Clinical trial results:
A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency

Summary

EudraCT number	2013-000051-40
Trial protocol	GB IT DE BE
Global end of trial date	06 September 2023

Results information

Result version number	v1 (current)
This version publication date	20 March 2024
First version publication date	20 March 2024

Trial information

Trial identification

Sponsor protocol code	LTS13632

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02004704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Genzyme
Sponsor organisation address	450, Water Street, Cambridge, Massachusetts, United States, 02141
Public contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001600-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To obtain safety data in paediatric and adult subjects with acid sphingomyelinase deficiency (ASMD) exposed to long-term treatment with olipudase alfa.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	25
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	15
Adolescents (12-17 years)	4
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 investigational sites in 6 countries between 04 Dec 2013 and 06 Sep 2023.

Pre-assignment

Screening details:

A total of 25 subjects [5 adult subjects from study DFI13412 (EudraCT number: 2012-003542-32) and 20 paediatric subjects from study DFI13803 (EudraCT number: 2014-003198-40)] directly rolled over and continued treatment in this study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Olipudase Alfa: Subjects From DFI13412 (Adults)

Arm description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13412 (up to 3.0 milligram/kilogram [mg/kg]) via intravenous (IV) infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible.

Arm type	Experimental
Investigational medicinal product name	olipudase alfa
Investigational medicinal product code	GZ402665
Other name	Xenpozyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Maximum of 3 mg/kg of olipudase alfa was administered as IV infusion every 2 weeks for 9 years or until olipudase alfa was commercially accessible.

Arm title	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)

Arm description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13803 (up to 3.0 mg/kg) via IV infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible. During the study, paediatric subjects who reached adult age (18 years old) received the adult infusion volume.

Arm type	Experimental
Investigational medicinal product name	olipudase alfa
Investigational medicinal product code	GZ402665
Other name	Xenpozyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Maximum of 3 mg/kg of olipudase alfa was administered as IV infusion every 2 weeks for 9 years or until olipudase alfa was commercially accessible.

Number of subjects in period 1	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)
Started	5	20
Completed	5	20

Baseline characteristics

Reporting groups	
Reporting group title	Olipudase Alfa: Subjects From DFI13412 (Adults)
Reporting group description:	
Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13412 (up to 3.0 milligram/kilogram [mg/kg]) via intravenous (IV) infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible.	
Reporting group title	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)
Reporting group description:	
Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13803 (up to 3.0 mg/kg) via IV infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible. During the study, paediatric subjects who reached adult age (18 years old) received the adult infusion volume.	

Reporting group values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)	Total
Number of subjects	5	20	25
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.0	7.6	
standard deviation	± 9.25	± 4.43	-
Gender categorical Units: Subjects			
Female	2	10	12
Male	3	10	13
Race Units: Subjects			
White	5	17	22
Other	0	1	1
Southeast Asian	0	2	2

End points

End points reporting groups

Reporting group title	Olipudase Alfa: Subjects From DFI13412 (Adults)

Reporting group description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13412 (up to 3.0 milligram/kilogram [mg/kg]) via intravenous (IV) infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible.

Reporting group title	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)

Reporting group description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13803 (up to 3.0 mg/kg) via IV infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible. During the study, paediatric subjects who reached adult age (18 years old) received the adult infusion volume.

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs) and Adverse Events of Special Interest (AESIs) Except Infusion-Associated Reactions (IARs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs) and Adverse Events of Special Interest (AESIs) Except Infusion-Associated Reactions (IARs)[1]

End point description:

An AE: Any untoward medical occurrence in subject or clinical investigation subject administered with pharmaceutical product, which did not necessarily have to have causal relationship with study treatment. SAEs: Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation/prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was congenital anomaly/birth defect, was medically important event. TEAEs: AEs that started during on-treatment period-either in this study or in original study. An AESI: AE (serious or nonserious) of scientific and medical concern specific to sponsor's product or program, for which ongoing monitoring and rapid communication by investigator to sponsor was appropriate. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

From the signature of informed consent up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
Any TEAE	5	20		
Any TESAE	1	10		
AESI: Any Pregnancies	0	0		

AESI: Symptomatic Overdose	0	0		
AESI: Dose-limiting toxicities	0	10		
Any TEAEs leading to treatment discontinuation	0	0		
Any TEAEs leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With IARs

End point title	Number of Subjects With IARs[2]

End point description:

Protocol-defined IARs were AEs that occurred during the infusion or within up to 24 hours after the start of infusion and were considered as related or possibly related to the study treatment by the investigator or the sponsor. Events occurring greater than or equal to (>=) 24 hours after the start of an infusion might have been judged an IAR at the discretion of the investigator or sponsor. Algorithm-defined IARs were all AEs that started between the start of infusion and the end of infusion plus 24 hours, irrespective of the perceived relation with study treatment. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Up to 24 hours after start of any infusion

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
Protocol-defined IARs	4	13		
Algorithm-defined IARs	5	20		

Statistical analyses

No statistical analyses for this end point

Primary: For Adults: Number of Subjects With Abnormality in Complete Physical Examinations Including Abbreviated Physical Exam

End point title	For Adults: Number of Subjects With Abnormality in Complete Physical Examinations Including Abbreviated Physical Exam[3][4]

End point description:

A complete physical examination included assessment of the subject's general appearance, general neurological status, skin, head, eyes, ears, nose, throat, lymph nodes, heart, lungs, abdomen, and

extremities/joints. Shift from Baseline was monitored. An abbreviated physical exam (general appearance only) was only performed pre- and post-infusion for those who did not do complete exam. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 4 adult subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study), Month 78

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
General Appearance	0			
General Neurological Status	0			
Skin	1			
Head, Eyes, Ears, Nose and Throat	1			
Lymph Nodes	0			
Heart	0			
Lungs	0			
Abdomen	1			
Extremities/Joints	0			
Abbreviated Physical Exam	0			

Statistical analyses

No statistical analyses for this end point

Primary: For Paediatrics: Number of Subjects With Abnormality in Complete Physical Examinations Including Abbreviated Physical Exam

End point title	For Paediatrics: Number of Subjects With Abnormality in Complete Physical Examinations Including Abbreviated Physical Exam[5][6]

End point description:

A complete physical examination included assessment of the subject's general appearance, skin, head, eyes, ears, nose, throat, lymph nodes, heart, lungs, abdomen, and extremities/joints. Shift from Baseline was monitored. An abbreviated physical exam (general appearance only) was only performed pre- and post-infusion for those who did not do complete exam. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study), Month 84

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
General Appearance	0			
Skin	1			
Head, Eyes, Ears, Nose and Throat	0			
Lymph Nodes	0			
Heart	0			
Lungs	0			
Abdomen	2			
Extremities/Joints	0			
Abbreviated Physical Exam	0			

Statistical analyses

No statistical analyses for this end point

Primary: For Adults: Number of Subjects With Abnormality in Extended Neurological Examinations

End point title	For Adults: Number of Subjects With Abnormality in Extended Neurological Examinations[7][8]

End point description:

Extended neurological examination for adults included examination of mental status. Shift from Baseline was monitored. The Safety analysis set consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 4 adult subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study), Month 78

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: For Paediatrics: Number of Subjects With Abnormality in Extended Neurological Examinations

End point title	For Paediatrics: Number of Subjects With Abnormality in Extended Neurological Examinations[9][10]

End point description:

The neurological examination in paediatric subjects included examination of mental status, cranial nerve examination, motor examination: tone, reflexes examination, sensory examination, coordination, gait and coordination, and strength examination. Shift from Baseline was monitored. The Safety analysis set consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study), Month 84

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
Mental Status	0			
Cranial Nerve Examination	0			
Motor Examination: Tone	0			
Reflexes Examination	0			
Sensory Examination	0			
Coordination	0			
Gait and Coordination	0			
Strength Examination	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs[11]

End point description:

PCSA: Heart Rate (HR) High: >=120 beats per minute (bpm) (adults [ad], adolescents [ado], children [chi]), >=140 bpm (early chi [ec]), >=175 bpm (infants[inf]) & increase from baseline (IFB)>=20 bpm for all age ranges (AAR), HR Low: <=50 bpm (ad, ado, chi), <=75 bpm (ec), <=80 bpm (inf) & decrease from baseline (DFB) >=20 bpm for AAR. Systolic blood pressure (SBP) High: >= 160 millimetres of mercury (mmHg) (ad); >=119 mmHg (ado), >=108 mmHg (chi), >=101 mmHg (ec), >=98 mmHg (inf) & IFB >=20 mmHg for AAR. SBP Low: <=95 mmHg (ad), <=90 mmHg (ado), <= 80mm Hg (chi), <=70 mmHg (ec), <=70 mmHg (inf) & DFB >=20 mmHg for AAR. Diastolic BP (DBP) High:>110 mmHg (ad), >=78 mmHg (ado), >=72 mmHg (chi), >=59 mmHg (ec), >=54 mmHg (inf) & IFB >=10 mmHg for AAR. DBP Low:<=45 mmHg (ad), <=54 mmHg (ado), <=48 mmHg (chi),<=34 mmHg (ec and inf) & DFB>=10 mmHg for AAR. Results are based on the Safety analysis set.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
HR: High	1	9		
HR: Low	2	10		
SBP: High	2	16		
SBP: Low	5	11		
DBP: High	0	19		
DBP: Low	5	19		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With PCSA in Clinical Chemistry Parameters

End point title	Number of Subjects With PCSA in Clinical Chemistry Parameters[12]

End point description:

PCSA: Creatinine High, category 1: >=150 micromole/L (umol) (ad), >=132 umol/L or 1.5 mg/decilitre (dL) (ado), >=90 umol/litre (L) or 1.1 mg/dL (chi), >53 umol/L or 0.6 mg/dL (ec,inf); category 2: >=30% and >=100% IFB (ad). Blood Urea Nitrogen: >=17 millimole (mmol)/L (ad), >=6.4 mmol/L or 18 mg/dL (paediatrics [paed]). Glucose Low<=3.9 mmol/L and <lower limit of normal (ad), <2.7 mmol/L (paed), High: >=11.1 mmol/L (unfasted), >7 mmol/L (fasted) (ad), >=7 mmol/L (fasted after

>12 hours of fast); >=10.0 mmol/L (unfasted) (paed). Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
Creatinine: High, category 1	0	0		
Creatinine: High, category 2	1	4		
Blood Urea Nitrogen: High	0	15		
Glucose: Low	5	2		
Glucose: High	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With PCSA in Liver Function Tests

End point title	Number of Subjects With PCSA in Liver Function Tests[13]

End point description:

PCSA: Alanine aminotransferase (ALT) High >3 x upper limit of normal (ULN), >5 x ULN, >10 x ULN, >20 x ULN. Aspartate aminotransferase (AST): High >3 x ULN, >5 x ULN, >10 x ULN, >20 x ULN. Alkaline phosphatase (ALP) > 1.5 x ULN. Total Bilirubin High >1.5 x ULN, >2 x ULN (ad), >2 x ULN, >= 1.3 x ULN (paed). ALT and total bilirubin: ALT > 3 x ULN and total bilirubin > 2 x ULN. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
ALT: High	0	5		
AST: High	0	6		
ALP: High	0	5		
Total Bilirubin: High	3	1		
ALT and Total Bilirubin	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With PCSA in Haematology Parameters

End point title	Number of Subjects With PCSA in Haematology Parameters[14]

End point description:

PCSA: White blood cells (WBC): Low: <3.0 Giga(G)/L (Non-Black [NB])/<2.0 G/L (Black [B])(ad), <4.5 G/L (ado), <5.0 G/L(chi), <3.0 G/L (ec), <4.0 G/L (inf), High: >=16.0 G/L(ad), >13.5 G/L (ado), >17.0 G/L(chi), >16 G/L (ec), >20 G/L (inf). Haemoglobin-ad: Low-1: <=115 g/dL (Male[M])/<=95 g/dL (Female[F]), 20% DFB for both, High:>=185 g/L (M)/>=165 g/L (F), Low-2: DFB>=20 g/L (ad), <10 g/dL (ado, chi, ec); <9.0 g/dL (inf); 20% DFB for all. Platelets: Low: <100 G/L (AAR) and 20% DFB and High: >=700 G/L (ad and paed). Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
WBC: Low	2	16		
WBC: High	0	0		
Haemoglobin: Low-1	0	0		
Haemoglobin: High	1	0		
Haemoglobin: Low-2	2	0		
Platelets: Low	2	7		
Platelets: High	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With PCSA in Electrocardiogram (ECG)

End point title	Number of Subjects With PCSA in Electrocardiogram (ECG)[15]

End point description:

PCSA: HR: High:>=120 bpm (ad, ado, chi), >=140 bpm (ec), >=175 bpm (inf) & IFB>=20 bpm for AAR, HR: Low: <=50 bpm (ad, ado, chi), <=75 bpm (ec), <=80 bpm (inf) & DFB >=20 bpm for AAR. PR duration: High: >=200 milliseconds (ms) (ad) and IFB>=20 ms, >180 ms (ado), 170 ms (chi), 160 ms (ec), and 140 ms (inf). QT correction-Bazett (QTcB): Borderline absolute (category 1): 431-450 ms (ad and ado M, chi, ec and inf), 451-470 ms (ad and ado F), Prolonged-absolute (category 2): >450 ms (ad and ado M and chi, ec and inf), >470 ms (ad and ado F), Additional-absolute (category 3): >=500 ms (AAR), Borderline increase (category 4): 30-60 ms (AAR), Prolonged increase (category 5): > 60 ms (AAR). Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
HR: High	0	3		
HR: Low	1	2		
PR duration: High	0	6		
QTcB: Category 1	5	13		
QTcB: Category 2	5	8		
QTcB: Category 3	0	0		
QTcB: Category 4	5	7		
QTcB: Category 5	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: For Adults: Percent Change From Baseline in Pre-Infusion Plasma

Ceramide at Month 90

End point title	For Adults: Percent Change From Baseline in Pre-Infusion Plasma Ceramide at Month 90[16][17]

End point description:

Plasma samples were collected to evaluate ceramide levels for safety biomarker analysis. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 4 adult subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) and Month 90 (pre-infusion)

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects were included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percent change				
arithmetic mean (standard deviation)	-65.66 (± 12.58)			

Statistical analyses

No statistical analyses for this end point

Primary: For Paediatrics: Percent Change From Baseline in Pre-Infusion Plasma Ceramide at Month 66

End point title	For Paediatrics: Percent Change From Baseline in Pre-Infusion Plasma Ceramide at Month 66[18][19]

End point description:

Plasma samples were collected to evaluate ceramide levels for safety biomarker analysis. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric subjects for a meaningful analysis.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) and Month 66 (pre-infusion)

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline

period.

Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent change				
arithmetic mean (standard deviation)	-69.16 (± 10.04)			

Statistical analyses

No statistical analyses for this end point

Primary: Adult Study: Number of Subjects With Abnormal Liver Biopsy

End point title	Adult Study: Number of Subjects With Abnormal Liver

End point description:

Liver biopsy samples were evaluated for sphingomyelin accumulation and liver pathology in the subjects who previously participated in the DFI13412 study who were at least 18 years old when they entered in this study. Sphingomyelin accumulation was quantified in liver by computer morphometry of high-resolution light microscopy images. Fibrosis grading was assessed on the Laennec scoring system, which grades the extent of fibrosis on a scale from 0 to 4 (0=none; 1=minimal; 2=mild; 3=moderate; 4=cirrhosis). Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) and Month 36

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
Baseline: Stage 0	1			
Baseline: Stage 1	1			
Baseline: Stage 2	2			
Baseline: Stage 3	1			
Baseline: Stage 4	0			
Month 36: Stage 0	0			
Month 36: Stage 1	1			

Month 36: Stage 2	1			
Month 36: Stage 3	2			
Month 36: Stage 4	1			

Statistical analyses

No statistical analyses for this end point

Primary: Paediatric Study: Number of Subjects With Abnormalities in Liver Ultrasound Doppler

End point title	Paediatric Study: Number of Subjects With Abnormalities in Liver Ultrasound Doppler[22][23]

End point description:

Liver ultrasound doppler was performed for paediatric subjects transitioning from DFI13803 to document hepatic blood flow characteristics, principally portal vein pressure, and blood flow direction. The parameters evaluated were liver dysmorphic findings, liver surface abnormalities, mild ascites and hepatic steatosis. Liver ultrasound Doppler was performed using methods that were compatible with the standard institutional procedures of the investigational site. Results are based on the Safety analysis set consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study), Week 2 and Months 12, 18 and 24

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: subjects				
Liver dysmorphic findings: Baseline	6			
Liver dysmorphic findings: Month 12	3			
Liver dysmorphic findings: Month 18	1			
Liver dysmorphic findings: Month 24	0			
Liver surface abnormalities: Baseline	5			
Liver surface abnormalities: Month 12	0			
Mild ascites: Baseline	3			
Mild ascites: Week 2	2			
Mild ascites: Month 12	0			
Hepatic steatosis: Baseline	1			
Hepatic steatosis: Month 12	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Olipudase Alfa

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against Olipudase Alfa[24]

End point description:

Blood samples were collected for the presence of ADAs against olipudase alfa. Treatment-boosted ADA: Positive ADA status positive at baseline (pre-existing ADA) and ADA titer level anytime post-baseline significantly higher than that at baseline. Transient ADA:Treatment-induced ADA detected only at 1 sampling time point post-baseline and treatment-induced ADA detected at 2 or more sampling time points post-baseline, where first and last ADA-positive samples (irrespective of any negative samples in between) separated by period of less than 16 weeks, and subject's last sampling time point was ADA-negative. Persistent ADA response: Treatment-induced ADA detected at 2 or more sampling time points post-baseline, where first and the last ADA-positive on-treatment sample (irrespective of any negative samples in between) separated by at least 16 weeks. Treatment-induced: ADA detected in the last 2 sampling time points, irrespective of the time period in between. The Safety analysis set.

End point type	Primary

End point timeframe:

Baseline (Day 1 of original study) up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: subjects				
ADA positive at baseline	0	2		
Treatment-boosted ADA	0	1		
Treatment-induced ADA	3	14		
Transient ADA response	0	1		
Indeterminate ADA response	0	0		
Persistent ADA response	3	12		
ADA positive since first dose of olipudase alfa	3	15		
Treatment-emergent ADA	3	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen and Liver Volumes at Month 102 for Adults and Month 84 for Paediatrics

End point title	Percent Change From Baseline in Spleen and Liver Volumes at Month 102 for Adults and Month 84 for Paediatrics

End point description:

Spleen and liver volumes were assessed by abdominal magnetic resonance imaging (MRI) to quantify

the degree of splenomegaly and hepatomegaly at specified time points. Subjects were required to fast from solid foods (liquids, such as water, milk, and juice were allowed) for 6 hours prior to the MRI to reduce the effect of a meal. Spleen/Liver volume in multiples of normal (MN) = Spleen/Liver volume (cubic centimetre [cm^3]) / [2xweight (kg)] where weight was the available value closest to the MRI scan date. Negative value signifies reduction of volume. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric and 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study), Month 102 for adults and Month 84 for paediatrics

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: percent change				
arithmetic mean (standard deviation)				
Spleen volume	-63.60 (± 6.34)	-75.56 (± 7.15)		
Liver volume	-46.71 (± 14.40)	-59.55 (± 14.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Imaging by High Resolution Computed Tomography (HRCT) at Month 102 for Adults and Month 84 for Paediatrics

End point title	Change From Baseline in Pulmonary Imaging by High Resolution Computed Tomography (HRCT) at Month 102 for Adults and Month 84 for Paediatrics

End point description:

Pulmonary imaging of chest using HRCT was obtained to quantitate degree of possible interstitial lung disease. Lung fields were assessed by a central reader and scored subjectively for degree of diffuse lung disease (infiltrative lung disease) in scale of 0-3 ranging from 0 = No disease, 1 = Mild (affecting 1% to 25% of the lung volume), 2 = Moderate (affecting 26% to 50% of the lung volume), 3 = Severe (affecting 51% to 100% of the lung volume) where higher scores indicated more severity. The score of each subject was averaged over all 4 levels and both sides of lung. Mean score across 4 levels and both lungs = (Mean score across X levels for left lung + Mean score across X levels for right lung)/2. Baseline was defined as the last available non-missing value prior to the first infusion in original study. The Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric and 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study), Month 102 for adults and Month 84 for paediatrics

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: score on a scale				
arithmetic mean (standard deviation)				
Ground Glass Appearance	-1.21 (± 0.94)	-0.42 (± 0.41)		
Interstitial Lung Disease	-1.66 (± 1.20)	-1.35 (± 1.27)		
Pleural Thickening	0.0 (± 0.0)	0.0 (± 0.0)		
Reticulo-nodular Density	-2.19 (± 1.07)	-1.20 (± 1.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Percent Predicted Diffusing Capacity of Lungs For Carbon Monoxide (DLco) (Heamoglobin-Adjusted) at Month 78 for Adults and Month 84 for Paediatrics

End point title	Percent Change From Baseline in Percent Predicted Diffusing Capacity of Lungs For Carbon Monoxide (DLco) (Heamoglobin-Adjusted) at Month 78 for Adults and Month 84 for Paediatrics

End point description:

DLco was used to measure gas exchange across the alveolocapillary membrane. Percent predicted haemoglobin-adjusted DLco was calculated as: 100 x Adjusted DLco/Predicted DLco in unit of mL CO/minute (min)/mmHg where, adjusted DLco = Observed DLco (in mL CO/min/mmHg) divided by Haemoglobin-adjusted factor. Baseline was defined as the last available non- missing value prior to the first infusion in original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric and 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study), Month 78 for adults and Month 84 for paediatrics

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: percent change				
arithmetic mean (standard deviation)	55.29 (± 48.08)	46.20 (± 48.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Platelet Count at Month 90 for Adults and Month 78 for Paediatrics

End point title	Percent Change From Baseline in Platelet Count at Month 90 for Adults and Month 78 for Paediatrics

End point description:

Blood samples were collected at specified timepoints for the estimation of platelet count as ASMD is known to result in haematologic disorders. Baseline was defined as the average of all available values before the start of first infusion from original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric and 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study), Month 90 for adults (pre-infusion) and Month 78 for paediatrics (pre-infusion)

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent change				
arithmetic mean (standard deviation)	21.83 (± 17.89)	63.97 (± 32.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Low-density Lipoprotein at Month 90 for Adults and Month 66 for Paediatrics

End point title	Percent Change From Baseline in Low-density Lipoprotein at Month 90 for Adults and Month 66 for Paediatrics

End point description:

Blood samples were collected at specified timepoints for fasting lipids as ASMD leads to progressive accumulation of lipids. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric and 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study), Month 90 for adults and Month 66 for paediatrics

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent change				
arithmetic mean (standard deviation)	-24.51 (± 11.05)	-37.30 (± 15.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Adult Study DFI13412: Change From Baseline in Brief Fatigue Inventory (BFI) Questionnaire at Month 78

End point title	Subjects from Adult Study DFI13412: Change From Baseline in Brief Fatigue Inventory (BFI) Questionnaire at Month 78[25]

End point description:

The BFI is a 9-item validated, self-administered questionnaire that was originally developed to assess fatigue severity. 9-items measured on a numerical rating scale (NRS) of 0 (no fatigue) to 10 (worst imaginable fatigue); total score being sum of subject's individual questions scores at a timepoint and ranged from 0 to 90. Subjects were asked to rate severity of their fatigue at its worst, usual,and now during normal waking hours was assessed in 3 items. Amount that fatigue interfered with different aspects of subject's life during preceding 24 hours (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life) was assessed in 6 items. Higher scores indicated more severe fatigue. Baseline was defined as last available non-missing value prior to first infusion in original study. Results are based on the Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 78

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
BFI-Fatigue Severity Scale Score	-0.9 (± 1.92)			
BFI-Fatigue Interference Scale Score	0.6 (± 2.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Adult Study DFI13412: Change From Baseline in Brief Pain Inventory-Short Form (BPI-SF) Questionnaire at Month 78

End point title	Subjects from Adult Study DFI13412: Change From Baseline in Brief Pain Inventory-Short Form (BPI-SF) Questionnaire at Month 78[26]

End point description:

The BPI-SF is 15-item, validated, self-administered questionnaire designed to measure subject's perceived level of pain. It measured intensity of pain (sensory dimension), interference of pain in subject's life (reactive dimension), and asked about pain relief, pain quality, and perception of cause of pain. Scoring was based on 4 out of 8 questions in pain severity domain, and 7 questions in pain interference domain, which used numerical rating scale. Pain severity response ranged from 0="No pain" to 10="Pain as bad as you can imagine". Pain interference response ranged from 0="Does not interfere" to 10="Completely interferes". Scores were averaged and mean is presented. Higher scores indicated greater intensity of pain. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 4 adult subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 78

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
BPI-SF: Pain Severity Scale Score	-1.5 (± 1.74)			
BPI-SF: Pain Interference Scale Score	0.7 (± 3.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Adult Study DFI13412: Change From Baseline in Chronic Respiratory Disease Questionnaire Self-Administered Standardised (CRQ-SAS) at Month 78

End point title	Subjects from Adult Study DFI13412: Change From Baseline in Chronic Respiratory Disease Questionnaire Self-Administered Standardised (CRQ-SAS) at Month 78[27]

End point description:

CRQ-SAS is validated, self-administered questionnaire designed to evaluate health related quality of life (HRQoL) in adults with chronic airflow limitation, chronic respiratory disease and cystic fibrosis. It had 20 items,evaluated 4 dimensions of respiratory impairment(dyspnea,emotional function,fatigue and subject's feeling of control over disease [mastery]).Each domain was measured on 7-point-scale, with 8 reserved for "not done" (1: worst and 7: best).Each domain score was calculated separately.Scores for each question of each domain were added together&divided by number of questions answered in each domain.Only items answered were scored.Mean of average score of completed items is reported.Higher scores indicated better HRQoL in each domain.Baseline was defined as last available non-missing value prior to first infusion in original study.Results are based on Safety analysis set. Timepoint chosen for analysis was latest assessment with at least 4 adults for meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 78

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only adult subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13412 (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
Dyspnea Scale Score	0.3 (± 0.59)			
Emotional Function Scale Score	0.2 (± 1.49)			
Fatigue Scale Score	0.3 (± 0.82)			
Mastery Scale Score	-0.5 (± 0.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Paediatric Study DFI13803: Change From Baseline in Paediatric Quality of Life (PedsQL) Generic Core Total Scale Score at Month 72

End point title	Subjects from Paediatric Study DFI13803: Change From Baseline in Paediatric Quality of Life (PedsQL) Generic Core Total Scale Score at Month 72[28]

End point description:

PedsQL included a child self-report for subjects 5 to 18 years and parents' report of subjects from 2 to 18 years. Child-reported: 23-item PedsQL Generic Core Scales report included 4 scales, physical functioning, emotional functioning, social functioning, and school functioning. Parent-reported: 21-item PedsQL Generic Core Scales report and included similar scales as above. Each item used a 5-point rating scale (from 0=never to 4=almost always). Items are reverse scored and linearly transformed to a 0 (almost always) -100 (never) scale. All summary/total scores were mean of specific items where higher score indicated better HRQoL. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 5 peadiatric subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 72

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: score on a scale				
arithmetic mean (standard deviation)				
Child-reported	10.4 (± 19.4)			
Parent-reported	14.6 (± 20.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Paediatric Study DFI13803: Change From Baseline in Difference Between Bone Age and Actual Age of Subjects at Month 72

End point title	Subjects from Paediatric Study DFI13803: Change From Baseline in Difference Between Bone Age and Actual Age of Subjects at Month 72[29]

End point description:

Hand X-ray was performed on subject's left hand, fingers and wrist to assess the bone age. At each visit, difference between the bone age and actual age at that visit was calculated. Difference in age in months was calculated as bone age in months minus real age at time of assessment in months. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set which consisted of all enrolled subjects who received at least 1 infusion (partial or total) of olipudase alfa in the current study. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 72

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: month				
arithmetic mean (standard deviation)	28.34 (± 24.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects from Paediatric Study DFI13803: Change From Baseline in

Height Z-score at Month 72

End point title	Subjects from Paediatric Study DFI13803: Change From Baseline in Height Z-score at Month 72[30]

End point description:

Linear growth in paediatric subjects was assessed by height Z-scores. Height Z-score, i.e., the height-for-age Z-score, is the number of standard deviations of the actual height of a child from the median height of the children of the corresponding age and sex as determined from the standard sample. A height Z-score of 0 is equal to the median and is considered normal. Negative numbers indicate values lower than the median and positive numbers indicate values higher than the median. For analysis, mean Z-score was calculated and an increase of mean height Z-score from baseline indicated an improvement on growth. Baseline was defined as the last available non-missing value prior to the first infusion in original study. Results are based on the Safety analysis set. The timepoint chosen for analysis was the latest assessment with at least 5 paediatric subjects for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of original study) and Month 72

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only paediatric subjects are included in this endpoint.

End point values	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Z-score				
arithmetic mean (standard deviation)	2.31 (± 1.34)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of informed consent up to 9 years or until olipudase alfa was commercially accessible, whichever came first

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)

Reporting group description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13803 (up to 3.0 mg/kg) via IV infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible. During the study, paediatric subjects who reached adult age (18 years old) received the adult infusion volume.

Reporting group title	Olipudase Alfa: Subjects From DFI13412 (Adults)

Reporting group description:

Subjects continued to receive olipudase alfa at the same dose as at the completion of original study-DFI13412 (up to 3.0 mg/kg) via IV infusion every 2 weeks for 9 years, or until olipudase alfa was commercially accessible, whichever came first, unless the subject decided to enter another olipudase alfa clinical trial within the 9-year period prior to when olipudase alfa was commercially accessible.

Serious adverse events	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)	Olipudase Alfa: Subjects From DFI13412 (Adults)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 20 (50.00%)	1 / 5 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 20 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Poor Venous Access			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food Allergy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 20 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Hypertrophy			

subjects affected / exposed	0 / 20 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniofacial Injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull Fractured Base			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Talipes			

subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Nuchal Rigidity			

subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Mycoplasmal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Olipudase Alfa: Subjects From DFI13803 (Paediatrics)	Olipudase Alfa: Subjects From DFI13412 (Adults)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	5 / 5 (100.00%)	
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	9 / 20 (45.00%) 148	4 / 5 (80.00%) 55	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	13 / 20 (65.00%) 91	5 / 5 (100.00%) 178	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	18 / 20 (90.00%) 98	4 / 5 (80.00%) 97	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2016	Changed expected number of subjects from "65-70" to "up to 17". Provided option for home infusions. Provided specific guidelines on treatment "reintroduction". Removed the requirement that sponsor must be consulted to determine the appropriate dose of olipudase alfa for dose adjustments or if a subject misses 1 or more doses. Removed continuous heart rate monitoring as an endpoint. Additional primary, secondary and other endpoints added. Specified that, "The term 'paediatric subjects only' means subjects coming from the original paediatric trial, DFI13803. Some of these subjects reached adult age (18 years old) while in this study but continued the assessments schedule they were on in the original trial. Though adults by age, they remained part of "paediatric subjects" cohort; did not follow the adult procedures in this study (liver biopsy). Added that for subjects who missed 3 or more infusions between trials, some assessments may be repeated at study entry after discussion between sponsor and investigator. Added "If a subject has missed 3 or more doses >=0.6 mg/kg, reintroduction of olipudase alfa for subjects receiving infusions at home should occur at the hospital/study site. If subject misses 2 or fewer doses, the investigator can decide whether reintroduction for subjects receiving infusions at home should occur at the hospital/study site.". Added assessments for subjects who required dose reintroduction. Clarified pharmacokinetic (PK) and immune response specifications upon the introduction of a new manufacturing scale and PK sampling specifications. Added that the subjects must be willing and able to avoid certain medications and herbal supplements for 10 days before and 3 days after liver biopsies. Clarified subjects stopping criteria. Removed oxygen saturation from vital signs. Changed safety biomarker test from multiplex immunoassay to specific biomarkers. Changed definition of overdose.
25 April 2017	Change in assessments that were not repeated at the end of study/early discontinuation visit was made to correct an error in a previous section. Dose calculation based on weight in site and home infusion visits was made because weight change between visits was considered insignificant. Clarification of time points at which vital signs should be taken was added as they were missing from previous version. Clarification of assessments needed upon manufacturing scale change was made to adhere to assessments requested by health authorities. Clarification of neurological examination was made that the same neurologist would perform the examinations through this study and all throughout this study if possible. Change in dose stopping (and AESI) criteria was made to correct errors and clarify the level of liver function criteria. Recommendations on the usage of cationic amphilphillic antihistamines in rules on concomitant medications was added. Clarification on IAR definition and treatment and caution of IAR suggestive of hypersensitivity treatment about medications that may affect study medication efficacy was made. Clarification about liver biopsy evaluation was made to clarify the assessment language. Future use of samples section was added as it was missing from a previous version.

25 April 2018	Extension of the study treatment period from 5 to 9 years was made to extend the safety and efficacy follow up of the enrolled subjects. Removal of redundant exclusion criterion was made. The option of another liver biopsy after 5 years treatment in adult subjects was removed as the 3-year biopsy did not show evidence of a progressive worsening of fibrosis to cirrhosis in subjects treated with olipudase alfa. The target number of subjects was updated to be approximately 25 instead of 17. Assessments from the flow chart were removed such as cycle ergometry in paediatric subjects as this assessment did not provide any benefit to follow activities in children. Angiotensin converting enzyme measurement in both paediatric and adult subject populations was also removed as it did not provide any benefit to follow efficacy or safety. Options to conduct a future additional questionnaire about home infusion experience to subjects who received home infusion treatment was added. Differential liver deoxyribonucleic acid methylation densities of peroxisome proliferator-activated receptor gamma gene promoter in plasma circulating cell-free DNA was added as it had been shown to stratify subjects in terms of fibrosis severity. Language of collection of blood samples (beyond 5 years) and PK sample and analysis was clarified to address study extension and clarify other procedures. Clarification of reporting guidelines of AESI was made by adding laboratory values to the relevant table.
31 July 2019	This amendment was made to indicate the different assessments that were to be done after manufacturing process update as per regulatory authorities' requirements. Previous omissions and errors were corrected.
18 August 2020	This amendment was mainly made to change the reintroduction dose to a lower dose for subjects who missed 3 or more infusions and allow dose reintroduction and quarterly visits to be performed via home infusion for eligible subjects if the site visit was not possible due to site closure or extenuating circumstances that prevented an in-person site visit (during coronavirus disease-2019 [COVID-19] pandemic). This amended protocol extended cognitive and adaptive function assessments, adaptive behavior assessment system and developmental profile-3, to all paediatric subjects who had performed the assessment during the original DFI13803 study. The amendment also provided guidance regarding assessments related to updated manufacturing process and home infusion. Other changes, omissions and corrections were addressed.
29 January 2021	The primary reasons for this amendment were: During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic, to allow more flexibility with regard to additional options for monitoring techniques in compliance with applicable country-specific regulations. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic that can lead to site closure or extenuating circumstances that prevent an in-person site visit, for the switch from Process C(48) study treatment to the updated manufacturing Process C(32) study treatment, adding the possibility to perform the first infusion at home for eligible subjects in agreement between the Sponsor and the Investigator and in compliance with applicable country-specific regulations. Liver function test monitoring after infusion was already included in this protocol. However, review of the interim data from the clinical development program identified "Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa" as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation were added to the protocol. Other important changes included: In the context of this long-term study, the assessments were streamlined to reduce subject burden. Assessments to ensure subject safety were to be preserved. This change was implemented after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (the first cutoff date was on 10 December 2019). During the study, paediatric subjects who reached adult age (18 years) received the adult infusion volume. Other changes, omissions and corrections were addressed.
15 April 2022	The primary reasons for this amendment: To allow the continuity of treatment with olipudase alfa in the time frame between local regulatory approval and commercial accessibility by clarifying the duration of study treatment. To comply with the requirements agreed in the olipudase alfa Paediatric Investigational Plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported