



Clinical trial results:

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 Subjects Aged <18 Years with Acid Sphingomyelinase Deficiency

Summary

EudraCT number	2014-003198-40
Trial protocol	GB IT FR DE Outside EU/EEA
Global end of trial date	09 December 2019

Results information

Result version number	v2 (current)
This version publication date	16 December 2020
First version publication date	20 June 2020
Version creation reason	<ul style="list-style-type: none">• New data added to full data set based on the final CSR we would like to update the EudraCT results for this study

Trial information

Trial identification

Sponsor protocol code	DFI13803
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02292654
WHO universal trial number (UTN)	U1111-1160-6469
Other trial identifiers	Study Name: ASCEND-Peds

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation, a Sanofi company
Sponsor organisation address	50 Binney St, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, 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)	EMA-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	03 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of olipudase alfa administered intravenously in pediatric subjects every 2 weeks for 64 weeks.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric patients. The parent(s) or guardian(s) as well as the 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 minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 6
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
Worldwide total number of subjects	20
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

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)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 sites in 6 countries between 01 May 2015 and 09 December 2019.

Pre-assignment

Screening details:

A total of 23 subjects were screened out of which 20 subjects were included and treated 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
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Arm title	Olipudase alfa: Adolescent Cohort
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Arm description:

Subjects aged 12 to less than (<) 18 years received intravenous (IV) infusion of olipudase alfa once every 2 weeks (Q2W) for 64 weeks.

Arm type	Experimental
Investigational medicinal product name	Olipudase alfa
Investigational medicinal product code	GZ402665
Other name	recombinant human acid sphingomyelinase or rhASM
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 milligram per kilogram (mg/kg). The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of 64 treatment weeks.

Arm title	Olipudase alfa: Child cohort
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Arm description:

Subjects aged 6 to <12 years received IV infusion of olipudase alfa Q2W for 64 weeks.

Arm type	Experimental
Investigational medicinal product name	Olipudase alfa
Investigational medicinal product code	GZ402665
Other name	recombinant human acid sphingomyelinase or rhASM
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 mg/kg. The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of 64 treatment weeks.

Arm title	Olipudase alfa: Infant/Early Child cohort
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Arm description:

Subjects aged <6 years received IV infusion of olipudase alfa Q2W for 64 weeks.

Arm type	Experimental
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Investigational medicinal product name	Olipudase alfa
Investigational medicinal product code	GZ402665
Other name	recombinant human acid sphingomyelinase or rhASM
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 mg/kg. The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of 64 treatment weeks.

Number of subjects in period 1	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort
Started	4	9	7
Completed	4	9	7

Baseline characteristics

Reporting groups

Reporting group title	Olipudase alfa: Adolescent Cohort
Reporting group description: Subjects aged 12 to less than (<) 18 years received intravenous (IV) infusion of olipudase alfa once every 2 weeks (Q2W) for 64 weeks.	
Reporting group title	Olipudase alfa: Child cohort
Reporting group description: Subjects aged 6 to <12 years received IV infusion of olipudase alfa Q2W for 64 weeks.	
Reporting group title	Olipudase alfa: Infant/Early Child cohort
Reporting group description: Subjects aged <6 years received IV infusion of olipudase alfa Q2W for 64 weeks.	

Reporting group values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort
Number of subjects	4	9	7
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	14.84	8.69	3.77
standard deviation	± 2.22	± 1.69	± 1.44
Gender categorical Units: Subjects			
Female	1	5	4
Male	3	4	3
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Black	0	0	0
White	3	7	7
Southeast Asian	1	1	0
Northeast Asian	0	0	0
Not reported	0	0	0
Other	0	1	0
Native Hawaiian and other Pacific Islander	0	0	0
High Sensitivity C Reactive Protein (hsCRP) Level in Plasma			
Baseline data for hscRP is reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: milligrams per liter (mg/L)			
arithmetic mean	1.863	0.410	0.306
standard deviation	± 1.855	± 0.337	± 0.249
Safety Biomarker: Ceramide Level in Plasma Units: mg/L			
arithmetic mean	7.13	5.57	8.01

standard deviation	± 2.14	± 1.87	± 5.30
Safety Biomarker: Iron Level in Plasma			
Baseline data for Iron level are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micromole/liter (umol/L)			
arithmetic mean	10.13	10.96	8.52
standard deviation	± 2.38	± 2.31	± 1.81
Safety Biomarker: Cardiac Troponin I Level in Plasma			
Baseline data for cardiac troponin I are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micrograms per liter (µg/L)			
arithmetic mean	0.020	0.020	0.020
standard deviation	± 0.000	± 0.000	± 0.000
Safety Biomarker: Ferritin Level in Plasma			
Units: ug/L			
arithmetic mean	65.775	68.700	46.329
standard deviation	± 21.088	± 36.733	± 26.500
Safety Biomarker: Interleukin (IL)-6 Level in Plasma			
Baseline data for IL-6 are reported for "total=11" subjects i.e. adolescent cohort: 3 subjects, child cohort: 8 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: nanogram/liter (ng/L)			
arithmetic mean	2.27	11.15	99999
standard deviation	± 0.87	± 25.62	± 99999
Safety Biomarker: IL-8 Level in Plasma			
Baseline data for IL-8 are reported for "total=13" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: ng/L			
arithmetic mean	24.75	35.72	99999
standard deviation	± 14.50	± 29.15	± 99999
Safety Biomarker: Calcitonin Level in Plasma			
Units: ng/L			
arithmetic mean	7.675	9.031	12.991
standard deviation	± 13.330	± 8.601	± 7.843
Percent Left Ventricular Ejection Fraction			
Baseline data for percent ejection fraction are reported for "total=19" subjects i.e. adolescent cohort: 4 subjects, child cohort: 8 subjects, infant/early child cohort: 7 subjects			
Units: Percent ejection fraction			
arithmetic mean	60.50	64.25	68.71
standard deviation	± 4.04	± 6.27	± 7.16
Pharmacodynamic Biomarker: Sphingomyelin in Plasma			
Units: mg/L			
arithmetic mean	348.3	430.8	318.7
standard deviation	± 27.5	± 191.3	± 41.0
Pharmacodynamic Biomarker: Lyso-Sphingomyelin in Plasma			
Units: ug/L			
arithmetic mean	488.250	653.667	670.000
standard deviation	± 153.489	± 226.301	± 382.137

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	10		
Male	10		
Race Units: Subjects			
American Indian or Alaska Native	0		
Black	0		
White	17		
Southeast Asian	2		
Northeast Asian	0		
Not reported	0		
Other	1		
Native Hawaiian and other Pacific Islander	0		
High Sensitivity C Reactive Protein (hsCRP) Level in Plasma			
Baseline data for hscRP is reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: milligrams per liter (mg/L) arithmetic mean standard deviation	-		
Safety Biomarker: Ceramide Level in Plasma Units: mg/L arithmetic mean standard deviation	-		
Safety Biomarker: Iron Level in Plasma			
Baseline data for Iron level are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micromole/liter (umol/L) arithmetic mean standard deviation	-		
Safety Biomarker: Cardiac Troponin I Level in Plasma			
Baseline data for cardiac troponin I are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micrograms per liter (µg/L) arithmetic mean standard deviation	-		
Safety Biomarker: Ferritin Level in Plasma Units: ug/L arithmetic mean			

standard deviation	-		
Safety Biomarker: Interleukin (IL)-6 Level in Plasma			
Baseline data for IL-6 are reported for "total=11" subjects i.e. adolescent cohort: 3 subjects, child cohort: 8 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: nanogram/liter (ng/L)			
arithmetic mean			
standard deviation	-		
Safety Biomarker: IL-8 Level in Plasma			
Baseline data for IL-8 are reported for "total=13" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: ng/L			
arithmetic mean			
standard deviation	-		
Safety Biomarker: Calcitonin Level in Plasma			
Units: ng/L			
arithmetic mean			
standard deviation	-		
Percent Left Ventricular Ejection Fraction			
Baseline data for percent ejection fraction are reported for "total=19" subjects i.e. adolescent cohort: 4 subjects, child cohort: 8 subjects, infant/early child cohort: 7 subjects			
Units: Percent ejection fraction			
arithmetic mean			
standard deviation	-		
Pharmacodynamic Biomarker: Sphingomyelin in Plasma			
Units: mg/L			
arithmetic mean			
standard deviation	-		
Pharmacodynamic Biomarker: Lyso-Sphingomyelin in Plasma			
Units: ug/L			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Total Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects received IV infusion of olipudase alfa Q2W for 64 weeks. Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 mg/kg. The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of 64 treatment weeks.

Reporting group values	Total Subjects		
Number of subjects	20		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	8.20 ± 4.39		
Gender categorical Units: Subjects			
Female	10		
Male	10		
Race Units: Subjects			
American Indian or Alaska Native	0		
Black	0		
White	17		
Southeast Asian	2		
Northeast Asian	0		
Not reported	0		
Other	1		
Native Hawaiian and other Pacific Islander	0		
High Sensitivity C Reactive Protein (hsCRP) Level in Plasma			
Baseline data for hscRP is reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: milligrams per liter (mg/L) arithmetic mean standard deviation	0.704 ± 1.041		
Safety Biomarker: Ceramide Level in Plasma Units: mg/L arithmetic mean standard deviation	6.74 ± 3.51		
Safety Biomarker: Iron Level in Plasma			
Baseline data for Iron level are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micromole/liter (umol/L) arithmetic mean standard deviation	10.09 ± 2.32		
Safety Biomarker: Cardiac Troponin I Level in Plasma			
Baseline data for cardiac troponin I are reported for "total=18" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 5 subjects.			
Units: micrograms per liter (µg/L) arithmetic mean standard deviation	0.020 ± 0.000		
Safety Biomarker: Ferritin Level in Plasma Units: ug/L arithmetic mean standard deviation	60.285 ± 31.173		
Safety Biomarker: Interleukin (IL)-6 Level in Plasma			
Baseline data for IL-6 are reported for "total=11" subjects i.e. adolescent cohort: 3 subjects, child cohort: 8 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: nanogram/liter (ng/L)			

arithmetic mean	8.73		
standard deviation	± 21.84		
Safety Biomarker: IL-8 Level in Plasma			
Baseline data for IL-8 are reported for "total=13" subjects i.e. adolescent cohort: 4 subjects, child cohort: 9 subjects, infant/early child cohort: 0 subjects. Here '99999' = data not collected in subjects <6 years old per protocol.			
Units: ng/L			
arithmetic mean	32.35		
standard deviation	± 25.43		
Safety Biomarker: Calcitonin Level in Plasma			
Units: ng/L			
arithmetic mean	10.146		
standard deviation	± 9.137		
Percent Left Ventricular Ejection Fraction			
Baseline data for percent ejection fraction are reported for "total=19" subjects i.e. adolescent cohort: 4 subjects, child cohort: 8 subjects, infant/early child cohort: 7 subjects			
Units: Percent ejection fraction			
arithmetic mean	65.11		
standard deviation	± 6.72		
Pharmacodynamic Biomarker: Sphingomyelin in Plasma			
Units: mg/L			
arithmetic mean	375.1		
standard deviation	± 137.3		
Pharmacodynamic Biomarker: Lyso-Sphingomyelin in Plasma			
Units: ug/L			
arithmetic mean	626.300		
standard deviation	± 276.528		

End points

End points reporting groups

Reporting group title	Olipudase alfa: Adolescent Cohort
Reporting group description: Subjects aged 12 to less than (<) 18 years received intravenous (IV) infusion of olipudase alfa once every 2 weeks (Q2W) for 64 weeks.	
Reporting group title	Olipudase alfa: Child cohort
Reporting group description: Subjects aged 6 to <12 years received IV infusion of olipudase alfa Q2W for 64 weeks.	
Reporting group title	Olipudase alfa: Infant/Early Child cohort
Reporting group description: Subjects aged <6 years received IV infusion of olipudase alfa Q2W for 64 weeks.	
Subject analysis set title	Total Subjects
Subject analysis set type	Full analysis
Subject analysis set description: All subjects received IV infusion of olipudase alfa Q2W for 64 weeks. Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 mg/kg. The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of 64 treatment weeks.	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) ^[1]
End point description: TEAEs were defined as adverse events (AEs) that occurred or worsened during the on-treatment period (time from the start of investigational medicinal product [IMP] administration until end of study (i.e up to 64 weeks). Analysis was performed on safety population that included all subjects who received at least 1 infusion (partial or total) of olipudase alfa.	
End point type	Primary
End point timeframe: From baseline up End of Study (64 weeks)	

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
Any TEAEs	4	9	7	20
Any TEAEs leading to death	0	0	0	0
Any TEAEs leading to dose reduction	0	4	3	7
Any TEAEs potentially related to study drug	2	6	5	13

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Infusion-Associated Reactions (IARs)

End point title	Number of Subjects With Infusion-Associated Reactions
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End point description:

IARs were defined as 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. Protocol-defined IAR: all AEs that were identified as an IAR by the investigator. Events occurring greater than or equal to (\geq) 24 hours after the start of an infusion may have been judged an IAR at the discretion of the investigator or sponsor. Analysis was performed on the safety population.

End point type	Primary
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End point timeframe:

Within up to 24 hours after start of any infusion (during the treatment period i.e. from baseline up to 64 weeks)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects	0	6	5	11

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Change in Physical Examination

End point title	Number of Subjects With Change in Physical Examination ^[3]
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End point description:

Change from Normal assessment (at baseline) to Abnormal assessment (at Week 52) was reported. Physical examinations included following observations/measurements: examination of the skin, head, eyes, ears, nose, and throat; lymph nodes; heart, lungs, and abdomen; extremities and joints. Abnormality in physical examinations was based on investigator's discretion. Analysis was performed on safety population. One subject may be counted in multiple categories.

End point type	Primary
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End point timeframe:

Baseline, Week 52 (last complete assessment)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	6
Units: subjects				
Abdomen	0	0	0	0
Heart	0	0	0	0
Skin	0	1	1	2
Extremities/Joints	0	1	0	1
General Appearance	0	1	1	2
Head, Eyes, Ears, Nose and Throat	2	0	2	4
Lymph Nodes	0	0	0	0
Lungs	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Change in Neurological Examination

End point title	Number of Subjects With Change in Neurological Examination ^[4]
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End point description:

Change from Normal assessment (at baseline) to Abnormal assessment (at Week 52) was reported. Neurological examination included: coordination examination, cranial nerve examination, extrapyramidal features, fundoscopy, gait and coordination examination, motor examination, tone peripheral nervous system, reflexes examination, sensory examination, strength examination, mental status. Analysis was performed on safety population. One subject may be counted in multiple categories.

End point type	Primary
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End point timeframe:

Baseline, Week 52 (last assessment)

Notes:

[4] - 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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
Coordination Examination	0	0	0	0
Cranial Nerve Examination	0	0	0	0
Extrapyramidal Features	0	0	0	0
Fundoscopy	0	0	1	1
Gait and Coordination Examination	0	0	0	0
Motor Examination, Tone	0	0	0	0
Peripheral Nervous System	0	0	0	0
Reflexes Examination	0	0	0	0
Sensory Examination	0	0	0	0
Strength Examination	0	0	1	1
Mental Status	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Liver Function laboratory Values at the End of Study

End point title	Number of Subjects With Abnormal Liver Function laboratory Values at the End of Study ^[5]
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End point description:

Abnormal values in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase were reported. Analysis was performed on safety population. One subject may be counted in multiple categories.

End point type	Primary
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End point timeframe:

At End of Study (Week 64)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
ALT	0	1	1	2
AST	0	1	0	1
Total Bilirubin	0	0	0	0
Alkaline Phosphatase	2	2	0	4

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Vital Sign Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Vital Sign Abnormalities ^[6]
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End point description:

•Heart Rate (HR) High: ≥ 120 bpm(adolescents), ≥ 120 bpm (children), ≥ 140 bpm (early children), ≥ 175 bpm(infants) & increase from baseline(IFB) ≥ 20 bpm for all age categories. •HR Low: ≤ 50 bpm (adolescents), ≤ 50 bpm(children), ≤ 75 bpm (early children), ≤ 80 bpm(infants) & decrease from baseline(DFB) ≥ 20 bpm for all age categories. •Systolic BP(SBP)High: ≥ 119 mmHg(adolescents), 108 mmHg(children),101 mmHg(in early children), 98 mmHg(infants) & IFB ≥ 20

for all age categories. •SBP Low: <=90 mmHg(adolescents), <= 80mm Hg(children), <=70 mmHg(early children), <=70 mmHg (infants) & DFB >=20 mmHg for all age categories. •Diastolic BP(DBP) High:>=78 mmHg (adolescents), >=72 mmHg(children), >=59 mmHg(in early children), >=54 mmHg(infants) & IFB >=10 mmHg for all age categories. •DBP Low:<=54 mmHg(adolescents), <=48 mmHg(children), <=34 mmHg (early children),<=34 mmHg(infants) & DFB >=10 mmHg for all age categories. Safety population.1 subject may be counted in multiple categories.

End point type	Primary
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End point timeframe:

From Baseline up to End of Study (64 weeks)

Notes:

[6] - 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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
Heart Rate High	0	5	3	8
Heart Rate Low	1	0	7	8
SBP High	3	6	6	15
SBP Low	2	5	0	7
DBP High	4	8	7	19
DBP Low	4	9	2	15

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With potentially Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With potentially Clinically Significant Electrocardiogram (ECG) Abnormalities ^[7]
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End point description:

Criteria for potentially clinically significant ECG abnormalities:

High PR Interval: >=180 milliseconds (ms) in adolescents, 170 ms in children, 160 ms in early children, and 140 ms in infants;

High QRS Interval: >=110 ms in adolescents, 100 ms in children, 95 ms in early children and 85 ms in infants;

Prolonged QTc Fridericia (QTc F): >450 ms in male adolescents, children, early children and infants or 470 ms in female adolescents,;

QTc F >500 ms;

QTc F increase from baseline >60 ms.

Analysis was performed on the safety population.

End point type	Primary
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End point timeframe:

From Baseline up to End of Study (64 weeks)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
High PR Duration	2	2	2	6
High QRS Duration	0	0	0	0
Prolonged QTc F	1	1	0	2
QTc F >500 ms	0	0	0	0
QTc F increase from baseline >60 ms	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker Level: High sensitivity C Reactive Protein (hsCRP) at Week 64

End point title	Change From Baseline in Safety Biomarker Level: High sensitivity C Reactive Protein (hsCRP) at Week 64 ^[8]
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End point description:

Analysis was performed on safety population. Here, number of subjects analysed=subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

Baseline, Week 64 (pre-infusion)

Notes:

[8] - 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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	5	18
Units: mg/L				
arithmetic mean (standard deviation)	-1.603 (± 1.976)	-0.168 (± 0.411)	-0.206 (± 0.249)	-0.497 (± 1.074)

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker: Ceramide Level at Week 64

End point title	Change From Baseline in Safety Biomarker: Ceramide Level at Week 64 ^[9]
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End point description:

Analysis was performed on safety population.

End point type	Primary
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End point timeframe:

Baseline, Week 64 (pre-infusion)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: mg/L				
arithmetic mean (standard deviation)	-3.90 (± 2.41)	-3.23 (± 2.17)	-5.93 (± 4.91)	-4.31 (± 3.48)

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker: Iron at Week 64

End point title	Change From Baseline in Safety Biomarker: Iron at Week 64 ^[10]
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End point description:

Analysis was performed on safety population. Here, number of subjects analysed=subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

Baseline, Week 64 (pre-infusion)

Notes:

[10] - 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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	8	5	17
Units: umol/L				
arithmetic mean (standard deviation)	1.40 (± 3.53)	-0.41 (± 5.07)	1.52 (± 4.31)	0.58 (± 4.38)

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker: Cardiac Troponin I and Ferritin at Week 64

End point title	Change From Baseline in Safety Biomarker: Cardiac Troponin I and Ferritin at Week 64 ^[11]
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End point description:

Analysis was performed on safety population. Here 'n' = number of subjects with available data for specified categories.

End point type	Primary
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End point timeframe:

Baseline, Week 64 (pre-infusion)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: µg/L				
arithmetic mean (standard deviation)				
Troponin: Pre-infusion: Week 64 (n=4, 9, 5, 18)	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)
Ferritin: Pre-infusion: Week 64 (n=4,9,7,20)	-38.325 (± 16.438)	-45.611 (± 32.963)	-28.186 (± 19.793)	-38.055 (± 26.207)

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker: Interleukin (IL)-6 and IL-8 at Week 24

End point title	Change From Baseline in Safety Biomarker: Interleukin (IL)-6 and IL-8 at Week 24 ^{[12][13]}
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End point description:

Analysis was performed on safety population. Here 'n' = number of subjects with available data for specified categories. For the arm "Olipudase alfa: Infant/Early Child cohort" data was not collected in subjects <6 years old, per protocol.

End point type	Primary
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End point timeframe:

Baseline, Week 24 (pre-infusion, last assessment)

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 was descriptive in nature, no statistical analysis was provided.

[13] - 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: For the arm "Olipudase alfa: Infant/Early Child cohort" data was not collected in subjects <6 years old, per protocol.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Total Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	9	13	
Units: nanogram/liter (ng/L)				
arithmetic mean (standard deviation)				
IL-6 (n= 3, 8, 11)	0.47 (± 3.23)	0.89 (± 5.66)	0.77 (± 4.95)	
IL-8 (n= 4, 9, 13)	-7.25 (± 14.50)	-18.22 (± 29.15)	-14.85 (± 25.43)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Safety Biomarker: Calcitonin at Week 64

End point title	Change From Baseline in Safety Biomarker: Calcitonin at Week 64 ^[14]
End point description:	
Analysis was performed on safety population.	
End point type	Primary
End point timeframe:	
Baseline, Week 64 (pre-infusion)	

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: ng/L				
arithmetic mean (standard deviation)	3.612 (± 7.225)	-5.377 (± 3.962)	-8.609 (± 6.359)	-4.710 (± 6.929)

Statistical analyses

No statistical analyses for this end point

Primary: Doppler Echocardiogram: Absolute Change from Baseline in Left Ventricular Ejection Fraction at Week 52

End point title	Doppler Echocardiogram: Absolute Change from Baseline in Left Ventricular Ejection Fraction at Week 52 ^[15]
End point description:	
Analysis was performed on safety population. Here, number of subjects analysed = subjects with available data for this endpoint.	
End point type	Primary

End point timeframe:

Baseline, Week 52 (last assessment)

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	7	6	16
Units: Percent ejection fraction				
arithmetic mean (standard deviation)	0.33 (\pm 4.51)	-1.00 (\pm 5.16)	1.17 (\pm 4.83)	0.06 (\pm 4.71)

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Emergent Antibody: Treatment-Induced/Treatment-Boosted Anti-drug Antibodies and Neutralizing Antibody (NAb)

End point title	Number of Subjects With Treatment-Emergent Antibody: Treatment-Induced/Treatment-Boosted Anti-drug Antibodies and Neutralizing Antibody (NAb) ^[16]
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End point description:

Serum samples for immunogenicity assessment were analyzed to detect ADA. ADA response were categorized as: treatment emergent antibody i.e. treatment-induced/treatment-boosted response. A subject whose ADA status was positive anytime post-baseline and was negative or missing at baseline was considered to have treatment-induced ADA. A subject whose ADA status is positive at baseline (pre-existing ADA) and the ADA titer level anytime post-baseline is significantly higher than that at baseline is considered to have treatment boosted ADA. Positive samples in the ADA assay were further analyzed in the NAb assay as positive NAb inhibition of catalytic activity and positive NAb inhibition of cellular uptake. Analysis was performed on safety population.

End point type	Primary
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End point timeframe:

From baseline up to Week 64

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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects				
ADA positive since first dose of olipudase alfa	2	7	3	12
Positive NAb of catalytic activity	0	1	0	1
Positive NAb of cellular uptake	0	0	0	0
Treatment induced ADA	2	6	3	11
Treatment boosted ADA	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormalities in Liver Ultrasound Doppler at Week 52

End point title	Number of Subjects With Abnormalities in Liver Ultrasound Doppler at Week 52 ^[17]
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End point description:

Evidence of portal hypertension was assessed by portal vein direction from liver ultrasound doppler. Analysis was performed on safety population.

End point type	Primary
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End point timeframe:

Week 52 (last assessment)

Notes:

[17] - 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 was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameter: Plasma Concentration of Olipudase Alfa at the End of infusion (Ceoi)

End point title	Pharmacokinetic (PK) Parameter: Plasma Concentration of Olipudase Alfa at the End of infusion (Ceoi)
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End point description:

Ceoi was defined as the plasma concentration at the end of infusion (EOI). Data collected for child and Infant/child age groups at 0-30 min from end of infusion was considered at end of infusion. Analysis was performed on PK population which included all subjects who received at least 1 infusion of study medication and had evaluable PK data.

End point type	Secondary
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End point timeframe:

At the end of infusion of the first 3.0 mg/kg dose and at Week 52

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
3.0 mg/kg at First dose	28.0 (± 4.88)	23.0 (± 3.93)	22.1 (± 7.19)	
3.0 mg/kg at Day 52	22.4 (± 1.02)	24.4 (± 7.51)	22.4 (± 4.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Maximum Observed Plasma Concentration (C_{max}) of olipudase alfa

End point title	Pharmacokinetic Parameter: Maximum Observed Plasma Concentration (C _{max}) of olipudase alfa
End point description:	C _{max} : maximum plasma concentration observed. Analysis was performed on PK population.
End point type	Secondary
End point timeframe:	Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week 52) post EOI; Child & infant/early child: pre-infusion, 0-30 min, 2-4 h, 6-12 h, 24-36 h, and 84-96 h post EOI at the first 3.0 mg/kg dose & Week 52

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
3.0 mg/kg at First dose	28.0 (± 4.88)	23.0 (± 3.93)	22.1 (± 7.19)	
3.0 mg/kg at Week 52	22.4 (± 1.02)	24.4 (± 7.51)	22.4 (± 4.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: AUC_{0-last}, AUC(0-tau) of Olipudase Alfa

End point title	Pharmacokinetic Parameter: AUC _{0-last} , AUC(0-tau) of Olipudase Alfa
End point description:	AUC _{last} : Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the time of last measured concentration real time. AUC(0-tau): area under the plot of the drug concentration versus the time curve from time "0" to the end of the dosing interval

(tau), where dosing interval was 2 weeks. Analysis was performed on PK population.

End point type	Secondary
End point timeframe:	
Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week 52) post EOI; Child & infant/early child: pre-infusion, 0-30 min, 2-4 h, 6-12 h, 24-36 h, and 84-96 h post EOI at the first 3.0 mg/kg dose & Week 52	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: µg*h/mL				
arithmetic mean (standard deviation)				
AUClast: at 3.0 mg/kg First dose	452 (± 49.7)	441 (± 97.8)	412 (± 87.4)	
AUClast: at 3.0 mg/kg at Week 52	461 (± 28.1)	482 (± 101)	429 (± 62.6)	
AUC(0-τ): at 3.0 mg/kg First dose	478 (± 55.4)	465 (± 102)	432 (± 93.0)	
AUC(0-τ): at 3.0 mg/kg at Week 52	489 (± 32.7)	508 (± 108)	451 (± 68.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Terminal Half-Life of Olipudase Alfa

End point title	Pharmacokinetic Parameter: Terminal Half-Life of Olipudase Alfa
End point description:	
Half-life is the time measured for the plasma concentration of drug to decrease by one half. Analysis was performed on PK population.	
End point type	Secondary
End point timeframe:	
Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week 52) post EOI; Child & infant/early child: pre-infusion, 0-30 min, 2-4 h, 6-12 h, 24-36 h, and 84-96 h post EOI at the first 3.0 mg/kg dose & Week 52	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: hours (h)				
arithmetic mean (standard deviation)				
3.0 mg/kg at First dose	17.1 (± 1.15)	23.1 (± 2.11)	22.6 (± 1.25)	
3.0 mg/kg at Week 52	24.3 (± 2.88)	23.3 (± 1.42)	23.6 (± 1.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Total body clearance (CL) of Olipudase Alfa

End point title	Pharmacokinetic Parameter: Total body clearance (CL) of Olipudase Alfa
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End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. Total body clearance of a drug from the plasma calculated using equations below: $CL = \text{Dose} / \text{AUC}$ after the first dose. Analysis was performed on PK population.

End point type	Secondary
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End point timeframe:

Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week 52) post EOI; Child & infant/early child: pre-infusion, 0-30 min, 2-4 h, 6-12 h, 24-36 h, and 84-96 h post EOI at the first 3.0 mg/kg dose & Week 52

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: milliliter/hour/kilograms (mL/h/kg)				
arithmetic mean (standard deviation)				
3.0 mg/kg at First dose	6.34 (± 0.741)	6.75 (± 1.57)	7.20 (± 1.40)	
3.0 mg/kg at Week 52	6.16 (± 0.411)	6.16 (± 1.38)	6.79 (± 1.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Volume of Distribution at Steady State (Vss) of Olipudase Alfa

End point title	Pharmacokinetic Parameter: Volume of Distribution at Steady State (Vss) of Olipudase Alfa
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End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Analysis was performed on PK population.

End point type	Secondary
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End point timeframe:

Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: milliliter per kilogram (mL/kg)				
arithmetic mean (standard deviation)				
3.0 mg/kg at First dose	133 (± 13.5)	166 (± 39.1)	165 (± 31.0)	
3.0 mg/kg at Week 52	172 (± 11.6)	153 (± 32.7)	161 (± 20.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Time to Reach Cmax (tmax) of Olipudase Alfa

End point title	Pharmacokinetic Parameter: Time to Reach Cmax (tmax) of Olipudase Alfa
End point description:	
tmax: time to reach maximum plasma concentration observed. Analysis was performed on PK population.	
End point type	Secondary
End point timeframe:	
Adolescent: at pre-infusion, EOI, 2 h, 6 h, 24 h, 48 h & 72 h (at first 3.0 mg/kg dose) or 96 h (at Week 52) post EOI; Child & infant/early child: pre-infusion, 0-30 min, 2-4 h, 6-12 h, 24-36 h, and 84-96 h post EOI at the first 3.0 mg/kg dose & Week 52	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	7	
Units: hours (h)				
median (full range (min-max))				
3.0 mg/kg at First dose	3.94 (3.87 to 4.08)	4.00 (3.83 to 7.07)	4.13 (3.75 to 8.70)	
3.0 mg/kg at Week 52	3.81 (3.67 to 4.03)	4.25 (3.75 to 9.78)	4.42 (4.08 to 5.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen Volume and Liver Volume at Week 52

End point title	Percent Change From Baseline in Spleen Volume and Liver Volume at Week 52
End point description: Spleen and liver volumes was assessed by abdominal magnetic resonance imaging (MRI). Analysis was performed on modified intent-to-treat (mITT) population which included all subjects who were exposed to IMP, regardless of the amount of treatment administered (partial or total).	
End point type	Secondary
End point timeframe: Baseline, Week 52 (last assessment)	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: percent change in volume				
arithmetic mean (standard deviation)				
Change in Spleen Volume	-46.936 (± 3.041)	-46.038 (± 11.767)	-54.590 (± 7.562)	-49.211 (± 9.713)
Change in Liver Volume	-41.276 (± 6.130)	-36.741 (± 10.469)	-45.060 (± 8.203)	-40.560 (± 9.370)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Interstitial Lung Disease Score Measured Using High Resolution Computed Tomography (HRCT) at Week 52 for Both Lungs

End point title	Change From Baseline in Interstitial Lung Disease Score Measured Using High Resolution Computed Tomography (HRCT) at Week 52 for Both Lungs
End point description: Pulmonary imaging of chest using HRCT was obtained to quantitate the degree of possible infiltrative lung disease. Lung fields were assessed by a central reader & scored subjectively for the degree of interstitial lung disease on a scale ranges from 0 =normal, 1 =mild, 2=moderate and 3 =severe, where higher scores indicate more severity. Analysis was performed on mITT population. Here, number of subjects analysed=subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 52 (last assessment)	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	6	19
Units: score on a scale				
arithmetic mean (standard deviation)	-0.2188 (\pm 1.0020)	-0.5833 (\pm 0.7906)	-0.8958 (\pm 0.9982)	-0.6053 (\pm 0.8851)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Z-Scores at Week 52

End point title	Change From Baseline in Height Z-Scores at Week 52
End point description: Z-score for height of subjects was evaluated. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 52 (last assessment)	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	8	7	19
Units: Z-score				
arithmetic mean (standard deviation)	0.606 (\pm 0.290)	0.371 (\pm 0.344)	0.736 (\pm 0.423)	0.555 (\pm 0.385)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Percent Predicted Hemoglobin-Adjusted Lung Diffusing Capacity for Carbon Monoxide (DLco) at Week 52

End point title	Percent Change From Baseline in Percent Predicted Hemoglobin-Adjusted Lung Diffusing Capacity for Carbon Monoxide (DLco) at Week 52 ^[18]
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End point description:

Percent predicted Hemoglobin-adjusted DLco was calculated as:

100*Adjusted DLco/Predicted DLco in unit of mL CO/min/mmHg where, adjusted DLco = Observed DLco (in mL CO/min/mmHg) divided by Hemoglobin-adjusted factor. Per planned analysis, pulmonary function testing (PFT) was to be performed only on subjects ≥ 5 years of age and who could perform the test, therefore, for subjects in "age cohort: infant/early child" data was not collected. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Week 52 (last assessment)	
Notes:	
[18] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: percent change				
arithmetic mean (standard deviation)	28.01 (± 16.22)	35.41 (± 35.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Difference Between Actual Age and Bone age of Subjects at Week 52

End point title	Change From Baseline in Difference Between Actual Age and Bone age of Subjects at Week 52
End point description:	
Hand X-ray was performed on subject's left hand, fingers and wrist to assess bone age of subjects. At each visit (baseline and Week 52), 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) at specified time points. In this endpoint change from baseline at Week 52 in the difference between actual age and bone age (in months) is reported. Analysis was performed on mITT population.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52 (last assessment)	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: months				
arithmetic mean (standard deviation)	1.595 (± 3.114)	2.876 (± 14.048)	-0.702 (± 9.573)	1.368 (± 10.781)

Statistical analyses

Secondary: Change From Baseline in Cycle Ergometry: Maximum Workload at Week 52

End point title	Change From Baseline in Cycle Ergometry: Maximum Workload at Week 52 ^[19]
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End point description:

Cardiopulmonary status was assessed using a stationary one-wheeled cycle used as an ergometer to measure a person's work output under controlled conditions. Subjects were asked to ride the cycle at increasing workload levels until they could no longer proceed. The workload at which subject stopped and cannot proceed was considered as maximum workload (in watt). As per the planned analysis, this assessment was not to be performed on subjects that were ≤ 6 years of age or < 120 cm in height on day 1/week 0, therefore data was not collected for the infant/early child cohort. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 (last assessment)

Notes:

[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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: watts				
arithmetic mean (standard deviation)	38.3 (\pm 10.7)	20.5 (\pm 7.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment of Subject's Progress: Observed Scores at Week 52

End point title	Physician's Global Assessment of Subject's Progress: Observed Scores at Week 52
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End point description:

Physician assessed subject's current clinical status (refers to clinical status at Weeks 52 in comparison to Baseline) was evaluated by marking 1 of the following 7 categories: • marked improvement, • moderate improvement, • mild improvement, • no change, • mild worsening, • moderate worsening, or • marked worsening. These 7 categories were converted to scores as follows: 3 = marked improvement of daily activities, 2 = moderate improvement of daily activities, 1 = mild improvement of daily activities, 0 = no change, -1 = mild worsening of daily activities, -2 = moderate worsening of daily activities, -3 = marked worsening of daily activities where higher score indicated improvement in daily activities as compared to baseline. In this endpoint, observed scores of subject's clinical status at Week 52 are reported. Analysis was performed on mITT population.

End point type	Secondary
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End point timeframe:

Week 52 (last assessment)

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: score on a scale				
arithmetic mean (standard deviation)	1.3 (± 1.5)	2.4 (± 1.0)	2.7 (± 0.8)	2.3 (± 1.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Efficacy Biomarkers Level at Week 52

End point title	Percent Change From Baseline in Efficacy Biomarkers Level at Week 52
End point description: Efficacy biomarkers included chitotriosidase, chemokine ligand 18 (CCL18), angiotensin-converting enzyme (ACE). Analysis was performed on mITT population. Here 'n' = number of subjects with available data for specified category.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: percent change				
arithmetic mean (standard deviation)				
Chitotriosidase at Week 52 (n= 4, 8, 7, 19)	-55.8 (± 21.1)	-44.7 (± 25.0)	-74.6 (± 18.1)	-58.0 (± 24.8)
CCL18 at Week 52 (n= 4, 9, 7, 20)	-55.25 (± 13.23)	-66.20 (± 22.97)	-68.13 (± 16.63)	-64.68 (± 19.01)
ACE at Week 52 (n= 4, 9, 7, 20)	-29.92 (± 19.59)	-24.57 (± 14.15)	-29.64 (± 17.80)	-27.41 (± 15.87)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lipid Profile at Week 52

End point title	Percent Change From Baseline in Lipid Profile at Week 52
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End point description:

Lipid profile parameters included low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol and triglycerides. Analysis was performed on mITT population. Here 'n'=number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: percent change				
arithmetic mean (standard deviation)				
LDL Cholesterol at Week 52 (n=4,9,6,19)	-38.31 (± 7.44)	-35.82 (± 23.00)	-34.04 (± 16.69)	-35.78 (± 18.00)
HDL Cholesterol at Week 52 (n=4,9,7,20)	118.63 (± 66.75)	87.49 (± 52.89)	124.74 (± 84.57)	106.76 (± 66.82)
Triglycerides at Week 52 (n=4, 9, 7, 20)	-56.28 (± 5.95)	-47.45 (± 18.08)	-56.44 (± 25.01)	-52.37 (± 19.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Bone Biomarkers at Week 52

End point title	Percent Change From Baseline in Bone Biomarkers at Week 52
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End point description:

Bone biomarkers included bone specific alkaline phosphatase, C-Telopeptide. Analysis was performed on mITT population. Here 'n'= number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: percent change				
arithmetic mean (standard deviation)				
Alkaline phosphatase: Week 52 (n= 3, 9, 5, 17)	-9.154 (± 50.568)	44.768 (± 50.111)	35.040 (± 61.983)	32.391 (± 54.292)
C-Telopeptide: Week 52 (n= 4, 8, 5, 17)	69.0 (± 93.7)	92.5 (± 78.4)	50.6 (± 37.0)	74.7 (± 70.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Outcome Questionnaires: Pediatric Quality of Life (PedsQL) Generic Core Scale Scores at Week 52

End point title	Change From Baseline in Health Outcome Questionnaires: Pediatric Quality of Life (PedsQL) Generic Core Scale Scores at Week 52
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End point description:

PedsQL included 23 items which covered 4 sub scales: physical, emotional, social & school functioning. Each item in every scale used 5-point rating scale (0=never to 4=almost always). Scale items were reversely scored & linearly transformed from 0-4 to 0-100 scale where 0=100, 1=75, 2=50, 3=25 & 4=0, higher scores=better health related quality of life (QoL). Psychosocial health summary score: mean was computed as sum of items scored over number of items answered in emotional, social & school functioning scale. Total score: mean was computed as sum of all items scored over number of items answered on all scales & was calculated based on 0 (almost always)-100 (never) scale scores, higher scores=better health related QoL. Scale assessed subject's & parent's perceptions of health related QoL in pediatric subjects with chronic health condition. mITT population. Number of subjects analysed=subjects with available data for this endpoint. 'n'=number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 (last assessment)

End point values	Total Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning Scale: Child Report (n= 13)	9.4 (± 7.9)			
Emotional Functioning Scale: Child Report (n= 13)	14.6 (± 15.1)			
Social Functioning Scale: Child Report (n= 13)	4.2 (± 13.2)			
School Functioning Scale: Child Report (n=13)	2.1 (± 12.6)			
Psychosocial Health Summary Score: Child Report n=13	6.8 (± 8.3)			
Generic Core Total Scale Score: Child Report (n=13)	7.6 (± 5.5)			
Physical Functioning Scale: Parent Report (n=18)	15.5 (± 15.3)			
Emotional Functioning Scale: Parent Report (n=18)	12.2 (± 22.9)			
Social Functioning Scale: Parent Report (n=18)	11.7 (± 19.8)			

School Functioning Scale: Parent Report (n=17)	1.0 (± 20.5)			
Psychosocial Health Summary Score: Parent Report n=18	8.2 (± 14.5)			
Generic Core Total Scale Score: Parent Report (n=18)	10.8 (± 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Pharmacodynamic Biomarkers: Plasma Sphingomyelin and Lyso-Sphingomyelin Levels at Week 52

End point title	Percent Change From Baseline in Pharmacodynamic Biomarkers: Plasma Sphingomyelin and Lyso-Sphingomyelin Levels at Week 52
End point description:	Sphingomyelin and Lyso-sphingomyelin levels were assessed in plasma. Lyso-sphingomyelin is a metabolite of sphingomyelin. Analysis was performed on pharmacodynamic PD population.
End point type	Secondary
End point timeframe:	Baseline, Week 52 (Pre- infusion)

End point values	Olipudase alfa: Adolescent Cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort	Total Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	9	7	20
Units: percent change				
arithmetic mean (standard deviation)				
Sphingomyelin: Pre-infusion at Week 52	-4.4 (± 24.6)	-37.1 (± 24.2)	-18.6 (± 40.3)	-24.1 (± 32.0)
Lyso-Sphingomyelin: Pre-infusion at Week 52	-84.050 (± 5.249)	-88.029 (± 8.156)	-87.951 (± 1.775)	-87.206 (± 5.998)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from first IMP administration up to 64 weeks regardless of seriousness or relationship to IMP. Reported AEs are treatment-emergent AEs that is AEs that developed/worsened during the 'on-treatment period'.

Adverse event reporting additional description:

Occurrences "related to treatment" only include events assessed as "related" by the investigator, and it does not include events assessed as "possibly related" by investigator. The other Non-serious adverse events section contains Events $\geq 2\%$ and subjects ≥ 2 . Analysis was performed on safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Olipudase alfa: Adolescent cohort
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Reporting group description:

Subjects aged 12 to <18 years received IV infusion of olipudase alfa Q2W for 64 weeks.

Reporting group title	Olipudase alfa: Child cohort
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Reporting group description:

Subjects aged 6 to <12 years received IV infusion of olipudase alfa Q2W for 64 weeks.

Reporting group title	Olipudase alfa: Infant/Early Child cohort
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Reporting group description:

Subjects aged <6 years received IV infusion of olipudase alfa Q2W for 64 weeks.

Reporting group title	Total Subjects
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Reporting group description:

All subjects received IV infusion of olipudase alfa Q2W for 64 weeks. Each subject underwent a dose escalation according to the following paradigm: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0 mg/kg. The target maintenance dose was 3.0 mg/kg, which was maintained for the remaining duration of the 64 treatment weeks.

Serious adverse events	Olipudase alfa: Adolescent cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	4 / 7 (57.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Femur Fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Talipes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Mycoplasmal			

subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Talipes			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia Mycoplasmal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Olipudase alfa: Adolescent cohort	Olipudase alfa: Child cohort	Olipudase alfa: Infant/Early Child cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	9 / 9 (100.00%)	7 / 7 (100.00%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	3 / 9 (33.33%)	3 / 7 (42.86%)
occurrences (all)	0	55	33
Scratch			
subjects affected / exposed	0 / 4 (0.00%)	2 / 9 (22.22%)	2 / 7 (28.57%)
occurrences (all)	0	36	8
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 4 (50.00%)	5 / 9 (55.56%)	1 / 7 (14.29%)
occurrences (all)	12	21	5
General disorders and administration			

site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	7 / 9 (77.78%) 24	7 / 7 (100.00%) 29
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 2 / 4 (50.00%) 5 2 / 4 (50.00%) 3	5 / 9 (55.56%) 19 5 / 9 (55.56%) 10 6 / 9 (66.67%) 21	1 / 7 (14.29%) 1 4 / 7 (57.14%) 7 4 / 7 (57.14%) 14
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 3 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	7 / 9 (77.78%) 15 3 / 9 (33.33%) 6 3 / 9 (33.33%) 5	5 / 7 (71.43%) 13 1 / 7 (14.29%) 11 3 / 7 (42.86%) 13
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	3 / 9 (33.33%) 13 2 / 9 (22.22%) 20	2 / 7 (28.57%) 3 1 / 7 (14.29%) 3
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection	2 / 4 (50.00%) 4 Upper Respiratory Tract Infection	5 / 9 (55.56%) 13 Upper Respiratory Tract Infection	4 / 7 (57.14%) 11 Upper Respiratory Tract Infection

subjects affected / exposed	0 / 4 (0.00%)	3 / 9 (33.33%)	5 / 7 (71.43%)
occurrences (all)	0	4	13

Non-serious adverse events	Total Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	88		
Scratch			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	44		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	38		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 20 (75.00%)		
occurrences (all)	56		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	11 / 20 (55.00%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	38		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 20 (70.00%)		
occurrences (all)	31		
Epistaxis			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal Congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 20 (20.00%)</p> <p>17</p> <p>6 / 20 (30.00%)</p> <p>18</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 20 (25.00%)</p> <p>16</p> <p>3 / 20 (15.00%)</p> <p>23</p>		
<p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper Respiratory Tract Infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 20 (55.00%)</p> <p>28</p> <p>8 / 20 (40.00%)</p> <p>17</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2015	Following changes were made: <ul style="list-style-type: none">• The International Nonproprietary Name (INN) olipudase alfa was recommended for recombinant human acid sphingomyelinas: Refinement of clinical laboratory assessments and safety biomarker assessments in the child and early child/infant age cohorts;• Correction of typographical error in exclusion criteria: The SMPD1 gene mutation was corrected to R496L;• Replacement of cognitive and adaptive function assessment tools: Modification to pregnancy reporting requirements: Pregnancy was reported as an adverse event per updates to the sponsor's standard operating procedures.
13 November 2015	Following changes were made: <ul style="list-style-type: none">• Pharmacokinetic sample collection schedule was modified: The Food and Drug Administration recommended the inclusion of a 96 hour pharmacokinetic sample. In order to avoid increased subject burden and increased blood collection volumes in pediatric subjects, the 72 hour pharmacokinetic sample in the adolescent cohort was to be replaced by a 96 hour sample. As a result of this change the 60-72 hour sample window in the child and infant/early child cohorts was to be replaced by an 84-96 hour sample window.
18 February 2016	Following changes were made <ul style="list-style-type: none">• Extension of the olipudase alfa treatment period to 64 weeks.• subjects stopping criteria was clarified.• Removal of a desensitization regimen with acute or recurrent adverse events suggestive of a hypersensitivity reaction with a positive immunoglobulin E titer.• Removal of consolidation as a qualitative high resolution computed tomography (HRCT) assessment.• overdose definition was updated.
21 August 2017	Following changes were made <ul style="list-style-type: none">• Included enrolment of at least 8 additional ASMD subjects < 12 years of age: additional acid sphingomyelinase deficiency (ASMD) subjects <12 years were enrolled to evaluate the safety, tolerability, PK, Pharmacodynamic, and exploratory efficacy of olipudase alfa manufactured using the intended commercial process and scale.• Guidelines for Serious Adverse Event and adverse event of special interest (AESIs) were modified to be consistent with other ongoing studies and take into account the underlying disease.• Updated dose limiting toxicity (DLT) subject stopping criteria to be consistent with other ongoing studies and as agreed upon by the data monitoring committee (DMC).• Updated addition of recommendation on usage of cationic amphiphilic antihistamines in rules on concomitant medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported