Clinical trial results:
A Phase 2/3, Multicenter, Randomized, Double-blinded, Placebo-controlled, Repeat-dose Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency

Summary

EudraCT number	2015-000371-26
Trial protocol	DE GB NL FR PT ES IT BE
Global end of trial date	

Results information

Result version number	v1
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	DFI12712

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02004691
WHO universal trial number (UTN)	U1111-1142-5963

Notes:

Sponsors

Sponsor organisation name	Sanofi Genzyme
Sponsor organisation address	450 Water Street, Cambridge, MA, United States, 02141
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)	No
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	Interim
Date of interim/final analysis	15 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this Phase 2/3 study was to evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult subjects with acid sphingomyelinase deficiency (ASMD) by assessing changes in: 1) spleen volume as measured by abdominal magnetic resonance imaging (MRI); for the United States (US) only, the primary objective was spleen volume in association with subject perception related to spleen volume as measured by splenomegaly-related score (SRS), and 2) infiltrative lung disease as measured by the pulmonary function test diffusing capacity of the lung for carbon monoxide (DLco).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 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	Australia: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Brazil: 4
Worldwide total number of subjects	36
EEA total number of subjects	14

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	35
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 active centers in 17 countries. A total of 62 subjects were screened between 18 December 2015 and 1 October 2018, out of which 36 subjects were randomised.

Pre-assignment

Screening details:

A total of 18 subjects each were randomised to the placebo and the olipudase alfa groups, respectively. Data reported based on date, 15 March 2021. Primary Analysis Period (PAP) is complete.

Period 1

Period 1 title	PAP: Up to 52 Weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received intravenous (IV) infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of primary analysis period (PAP). Subjects who completed PAP entered in extension treatment period (ETP) and crossed over to olipudase alfa with a target maintenance dose of 3 milligram per kilogram (mg/kg) after dose escalation.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (matched to olipudase alfa) IV infusion once every 2 weeks during the 52 weeks of PAP.

Arm title	Olipudase alfa

Arm description:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.

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

Dosage and administration details:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. The dose was escalated to a target dose of 3.0 mg/kg of olipudase alfa.

Number of subjects in period 1	Placebo	Olipudase alfa
Started	18	18
Completed	17	18
Not completed	1	0
Poor compliance	1	-

Period 2

Period 2 title	ETP: Ongoing From Week 52
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Placebo/Olipudase alfa: PAP/ETP

Arm description:

Subjects received IV infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of PAP. Subjects who completed PAP entered in ETP and crossed over to olipudase alfa with a target maintenance dose of 3 mg/kg after dose escalation.

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

Dosage and administration details:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. The dose was escalated to a target dose of 3.0 mg/kg of olipudase alfa.

Arm title	Olipudase alfa/Olipudase alfa: PAP/ETP

Arm description:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.

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

Dosage and administration details:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. The dose was escalated to a target dose of 3.0 mg/kg of olipudase alfa.

Number of subjects in period 2	Placebo/Olipudase alfa: PAP/ETP	Olipudase alfa/Olipudase alfa: PAP/ETP
Started	17	18
Completed	0	0
Not completed	17	18
Consent withdrawn by subject	-	1
Related to Coronavirus Disease (COVID-19)	1	-
Ongoing	16	16
Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received intravenous (IV) infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of primary analysis period (PAP). Subjects who completed PAP entered in extension treatment period (ETP) and crossed over to olipudase alfa with a target maintenance dose of 3 milligram per kilogram (mg/kg) after dose escalation.	
Reporting group title	Olipudase alfa
Reporting group description:	
Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.	

Reporting group values	Placebo	Olipudase alfa	Total
Number of subjects	18	18	36
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.46	36.17	
standard deviation	± 17.06	± 12.72	-
Gender categorical Units: Subjects			
Female	13	9	22
Male	5	9	14
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	2
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	16	16	32
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Other	1	1	2

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received intravenous (IV) infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of primary analysis period (PAP). Subjects who completed PAP entered in extension treatment period (ETP) and crossed over to olipudase alfa with a target maintenance dose of 3 milligram per kilogram (mg/kg) after dose escalation.

Reporting group title	Olipudase alfa

Reporting group description:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.

Reporting group title	Placebo/Olipudase alfa: PAP/ETP

Reporting group description:

Subjects received IV infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of PAP. Subjects who completed PAP entered in ETP and crossed over to olipudase alfa with a target maintenance dose of 3 mg/kg after dose escalation.

Reporting group title	Olipudase alfa/Olipudase alfa: PAP/ETP

Reporting group description:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.

Primary: Percent Predicted (% Predicted) Hemoglobin (Hb) and Altitude-Adjusted Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Baseline

End point title	Percent Predicted (% Predicted) Hemoglobin (Hb) and Altitude-Adjusted Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Baseline[1]

End point description:

Percent predicted Hb and Altitude-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) times Hemoglobin-adjusted factor times Altitude-adjustment factor. Analysis was performed on modified intent-to-treat (mITT) population which included all randomised subjects who had received at least 1 infusion (partial or total) and were analysed according to the treatment arm allocated by randomisation.

End point type	Primary

End point timeframe:

Baseline (Day 1)

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 Baseline endpoint was descriptive in nature, no statistical analysis was performed.

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: % Predicted DLco				
arithmetic mean (standard deviation)	48.45 (± 10.76)	49.44 (± 10.99)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Percent Predicted (% Predicted) Hemoglobin (Hb) and Altitude-Adjusted Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Week 52

End point title	Percent Change from Baseline in Percent Predicted (% Predicted) Hemoglobin (Hb) and Altitude-Adjusted Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Week 52

End point description:

Percent predicted Hb and Altitude-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) times Hemoglobin-adjusted factor times Altitude-adjustment factor. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: percent change				
least squares mean (standard error)	2.961 (± 3.3832)	21.968 (± 3.3362)		

Statistical analyses

Statistical analysis title	Placebo, Olipudase alfa
Comparison groups	Olipudase alfa v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0004 [3]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares Mean Difference
Point estimate	19.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.319
upper limit	28.696

Variability estimate	Standard error of the mean
Dispersion value	4.7576

Notes:

[2] - The 95% Confidence Interval (CI) and p-values were based on mixed model for repeated measures approach with Baseline Derived % Predicted DLco adjusted for Hb and pressure, age, treatment group, visit, and study visit by treatment group as covariates.
[3] - Threshold for significance was 0.05.

Primary: Spleen Volume (in MN) at Baseline

End point title	Spleen Volume (in MN) at Baseline[4]

End point description:

Spleen volume was assessed by abdominal magnetic resonance imaging (MRI) to quantitate the degree of splenomegaly in multiples of normal (MN). Analysis was performed on mITT population.

End point type	Primary

End point timeframe:

Baseline (Day 1)

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 Baseline endpoint was descriptive in nature, no statistical analysis was performed.

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: multiples of normal (MN)				
arithmetic mean (standard deviation)	11.21 (± 3.84)	11.69 (± 4.92)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Spleen Volume (in MN) at Week 52

End point title	Percent Change from Baseline in Spleen Volume (in MN) at Week 52

End point description:

Spleen volume was assessed by abdominal MRI to quantitate the degree of splenomegaly in MN. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: percent change				
least squares mean (standard error)	0.481 (± 2.5002)	-39.446 (± 2.4294)		

Statistical analyses

Statistical analysis title	Placebo, Olipudase alfa
Comparison groups	Placebo v Olipudase alfa
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-39.927
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.051
upper limit	-32.803
Variability estimate	Standard error of the mean
Dispersion value	3.4957

Notes:

[5] - The 95% CI and p-values were based on a mixed model for repeated measures approach with Baseline Spleen Volume (MN), Baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
[6] - Threshold for significance was 0.05.

Secondary: Percent Change from Baseline in Liver Volume (in MN) at Week 52

End point title	Percent Change from Baseline in Liver Volume (in MN) at Week 52

End point description:

Liver volume was assessed by abdominal MRI in MN. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: percent change				
least squares mean (standard error)	-1.468 (± 2.5409)	-28.064 (± 2.4899)		

Statistical analyses

Statistical analysis title	Placebo, Olipudase alfa

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in an order the endpoint were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Olipudase alfa
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-26.596
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.911
upper limit	-19.281
Variability estimate	Standard error of the mean
Dispersion value	3.5862

Notes:

[7] - The 95% CI and p-values are based on a mixed model for repeated measures approach with Baseline Liver Volume (MN), Baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
[8] - Threshold for significance was 0.05.

Secondary: Percent Change from Baseline in Platelet Counts at Week 52

End point title	Percent Change from Baseline in Platelet Counts at Week 52

End point description:

Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: percent change				
least squares mean (standard error)	2.490 (± 4.1923)	16.822 (± 3.9596)		

Statistical analyses

Statistical analysis title	Placebo, Olipudase alfa

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed

sequentially in an order the outcome measure were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Olipudase alfa
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0185 [10]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares Mean Difference
Point estimate	14.332
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.564
upper limit	26.099
Variability estimate	Standard error of the mean
Dispersion value	5.7822

Notes:

[9] - The 95% CI and p-values are based on a mixed model for repeated measures approach with Baseline Platelets, Baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
[10] - Threshold for significance was 0.05.

Secondary: Change from Baseline in Fatigue Severity as Measured by Brief Fatigue Inventory (BFI)-Item 3 Scale Score at Week 52

End point title	Change from Baseline in Fatigue Severity as Measured by Brief Fatigue Inventory (BFI)-Item 3 Scale Score at Week 52

End point description:

The BFI is a 9-item, validated, self-administered questionnaire that was originally developed to assess fatigue severity. The 9-items were measured on a 0-10 scale, with 0 being 'does not interfere' and 10 being 'completely interferes.' BFI - Item 3 asks subjects to "Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your worst level of fatigue during the past 24 hours. Numerical rating scale ranges from 0 (no fatigue) to 10 (worst imaginable fatigue). Higher global scores were associated with more severe fatigue. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: score on a scale				
least squares mean (standard error)	-1.806 (± 0.5272)	-1.862 (± 0.5129)		

Statistical analyses

Statistical analysis title	Placebo, Olipudase alfa

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in an order the endpoint were reported and continued when previous endpoint was statistically significant at two-sided 0.05.

Comparison groups	Placebo v Olipudase alfa
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.94 [12]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.566
upper limit	1.454
Variability estimate	Standard error of the mean
Dispersion value	0.7384

Notes:

[11] - The 95% CI and p-values are based on a mixed model for repeated measures approach with Baseline BFI item 3 (Worst Fatigue), Baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
[12] - Threshold for significance was 0.05.

Secondary: Change from Baseline in Pain Severity as Measured by Brief Pain Inventory-Short Form (BPI-SF)-Item 3 Scale Score at Week 52

End point title	Change from Baseline in Pain Severity as Measured by Brief Pain Inventory-Short Form (BPI-SF)-Item 3 Scale Score at Week 52

End point description:

The BPI-SF is a validated, self-administered questionnaire designed to measure a subject's perceived level of pain. The BPI-SF consisted of 15 items that use a numeric rating scale to assess pain severity and pain interference in the past 24 hours and the past week. For BPI-SF Item 3 asks subjects to "Please rate your pain by marking the box beside the number that best describes your pain at its worst in the past 24 hours." The numeric rating scale ranged from 0 (no pain) to 10 (worst imaginable pain), where higher scores indicate greater intensity of pain. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: score on a scale				
least squares mean (standard error)	-2.293 (± 0.5899)	-1.404 (± 0.5742)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Dyspnea Severity as Measured by Functional Assessment of Chronic Illness Therapy (FACIT) Dyspnea Scale at Week 52

End point title	Change from Baseline in Dyspnea Severity as Measured by Functional Assessment of Chronic Illness Therapy (FACIT) Dyspnea Scale at Week 52

End point description:

FACIT-Dyspnea: 20 Item assessment split into two 10-item sections. First 10-item section asks subjects about severity of their shortness of breath during various activities. Second 10-item section asks subjects to rate difficulty due to shortness of breath associated with same activities that were referenced in first section. For dyspnea severity items, score range from 0=no shortness of breath; 1=mildly short of breath; 2=moderately short of breath; 3=severely short of breath. For functional limitation items, score range from no difficult=0, A little difficult=1, some difficult=2, and much difficulty=3. Raw score was calculated as: sum of individual item scores*10/number of items answered. Raw scores were then converted to scale scores using table included in FACIT Dyspnea Scale Short Form Scoring Guideline. FACIT dyspnea scale score range: 27.7 to 75.9. Higher score represented high levels of dyspnea. mITT population. Number of subjects analysed=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: score on a scale				
least squares mean (standard error)	-6.769 (± 1.9132)	-5.862 (± 1.6918)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Splenomegaly-Related Score (SRS) at Week 52

End point title	Change From Baseline in Splenomegaly-Related Score (SRS) at Week 52

End point description:

The SRS rates 5 items: abdominal pain, abdominal discomfort, early satiety, dissatisfaction with abdominal body image, and difficulty to bend down using a numerical rating scale of 0 (absent) to 10 (worst imaginable). The total score of SRS ranges from 0 to 50, with higher scores (50) indicated worst imaginable rating. Analysis was performed on mITT population. Here, number of subjects analysed = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo	Olipudase alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: score on a scale				
least squares mean (standard error)	-9.281 (± 2.4165)	-7.664 (± 2.3481)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from time from first infusion of investigational medicinal product (IMP) to time just prior to first infusion in extension treatment period i.e. up to 52 weeks of PAP regardless of seriousness or relationship to IMP

Adverse event reporting additional description:

Reported AEs were Treatment Emergent Adverse Events (TEAEs) i.e AEs that developed/worsened during treatment epoch for PAP (time from first infusion of IMP to time just prior to first infusion in ETP if subject had an infusion in ETP or to last date data are available if subject had no infusion in ETP i.e. up to Week 52). Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received IV infusion of placebo (matched to olipudase alfa) once every 2 weeks during the 52 weeks of PAP. Subjects who completed PAP entered in ETP and crossed over to olipudase alfa with a target maintenance dose of 3 mg/kg after dose escalation.

Reporting group title	Olipudase alfa

Reporting group description:

Subjects received IV infusion of olipudase alfa once every 2 weeks during the 52 weeks of PAP. Each subject underwent a dose escalation according to the following paradigm: 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, 3.0, 3.0 mg/kg. Three (3) mg/kg was the target maintenance dose, which was maintained for the remaining duration of 52 weeks of PAP. Subjects who completed PAP entered in ETP and continued the same treatment in ETP.

Serious adverse events	Placebo	Olipudase alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 18 (22.22%)	3 / 18 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lower Limb Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock Haemorrhagic			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (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			
Syncope			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (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			
Appendicitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis Viral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (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: 2 %

Non-serious adverse events	Placebo	Olipudase alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	17 / 18 (94.44%)	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 18 (44.44%)	12 / 18 (66.67%)	
occurrences (all)	32	64	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 18 (11.11%)	5 / 18 (27.78%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 18 (16.67%)	4 / 18 (22.22%)	
occurrences (all)	3	10	
Infections and infestations			
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 18 (22.22%)	6 / 18 (33.33%)	
occurrences (all)	6	8	
Nasopharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 18 (33.33%)	8 / 18 (44.44%)	
occurrences (all)	8	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2014	Following changes were made: modification of study title, study organisation, study design, study objectives, changes to assessments.
05 December 2014	Following changes were made: changed rhASM nomenclature; the primary endpoint was modified to include change from baseline to week 52 in infiltrative lung disease as measured by the diffusing capacity of carbon monoxide (DLco); removed key secondary endpoint and reorganized the secondary endpoints; added a PK sampling timepoint; increased the number of enrolled subjects from approximately 24 to approximately 35; removed requirement to stratify subjects based on baseline spleen volume; subjects assigned to the placebo arm in the PAP were rerandomised 1:1 in the ETP to 1.0 mg/kg or 3.0 mg/kg olipudase alfa; added an interim analysis of the primary endpoint after approximately 20 subjects completed 52 weeks of treatment with study drug.
28 January 2015	New EudraCT number updated.
08 May 2015	Following changes were made: added splenomegaly-related symptom efficacy endpoint; changes in the tools used to collect information for the composite secondary efficacy endpoint and included use of an eDiary; clarified that abdominal MRIs and pulmonary imaging by HRCT will be evaluated by readers blinded to subject, treatment arm, and timepoint; demoted to tertiary the secondary efficacy endpoint percentage change in liver function tests ALT and total bilirubin; removed requirement that inpatient hospitalisation was necessary during quarterly visits of years 3 through 5; added a provision for future use of samples; corrected reporting requirements for pregnancy; clarified the "Not applicable" taken regarding action to study drug for an AE; changed the Wilcoxon Mann Whitney test to the ANCOVA method for primary and secondary efficacy endpoint analyses.
01 February 2016	Following changes were made: removed 1.0 mg arm from the PAP; removed 1.0 mg arm from the ETP; removed "dose comparison"; changed randomisation ratio from 2:1:2 to 1:1 during the PAP; added inclusion criterion for mean splenomegaly-related symptoms score; added contraception requirements following the last olipudase alfa infusion; clarified that the longest study duration per subject will be for at least 3 years and up to 5 years and 3 months dependent upon continued regulatory approval of the protocol; changed interim analysis wording from "interim analysis may be conducted" to "no interim analysis is planned"; clarified subject stopping criteria.
08 February 2017	Following changes were made: changes in objectives and endpoints; addition of Patient Global Impression of Symptom Severity (PGIS) of ASMD and Patient Global Impression of Change (PGIC); changes in statistical analysis; clarification of time points at which vital signs should be taken; addition of rules on how to resume study drug administration in subjects who have missed infusion; change in some of the dose limiting toxicity (DLT) conditions; change in assessments to be done before rescue treatment was applied; addition of recommendation on usage of cationic amphiphilic antihistamines in rules on concomitant medications; added tobacco use monitoring.
24 August 2017	Following changes were made: change in 7.2 Exclusion Criteria to include subjects with non-melanoma skin cancer and simplify language; added Lab Values that already were part of Adverse Events of Special Interest (AESIs) to the relevant sections and table; corrected discrepancy of PK Collection; replaced all instances of "after infusion" text with "after the end of infusion" where applicable.

26 January 2018	Following changes were made: change in subject selection criteria to remove cirrhosis from Exclusion criteria; removed liver biopsy from assessments beyond Week 104; changed the secondary endpoints hierarchical order; clarified language of exclusion criteria.
18 September 2018	This amendment was made to clarify that portal hypertension would be detected for all subjects using already existing liver ultrasound echo parameters and also to clarify language in statistical analysis and pharmacokinetic assessments.
05 December 2018	This amendment was made to include the immunogenicity schedule of analysis to be followed in case of drug product from an updated manufacturing process is administered. Also, the language of dose reescalation was clarified.
12 August 2019	This amendment was made to indicate the different assessments that will be done after manufacturing process update as per regulatory authorities requirements. Previous omissions and errors were corrected. Clarified the plans for interim Clinical Study Report(s).
15 April 2020	This amendment was made to provide option of home infusion during the COVID-19 pandemic for eligible subjects during the ETP in compliance with applicable country specific regulations and in case of multiple missing infusions, to clarify the process of dose reintroduction, and change the reintroduction starting dose. Previous omissions and errors were corrected. To allow safer reintroduction at a lower level in case of missing >=3 infusions; updated hospitalisation requirements to be more flexible at PI discretion regarding quarterly and yearly visits in ETP.
02 February 2021	Following changes were made: 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) IMP to the updated manufacturing Process C(32) IMP, 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 (LFT) monitoring post infusion was already included in this protocol. However, review of the interim data from the clinical development program has 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 have been added to the protocol; conduct of treatment experience interviews to understand subject’s experience living with acid sphingomyelinase deficiency (ASMD) and participating in this study was added; assessments have been streamlined to reduce subject burden in the extension phase of this trial. Assessments to ensure subject safety have been 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 on 17 October 2019 was at the end of the PAP); other changes, omissions and corrections were addressed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported