headache, urticaria and pyrexia are known IARs and already labelled in the SmPC.

There were no deaths during the study and no adverse events that led to permanent discontinuation or study withdrawal.

There were two events during the long-term extension phase that were labelled as Dose Limiting Toxicity events. Both were labelled as DLT1 events, which is any increase in AST, ALT, total bilirubin, or AP >3 x baseline [prior to rhASM therapy]. One participant had an alkaline phosphatase increase at week 76 which was recovered by week 82. No corrective treatment was necessary and no action was taken with the IMP. This event was assessed as not related to the IMP nor to the procedure. The other DLT1 event was an increase in ALT level at week 146. The IMP was temporarily interrupted due to the event of transaminases increased. Transaminases gradually improved and levels were normalized after 27 days, and the IMP was restarted. It was assessed as unrelated to the treatment.

Physical Examinations

Nineteen paediatric participants (95.0%) had an abnormal baseline abdominal examination. Three out of the 5 available participants had a normal examination at Month 84. One participant with an abnormal baseline abdomen exam was normal at Month 96; 1 participant had abnormal general baseline exam which was normal at Month 96.

Extended Neurologic Examinations

At baseline, 20/20 (100%) had normal coordination exam, 19/20 (95%) had normal cranial nerve exam, 20/20 (100%) had normal extrapyramidal feature exam, 9/10 (90%) had normal fundoscopy, 17/19 (89.5%) had normal gait and coordination exam, 18/20 (90.0%) had normal motor tone exam, 18/19 (94.7%) had normal peripheral nervous system exam, 17/20 (85.0%) had normal reflex exam,

20/20 (100%) had normal sensory exam, 16/20 (80.0%) had normal strength exam, 20/20 (100%) had normal mental status exam. There were no clinically significant patterns of change in neurologic examinations throughout the study.

Weight and Height

Due to growth and development in the paediatric participant group, clinically meaningful increases in weight were observed. The mean (SD) values for weight in kg in paediatric participants at baseline were 23.38 (10.80) (n = 20), by Week 372, the change from baseline in the mean (SD) values for weight were +32.16 (9.53) [n = 5]).

The Mean (SD) values for height in cm paediatric participants at baseline were 117.09 [22.12] [n =19], by Week 364, the change from baseline in the mean (SD) values for height were +32.32 (9.75) [n=5].

Vital Sign Measurements

There were no clinically meaningful changes in mean heart rate, systolic blood pressure, diastolic blood pressure or temperature over time in paediatric participants.

Clinical Laboratory Tests

The clinical laboratory data consists of blood analyses (clinical chemistry, LFTs, haematology, coagulation) and urine test for women of childbearing potential. There were no clinically meaningful changes in chemistry, haematology, coagulation or urinalysis laboratory tests to impact the safety profile. The initial elevations of transaminases in the context of IARs and DLTs in the predecessor study decreased, reflecting improvement of the disease.

Electrocardiograms (ECGs)

Review of the ECGs at the ECG central reader showed potentially clinically significant findings in 3 paediatric participants during LTS13632: one adolescent participant had 1 episode of 1st degree AV block at Week 222, one adolescent had 1 episode of marked bradycardia at Week 250, and 1 child participant had 1 episode of 1st degree AV block at Week 92. All of the ECGs findings resolved by the subsequent ECG and the participants did not have any clinically significant abnormal ECG findings throughout the remainder of the study. Additionally, there were no AEs reported in association with any of the ECG events.

Doppler Echocardiography

Data for assessment of the presence or absence of baseline aortic regurgitation are available in 20 participants. At end of treatment period, among the 5 (25.0%) participants with baseline trace aortic regurgitation, there was 2 of 5 (40%) who had trace regurgitation, 1 of 5 (20.0%) had mild regurgitation, and the other 2 of 5 (40.0%) were reported as normal or not having regurgitation.

Also, none of the 15 participants reported as normal at baseline had other than normal/absent aortic regurgitation at the end of treatment period.

Data for assessment of the presence or absence of baseline pulmonary valve regurgitation are available in 19 participants. At the end of treatment period, among the 12 (63.2%) of 19 participants with no baseline pulmonary valve regurgitation, 11 had pulmonary valve regurgitation present and 1 participant had no pulmonary valve regurgitation. Among the 6 (31.2%) of 19 participants with baseline trace pulmonary valve regurgitation, 3 had pulmonary valve regurgitation reported as present, 2 reported as trace regurgitation, and 1 reported as absent. One participant at baseline had pulmonary valve regurgitation reported as 1+ and at end of study regurgitation was reported as present.

Data assessment of the present or absence of baseline tricuspid regurgitation are available in 20 participants. Eleven participants had normal tricuspid valve at baseline and at end of treatment had trace tricuspid valve regurgitation. Nine participants had trace tricuspid regurgitation at baseline, and at end of treatment 8 had trace regurgitation and in 1 participant tricuspid regurgitation was absent.

Assessor's comment

An enlarged abdomen, which is commonly observed in ASMD patient as a result of enlarged liver and/or spleen, improved in 4/5 patient with measurement up to month 84-96. Neurological examinations remained unchanged.

An increase in height and body weight was observed, as could be expected in a growing paediatric patient population.

There were no meaningful trends or changes in vital signs. The initial elevated levels of transaminases declined in the 12 months and then plateaued in paediatric patients.

There were three ECG findings during the long-term extension phase; first degree AV block in two participants (week 222 in an adolescent and week 92 in a child) and marked bradycardia (week 250, adolescent). All resolved at the next ECG and no AEs were reported in associations with these ECG findings. It must be noted that bradycardia was observed in preclinical studies; administration of a high dose (20 mg/kg) olipudase alfa to ASMKO mice caused significant bradycardia ($p<0.01$). However, it is reassuring that both the bradycardia and AV-block events were isolated events, that occurred only once in these patients and were resolved at the subsequent ECG measurement. In addition, ECG abnormalities are common in ASMD patients (McGovern et al, Pediatrics 2008).

Aortic regurgitation appears to improve in participants with baseline aortic regurgitation. Most of participants had no pulmonary valve regurgitation present at baseline (12/19), while at the end of the treatment most participants showed pulmonary valve regurgitation (11/19). Of those who had pulmonary valve regurgitation at baseline (6/19), half remained stable. Valve abnormalities are a common symptom of ASMD patients.

As this is an uncontrolled study, it is not possible to assess whether these ECG events and regurgitations are related to the treatment or symptoms of the disease.

Safety Biomarkers

No clinically meaningful changes in hsCRP, iron, ferritin, troponins, IL-6 or IL-8 or calcitonin from screening were observed in any of the safety biomarkers over the course of the study. Plasma ceramide showed sustained reduction over the course of the study.

Liver Ultrasound With Doppler

Data are available for 20 paediatric participants. Based on hepatoportal Portal Vein Direction of Flow, there was no evidence of portal hypertension in any participant. Five participants showed liver surface abnormalities at baseline that resolved at 12 months. Liver dysmorphic findings were present in 6 participants at baseline, resolved in 4 at 12 months, and in the other 2 at 18 months. One participant had no liver dysmorphic findings at baseline, but developed them at 12 months; these findings returned to normal at 24 months and did not recur. Mild ascites was detected in 3 participants at baseline, and was noted to resolve at 2 weeks in one participant and at 12 months in the other 2; there was no recurrence in any participant. Hepatic steatosis was noted in 1 participant at baseline and there were no comments about this in subsequent liver ultrasound reports.

Immune Response Assessments

For the purposes of this study, the impact of immunogenicity was only assessed for efficacy. Fifteen paediatric participants (75%) developed treatment-emergent anti-drug antibody (ADA). No participant had a high ADA response (considered as a titre >12800 based on general experience with replacement enzymes in these assays). Among the ADA positive participants, 9 paediatric participants tested transiently or intermittently positive for inhibition of enzyme catalytic activity. No participants tested positive for neutralizing antibodies (Nabs) that interfered with enzyme uptake into cells. The clinical relevance of Nab positivity in these in vitro assays is not known.

The effect of olipudase alfa on spleen volume multiple of normal (MN)] and on platelet count was analysed according to response to ADA (ie, treatment emergent ADA positive and negative). The mean percent change in spleen volume and the mean percent change in platelet count were similar between ADA positive and ADA negative groups. Therefore, overall, there was no impact of ADA observed on efficacy.

Home Infusion

After approval of Protocol Amendment 1 (23 March 2016) participants in LTS13632 could be considered by the Investigator to have olipudase alfa infused at home by a qualified health care professional.

There were a total of 19 participants who received an at-home infusion. In the at-home infusion locale, 14 participants (73.7%) experienced 456 TEAEs, 446 TEAEs were reported as mild and 10 as moderate. There was no severe TEAE reported during at-home infusion. Thirteen participants experienced a total of 160 protocol defined IARs. The majority of SAEs occurred while participants were on the at site infusion phase (21/25 [84%]). Of the 4 participants with TEAES leading to temporary treatment interruption, only 1 participant had a TEAE related to treatment (non-serious, mild event of urticaria).

Assessor's comment

There were no alarming of aberrant observations regarding biomarkers and liver ultrasound measurements. Liver abnormalities that were observed in a few patients also resolved within the course of the study.

There were 15 paediatric patients who developed ADAs, of whom no patients tested positive for neutralizing antibodies. The MAH is requested to clarify in the upcoming variation procedure, whether no patients tested positive for Nabs during the long-term extension phase of the study or during both the original study and the long-term extension. As the SmPC stated that of the 5/13 paediatric patients who tested positive for ADA developed Nabs.

The observed decrease in spleen volume and increase in platelet count was rather comparable between participants who tested positive and negative for ADAs at month 48 and 84. Suggesting that efficacy was not impacted by development of ADAs.

Home infusions were received by 19/20 participants. No severe TEAEs were reported during at-home infusions. The possibility for home infusion in patients tolerating the treatment well has already been included in the SmPC. This confirms that home infusions are safe for eligible patients.

2.3.3. Discussion on clinical aspects

The LTS13632 study was designed to assess the long-term safety and efficacy of olipudase alfa in participants with acid sphingomyelinase deficiency (ASMD) who already participated in studies with olipudase alfa. The duration of the original paediatric study (DFI13803) was 64 weeks, after which participant transitioned into the long-term extension phase of up to 84 months. In principle, data of all 20 paediatric participants of up to at least 3 years of olipudase treatment is available in the current application.

As patients number are limited and this concerns an uncontrolled study, it is impossible to draw robust conclusions regarding safety and efficacy. However, no alarming results were obtained and the long-term data that was gathered show a maintenance of efficacy; reduction in hepatosplenomegaly, increased platelet count, improvement in pulmonary function and improved growth parameters. The safety profile observed in this long-term stud is in line with the known safety profile of olipudase alpha treatment as no new safety concerns were reported. In addition, data confirms that home infusions are safe for eligible patients

The MAH considers no changes to the current SmPC of olipudase alpha are necessary. This is not fully agreed as it is considered of value to update the long term follow up data already presented in the SmPC. However, the MAH plans to submit the final CSR of the study in a type II variation in August 2024. Thus, an update of the SmPC can be submitted during that procedure. Furthermore, below is a list of concerns which the MAH is requested to address in that procedure.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No further action is required at this moment. However, the MAH should address the formulated concerns below in the upcoming variation application consisting of the final CSR of study LTS13632 which is expected to be submitted in August 2024.

☐ Not fulfilled:

4. Request for supplementary information

Based on the data submitted, the MAH is **not** required to address these questions as part of the current procedure. However, the MAH should address the formulated concerns in the variation application consisting (final CSR of LTS13632) which is expected to be submitted in August 2024.

- In general, data presentation could benefit from clarification as currently it is 1) not clear for all parameters what is data is from the original study and from the long-term extension phase and 2) of how many patients' data is available at what timepoint. Some suggestions and examples to improve clarity:
    - As data up to 3 years is in principle available for all paediatric patients (as per PIP), it would be informative to also display this timepoint in future procedures (besides the last time point at which 5 participants are enrolled). Justification for missing data at the 3-year timepoint would be appreciated.
    - It would be informative to have the patient numbers contributing data per timepoint more clearly displayed in the X-axis of the graphs.

- An example of unclarity regarding participant numbers; from the Participant disposition (16.2.1) is stated that data is available of n=12 participants at week 208 (= month 48), while spleen volume data is available for n=13 at month 48.
- The MAH is requested to clearly distinguish between safety data gathered in the original study and during the long-term extension phase to enable assessment of novel safety concerns. Currently, it is unclear for example whether the reported TEAEs are from the period of the long-term extension study or whether these numbers also include the observations from the original study. The reported percentages of events of cough (80%) and nasopharyngitis (70%) are the same as the percentages reported in the EPAR.
- There were 15 paediatric patients who developed ADAs, of whom none tested positive for neutralizing antibodies. The MAH is requested in the upcoming procedure whether no patients tested positive for Nabs during the long-term extension phase of the study or during both the original study and the long-term extension. As the SmPC stated that of the 5/13 paediatric patients who tested positive for ADA developed Nabs.

- Haemoglobin levels were analysed and presented in g/dL however, mmol/L is the more common unit used in the EU. The MAH is requested to present all information and data on haemoglobin levels in mmol/dL instead of g/dL in upcoming procedures. At the next regulatory opportunity, the MAH is also requested to implement these editorial changes in the SmPC.
- An additional editorial change to the SmPC proposed for the upcoming procedure is the use of the INN instead of the tradename Xenpozyme when discussing the efficacy and safety of olipudase alfa.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Olipudase alfa Active substance: GZ402665

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1, single-center, single-dose, dose escalation study of recombinant human acid sphingomyelinase in adults with acid sphingomyelinase deficiency	SPHINGO00605	21-July 2010	26-October 2021 Date of initial application EMA: 14-02-2014
An open-label, multicenter, ascending dose study of the tolerability and safety of recombinant human acid sphingomyelinase in patients with acid sphingomyelinase deficiency	DFI13412	13-November 2014	26-October 2021
A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency.	DFI13803	07-August 2020	26-October 2021
A Phase 2/3, multicenter, randomized, doubleblinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency.	DFI12712	19-october 2023	August 2024
A Phase 2, long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency	LTS13632	06-September 2023	05-March 2024