Clinical trial results:
A Phase 3 Randomized, Multicenter, Multinational, Double-blinded Study Comparing the Efficacy and Safety of Repeated Biweekly Infusions of Avalglucosidase Alfa (neoGAA, GZ402666) and Alglucosidase Alfa in Treatment naïve Patients with Late-onset Pompe Disease

Summary

EudraCT number	2016-000942-77
Trial protocol	GB DK SE NL ES CZ DE BE AT PL IT PT BG HU Outside EU/EEA
Global end of trial date	31 May 2023

Results information

Result version number	v2 (current)
This version publication date	07 December 2023
First version publication date	12 June 2021
Version creation reason	• New data added to full data set Final results that include data of secondary endpoints

Trial information

Trial identification

Sponsor protocol code	EFC14028

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02782741
WHO universal trial number (UTN)	U1111-1178-4806

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation, A Sanofi company
Sponsor organisation address	500 Kendall Street, 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)	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	Final
Date of interim/final analysis	31 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of avalglucosidase alfa treatment on respiratory muscle strength measured by percent (%) predicted forced vital capacity (% FVC) in the upright position, as compared to alglucosidase alfa.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric and adult 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 minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia might have been used to minimise distress and discomfort. Adult 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:

Alglucosidase alfa, a globally approved standard-of-care treatment, was used as a comparator in the blinded treatment period which was also known as primary analysis period (PAP).

Actual start date of recruitment	02 November 2016
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	Netherlands: 5
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 7

Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Turkey: 3
Worldwide total number of subjects	101
EEA total number of subjects	41

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)	1
Adolescents (12-17 years)	1
Adults (18-64 years)	85
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study: Conducted at 69 centers. 149 subjects were screened between 02 November 2016 and 22 March 2019, of which 100 subjects were enrolled and randomized (1:1 ratio) to receive avalglucosidase alfa or alglucosidase alfa. 48 subjects: screening failures. 1 pediatric participant entered open-label treatment period directly.

Pre-assignment

Screening details:

Randomization was stratified by baseline % predicted FVC: less than (<) 55% or greater than or equal to (>=) 55%, gender, age (<18 years and >=18 years), and country (Japan or ex- Japan). Data reported based on study completion date, i.e. 31 May 2023.

Period 1

Period 1 title	Blinded Treatment Period: up to Week 49
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Avalglucosidase Alfa-PAP

Arm description:

Avalglucosidase alfa 20 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (q2w) up to Week 49 in blinded treatment period (also known as primary analysis period [PAP]).

Arm type	Experimental
Investigational medicinal product name	Avalglucosidase alfa
Investigational medicinal product code	neoGAA, GZ402666
Other name	Nexviadyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg, IV infusion q2w for a total of 25 doses.

Arm title	Alglucosidase Alfa-PAP

Arm description:

Alglucosidase alfa 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).

Arm type	Active comparator
Investigational medicinal product name	Alglucosidase alfa
Investigational medicinal product code	
Other name	Myozyme® and Lumizyme®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg, IV infusion q2w for a total of 25 doses.

Number of subjects in period 1[1]	Avalglucosidase Alfa-PAP	Alglucosidase Alfa-PAP
Started	51	49
Safety Population	51	49
Completed	51	44
Not completed	0	5
Adverse event, non-fatal	-	4
Unspecified	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 pediatric participant entered open-label treatment period directly.

Period 2

Period 2 title	Open-label Long-term: Week 50-289
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Avalglucosidase Alfa-Open-label After Avalglucosidase Alfa-PAP

Arm description:

Avalglucosidase alfa 20 mg/kg IV infusion q2w from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.

Arm type	Experimental
Investigational medicinal product name	Avalglucosidase alfa
Investigational medicinal product code	neoGAA, GZ402666
Other name	Nexviadyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg, IV infusion q2w for a total 48 doses.

Arm title	Avalglucosidase Alfa-Open-label After Alglucosidase Alfa-PAP

Arm description:

Avalglucosidase alfa 20 mg/kg IV infusion q2w from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.

Arm type	Active comparator
Investigational medicinal product name	Alglucosidase alfa
Investigational medicinal product code	
Other name	Myozyme® and Lumizyme®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg, IV infusion q2w for a total 48 doses.

Number of subjects in period 2	Avalglucosidase Alfa-Open-label After Avalglucosidase Alfa-PAP	Avalglucosidase Alfa-Open-label After Alglucosidase Alfa-PAP
Started	51	44
Safety Population	51	44
Completed	44	36
Not completed	7	8
Adverse event, non-fatal	2	3
Unspecified	5	4
Poor compliance to protocol	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Avalglucosidase Alfa-PAP
Reporting group description:	
Avalglucosidase alfa 20 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (q2w) up to Week 49 in blinded treatment period (also known as primary analysis period [PAP]).	
Reporting group title	Alglucosidase Alfa-PAP
Reporting group description:	
Alglucosidase alfa 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).	

Reporting group values	Avalglucosidase Alfa-PAP	Alglucosidase Alfa-PAP	Total
Number of subjects	51	49	100
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	46.0	50.3	
standard deviation	± 14.5	± 13.7	-
Gender categorical			
Units: Subjects			
Female	24	24	48
Male	27	25	52
Race			
Units: Subjects			
Asian	3	0	3
Black or African American	1	2	3
White	47	47	94
Percent Predicted FVC in Upright Position			
Measure Description: FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air (in litres) that can be forcibly blown out after full inspiration in the upright position.			
Units: percent predicted FVC			
arithmetic mean	62.5	61.6	
standard deviation	± 14.4	± 12.4	-

End points

End points reporting groups

Reporting group title	Avalglucosidase Alfa-PAP
Reporting group description:	
Avalglucosidase alfa 20 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (q2w) up to Week 49 in blinded treatment period (also known as primary analysis period [PAP]).	
Reporting group title	Alglucosidase Alfa-PAP
Reporting group description:	
Alglucosidase alfa 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).	
Reporting group title	Avalglucosidase Alfa-Open-label After Avalglucosidase Alfa-PAP
Reporting group description:	
Avalglucosidase alfa 20 mg/kg IV infusion q2w from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.	
Reporting group title	Avalglucosidase Alfa-Open-label After Alglucosidase Alfa-PAP
Reporting group description:	
Avalglucosidase alfa 20 mg/kg IV infusion q2w from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.	
Subject analysis set title	PAP: Avalglucosidase Alfa
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Avalglucosidase alfa, 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).	
Subject analysis set title	PAP: Alglucosidase Alfa
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Alglucosidase alfa, 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).	

Primary: PAP: Change From Baseline in Percent Predicted FVC in Upright Position at Week 49

End point title	PAP: Change From Baseline in Percent Predicted FVC in Upright Position at Week 49
End point description:	
FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air (in litres) that can be forcibly blown out after full inspiration in the upright position. Least square (LS) mean and standard error (SE) were derived from mixed model for repeated measure (MMRM) model with Baseline FVC (% predicted, as continuous), sex, age (in years at Baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects. Percent of predicted FVC = (actual FVC measurement)/(predicted value of FVC) * 100. After non-inferiority (NI) testing, a test for superiority of avalglucosidase alfa versus alglucosidase alfa was performed with an overall 2- sided 5% level of significance. 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, Week 49	

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: percent predicted FVC				
least squares mean (standard error)	2.89 (± 0.88)	0.46 (± 0.93)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

Analysis performed using MMRM model with Baseline FVC (% predicted, as continuous), sex, age (in years at Baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0074
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	4.99
Variability estimate	Standard error of the mean
Dispersion value	1.29

Notes:

[1] - NI was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the difference of avalglucosidase alfa minus alglucosidase alfa was greater than (>) -1.1.

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

Analysis performed using MMRM model with Baseline FVC (% predicted, as continuous), sex, age (in years at Baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0626 [3]
Method	MMRM

Notes:

[2] - A test for superiority of avalglucosidase alfa versus alglucosidase alfa was performed with an overall 5% level of significance.
[3] - Threshold for significance at <0.05 level.

Secondary: PAP: Change From Baseline in Total Distance Walked During Six-minute Walk Test (6MWT) at Week 49

End point title	PAP: Change From Baseline in Total Distance Walked During Six-minute Walk Test (6MWT) at Week 49

End point description:

6MWT was a standardised test that measured the distance (in metres) covered by the subject by walking on a flat, hard surface in a period of a 6-minute walk. Mean distance walked gives an indication of functional endurance. The greater the distance (that a subject could walk in 6 minutes), the greater the endurance. LS mean and SE were derived from MMRM model with Baseline FVC (% predicted) and Baseline 6MWT (distance walked in metre), age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: metres				
least squares mean (standard error)	32.21 (± 9.93)	2.19 (± 10.40)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa Versus Alglucosidase Alfa

Statistical analysis description:

LS mean difference was derived from MMRM model with Baseline FVC (% predicted) and Baseline 6MWT (distance walked in metre), age (in years, at Baseline), gender, treatment group, visit, and treatment-by- visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0405
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	30.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	58.69
Variability estimate	Standard error of the mean
Dispersion value	14.43

Notes:

[4] - Per the protocol-defined statistical test strategy for multiplicity adjustment, and since superiority was narrowly missed for FVC % predicted, superiority testing for the secondary endpoints couldn’t be performed.

Secondary: PAP: Change From Baseline in Percent Predicted Maximal Inspiratory Pressure (MIP) in Upright Position at Week 49

End point title	PAP: Change From Baseline in Percent Predicted Maximal Inspiratory Pressure (MIP) in Upright Position at Week 49

End point description:

MIP is a quick and non-invasive test to measure strength of inspiratory muscles, primarily diaphragm, and allows for assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength. MIP refers to how much air pressure force an individual creates by inhaling through the mouth as hard as possible. LS mean and SE were derived from MMRM model for MIP % predicted adjusted for MIP % predicted at Baseline, age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: percent predicted MIP				
least squares mean (standard error)	0.17 (± 3.60)	-2.96 (± 3.79)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

LS mean difference was derived from MMRM model for MIP % predicted adjusted for MIP % predicted at Baseline, age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.5522
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.31
upper limit	13.57
Variability estimate	Standard error of the mean
Dispersion value	5.24

Notes:

[5] - Per the protocol-defined statistical test strategy for multiplicity adjustment, and since superiority was narrowly missed for FVC % predicted, superiority testing for the secondary endpoints couldn’t be performed.

Secondary: PAP: Change From Baseline in Percent Predicted Maximal Expiratory Pressure (MEP) in Upright Position at Week 49

End point title	PAP: Change From Baseline in Percent Predicted Maximal Expiratory Pressure (MEP) in Upright Position at Week 49

End point description:

MEP is a quick and non-invasive test to measure strength of expiratory muscles, primarily diaphragm, and allows for assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength. MEP is the greater pressure generated during maximal expiration. LS mean and SE was derived from MMRM model for MEP % predicted adjusted for MEP % predicted at Baseline, age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: percent predicted MEP				
least squares mean (standard error)	3.02 (± 3.87)	4.95 (± 4.07)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

LS mean difference was derived from MMRM model for MEP % predicted adjusted for MEP % predicted at Baseline, age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.7321
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.17
upper limit	9.29
Variability estimate	Standard error of the mean
Dispersion value	5.64

Notes:

[6] - Per the protocol-defined statistical test strategy for multiplicity adjustment, and since superiority was narrowly missed for FVC % predicted, superiority testing for the secondary endpoints couldn’t be performed.

Secondary: PAP: Change From Baseline in Lower Extremity Muscle Strength at Week 49 as Assessed by Hand-Held Dynamometry (HHD)

End point title	PAP: Change From Baseline in Lower Extremity Muscle Strength at Week 49 as Assessed by Hand-Held Dynamometry (HHD)

End point description:

HHD: portable method for strength quantitation. To complete a make test, subject exerted maximal force against dynamometer with gradual increase in force and completed isometric hold for 4-5 seconds. Muscle strengths were collected in Newton. Every muscle group (hip: flexion, extension, abduction; knee: flexion, extension and ankle dorsiflexion) were measured 2 times and highest value was reported. Summary score: sum of 12 measurements (2 measurements per muscle group) from 6 muscle groups on each side (left and right). Increase from Baseline was reflective of increased muscle strength, whereas decrease from Baseline was reflective of decreased muscle strength. LS mean and SE were derived from MMRM model for HHD lower extremity muscle strength composite score adjusted for summary HHD lower extremity score at Baseline, Baseline FVC (% predicted), age (in years, at Baseline), gender, treatment group, visit and treatment-by-visit interaction as fixed effects. Analysed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: newton				
least squares mean (standard error)	260.69 (± 46.07)	153.72 (± 48.54)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

LS mean difference was derived from MMRM model for HHD lower extremity muscle strength composite score adjusted for summary HHD lower extremity score at Baseline, Baseline FVC (% predicted), age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.115
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	106.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.56
upper limit	240.5
Variability estimate	Standard error of the mean
Dispersion value	67.17

Notes:

[7] - Per the protocol-defined statistical test strategy for multiplicity adjustment, and since superiority was narrowly missed for FVC % predicted, superiority testing for the secondary endpoints couldn't be performed.

Secondary: PAP: Change From Baseline in Quick Motor Function Test (QMFT) Total Scores at Week 49

End point title	PAP: Change From Baseline in Quick Motor Function Test (QMFT) Total Scores at Week 49

End point description:

The QMFT was an observer administered test to evaluate changes in motor function. QMFT comprised of 16 items specifically difficult for subjects with Pompe disease. Each item was scored separately on a 5-point ordinal scale (ranged from 0 to 4, higher score indicated better outcome). Total QMFT score was obtained by adding the scores of all items and ranged from 0 (unable to perform motor function tests) to 64 (normal muscle function), higher score represented better outcome. LS mean and SE were derived from MMRM models adjusted for total QMFT score at Baseline, Baseline FVC (% predicted), age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: scores on a scale				
least squares mean (standard error)	3.98 (± 0.63)	1.89 (± 0.69)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

LS mean difference was derived from MMRM models adjust for total QMFT score at baseline, baseline FVC (% predicted), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0288
Method	mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	3.95

Variability estimate	Standard error of the mean
Dispersion value	0.94

Secondary: PAP: Change From Baseline in 12-Item Short-Form Health Survey (SF-12): Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores at Week 49

End point title	PAP: Change From Baseline in 12-Item Short-Form Health Survey (SF-12): Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores at Week 49

End point description:

SF-12: 12 item-questionnaire, assessed health-related quality of life in subjects aged >=18 years at screening/Baseline. 12 items were categorised into 8 domains (subscales) of functioning and well-being: physical functioning, role-physical, role emotional, mental health, bodily pain, general health, vitality and social functioning, with each domain score range: 0 (poor health) to 100 (better health), higher scores=good health condition. These 8 domains were further summarised into 2 summary scores, PCS and MCS. Score range for each of these 2 summary scores was from 0 (poor health) to 100 (better health), higher scores=better health-related quality of life. LS mean and SE were derived from MMRM models adjust for Baseline score (PCS or MCS), Baseline FVC (% predicted), age (in years, at Baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Analysed on mITT population. Here, 'number of subjects analysed'=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: scores on a scale				
least squares mean (standard error)				
PCS score	2.37 (± 0.99)	1.60 (± 1.07)		
MCS score	2.88 (± 1.22)	0.76 (± 1.32)		

Statistical analyses

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

The MMRM models adjust for baseline score (PCS), baseline FVC (% predicted), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5996
Method	mixed model for repeated measures
Parameter estimate	Score difference
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	3.67
Variability estimate	Standard error of the mean
Dispersion value	1.46

Statistical analysis title	Avalglucosidase Alfa versus Alglucosidase Alfa

Statistical analysis description:

The MMRM models adjust for baseline score (MCS), baseline FVC (% predicted), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

Comparison groups	PAP: Avalglucosidase Alfa v PAP: Alglucosidase Alfa
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2427
Method	mixed model for repeated measures
Parameter estimate	Score difference
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	5.69
Variability estimate	Standard error of the mean
Dispersion value	1.8

Secondary: PAP: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Infusion-Associated Reactions (IARs)

End point title	PAP: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Infusion-Associated Reactions (IARs)

End point description:

AE: any untoward medical occurrence in subject who had drug and not necessarily had causal relationship with treatment. TEAEs:AEs-developed/worsened in grade/became serious during TEAE period in PAP (from time of 1st treatment date to last treatment date+4 weeks for subjects who didn't take any treatment in open-label or to time just prior to 1st treatment in open-label for subjects who had treatment in open-label). Protocol-defined IARs:AE of special interest (AESIs)-occurred during either infusion/observation period after infusion; deemed to be related/possibly related to drug. Algorithm-defined IARs: any TEAE meeting either criteria 1) event occurred from start to end of infusion+24 hours, considered related to drug or 2) If AE time component missed, compare AE start date with infusion start and end date. If AE start date was between infusion start and end date+1 day and related to drug. safety population:subjects who had at least 1 infusion (partial/total); analysed per treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: subjects				
Any TEAE	44	45		
Any Protocol-defined IARs	13	16		
Any Algorithm-defined IARs	15	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Period: Number of Subjects With TEAEs and IARs

End point title	Open-label Period: Number of Subjects With TEAEs and IARs

End point description:

AE: any untoward medical occurrence in a subject who received study drug and did not necessarily have to had a causal relationship with treatment. TEAEs in open-label: AEs that developed/worsened in grade/became serious during TEAE period in open-label (from time of 1st open-label treatment to last treatment date + 4 weeks). Protocol-defined IARs: defined as AESIs that occurred during either infusion/observation period following infusion which were deemed to be related/possibly related to study drug. Algorithm-defined IARs: any TEAE meeting either 1 of 2 criteria: 1) event occurred from start to end of infusion plus 24 hours, considered related to study drug, 2) If AE time component missed, compare AE start date with infusion start and end date. If AE start date was between infusion start and end date plus 1 day and it was related to study drug. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Week 50 to 289 in open-label long-term period

End point values	Avalglucosidase Alfa-PAP	Alglucosidase Alfa-PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	44		
Units: subjects				
Any TEAE	51	43		
Any Protocol-defined IARs	12	22		
Any Algorithm-defined IARs	16	24		

Statistical analyses

No statistical analyses for this end point

Secondary: PAP: Percentage of Subjects With Treatment-Emergent Antidrug Antibodies (ADA) Response

End point title	PAP: Percentage of Subjects With Treatment-Emergent Antidrug Antibodies (ADA) Response

End point description:

ADA response categories: 1) Treatment-induced: ADAs developed following administration of the study drug. If the Baseline ADA sample was missing or non-reportable and at least one reportable on-treatment ADA sample was available, the Baseline sample was considered as "negative". 2) Treatment boosted: Pre-existing ADAs that were boosted at least two titer steps from Baseline (i.e., 4-fold increase in titers) following administration of the study drug (any time after the first drug administration). 3) Treatment emergent: combination of treatment induced and treatment boosted. Analysis was performed on ADA evaluable population which consisted of subjects who had received at least 1 infusion (partial or total) and had at least one ADA sample taken post-baseline after drug administration that was appropriate for ADA testing with a reportable result.

End point type	Secondary

End point timeframe:

From Baseline up to Week 49

End point values	PAP: Avalglucosidase Alfa	PAP: Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	48		
Units: percentage of subjects				
number (not applicable)				
Treatment Induced	95.9	95.7		
Treatment-boosted ADA	100	100		
Treatment-emergent ADA	96.1	95.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 49 in PAP and from Week 50 to 289 in open-label long-term period

Adverse event reporting additional description:

AEs and deaths:TEAEs that developed/worsened in grade/became serious during 'TEAE period' (PAP:from 1st treatment date to last treatment date+4 weeks for subjects not exposed to treatment in open-label or to time just prior to 1st dose in open-label for those exposed to open-label [time from 1st study drug to last dose+4 weeks]). Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	PAP: Avalglucosidase Alfa

Reporting group description:

Avalglucosidase alfa, 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).

Reporting group title	Open-label: Alglucosidase Alfa-PAP Then Avalglucosidase Alfa

Reporting group description:

Included all subjects who received avalglucosidase alfa 20 mg/kg IV infusion q2w treatment from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.

Reporting group title	Open-label: Avalglucosidase Alfa

Reporting group description:

Included all subjects who received avalglucosidase alfa, 20 mg/kg IV infusion q2w from Week 50 up to 289 based on product approval status in an open-label avalglucosidase alfa long-term follow-up phase.

Reporting group title	PAP: Alglucosidase Alfa

Reporting group description:

Alglucosidase alfa, 20 mg/kg IV infusion q2w up to Week 49 in blinded treatment period (also known as PAP).

Serious adverse events	PAP: Avalglucosidase Alfa	Open-label: Alglucosidase Alfa-PAP Then Avalglucosidase Alfa	Open-label: Avalglucosidase Alfa
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 51 (15.69%)	14 / 44 (31.82%)	14 / 52 (26.92%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Pancreas			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal Oncocytoma			

subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast Cyst			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Bronchospasm			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Diaphragmatic Paralysis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	2 / 44 (4.55%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Acidosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Oxygen Saturation Decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Pressure Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body Temperature Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin Decreased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart Rate Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip Fracture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Viiith Nerve Injury			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Dehiscence			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Congenital, familial and genetic disorders			
Glycogen Storage Disease Type Ii			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Acute Myocardial Infarction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Moyamoya Disease			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Level Of Consciousness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar Ischaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Stem Stroke			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Eye disorders			
Visual Impairment			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Tongue Oedema			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cold Sweat			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Discolouration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
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 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvi-Ureteric Obstruction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Device Related Infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 44 (2.27%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Sepsis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	0 / 52 (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
Covid-19 Pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PAP: Alglucosidase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 49 (24.49%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Pancreas			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Oncocytoma			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive Crisis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Breast Cyst				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Distress Syndrome				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic Paralysis				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoventilation				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory Distress				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory Acidosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood Pressure Increased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Body Temperature Increased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin Decreased			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heart Rate Increased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Hip Fracture			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viiith Nerve Injury			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound Dehiscence			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Glycogen Storage Disease Type Ii			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Supraventricular Tachycardia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid Haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Moyamoya Disease				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed Level Of Consciousness				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebellar Ischaemia				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain Stem Stroke				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Visual Impairment			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Tongue Oedema			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Upper			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Cold Sweat			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Discolouration			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pruritus			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvi-Ureteric Obstruction			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Calculus Urinary			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Covid-19			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Covid-19 Pneumonia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PAP: Avalglucosidase Alfa	Open-label: Alglucosidase Alfa-PAP Then Avalglucosidase Alfa	Open-label: Avalglucosidase Alfa
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 51 (78.43%)	40 / 44 (90.91%)	50 / 52 (96.15%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 51 (1.96%)	4 / 44 (9.09%)	7 / 52 (13.46%)
occurrences (all)	2	4	21
Flushing			
subjects affected / exposed	0 / 51 (0.00%)	2 / 44 (4.55%)	1 / 52 (1.92%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 51 (1.96%)	5 / 44 (11.36%)	4 / 52 (7.69%)
occurrences (all)	1	13	13
Chest Discomfort			

subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	5	1
Pyrexia			
subjects affected / exposed	2 / 51 (3.92%)	6 / 44 (13.64%)	8 / 52 (15.38%)
occurrences (all)	2	11	10
Pain			
subjects affected / exposed	2 / 51 (3.92%)	6 / 44 (13.64%)	3 / 52 (5.77%)
occurrences (all)	3	14	5
Oedema Peripheral			
subjects affected / exposed	3 / 51 (5.88%)	4 / 44 (9.09%)	5 / 52 (9.62%)
occurrences (all)	4	4	7
Infusion Site Extravasation			
subjects affected / exposed	0 / 51 (0.00%)	5 / 44 (11.36%)	2 / 52 (3.85%)
occurrences (all)	0	8	2
Influenza Like Illness			
subjects affected / exposed	2 / 51 (3.92%)	1 / 44 (2.27%)	3 / 52 (5.77%)
occurrences (all)	4	1	8
Fatigue			
subjects affected / exposed	9 / 51 (17.65%)	9 / 44 (20.45%)	4 / 52 (7.69%)
occurrences (all)	11	75	8
Peripheral Swelling			
subjects affected / exposed	1 / 51 (1.96%)	5 / 44 (11.36%)	1 / 52 (1.92%)
occurrences (all)	3	6	1
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	3 / 52 (5.77%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	1 / 51 (1.96%)	2 / 44 (4.55%)	2 / 52 (3.85%)
occurrences (all)	1	2	2
Dyspnoea			
subjects affected / exposed	2 / 51 (3.92%)	3 / 44 (6.82%)	2 / 52 (3.85%)
occurrences (all)	2	5	3
Cough			

subjects affected / exposed	2 / 51 (3.92%)	5 / 44 (11.36%)	4 / 52 (7.69%)
occurrences (all)	2	7	7
Rhinorrhoea			
subjects affected / exposed	0 / 51 (0.00%)	5 / 44 (11.36%)	0 / 52 (0.00%)
occurrences (all)	0	6	0
Oropharyngeal Pain			
subjects affected / exposed	2 / 51 (3.92%)	4 / 44 (9.09%)	2 / 52 (3.85%)
occurrences (all)	2	7	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 44 (2.27%)	3 / 52 (5.77%)
occurrences (all)	1	1	3
Depression			
subjects affected / exposed	1 / 51 (1.96%)	2 / 44 (4.55%)	0 / 52 (0.00%)
occurrences (all)	1	2	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 51 (3.92%)	2 / 44 (4.55%)	1 / 52 (1.92%)
occurrences (all)	2	2	1
Blood Pressure Increased			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	3	1
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	4	1
Post-Traumatic Pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	0 / 52 (0.00%)
occurrences (all)	0	3	0
Joint Injury			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	3 / 52 (5.77%)
occurrences (all)	0	0	3
Fall			
subjects affected / exposed	7 / 51 (13.73%)	8 / 44 (18.18%)	10 / 52 (19.23%)
occurrences (all)	12	21	28
Contusion			

subjects affected / exposed	5 / 51 (9.80%)	3 / 44 (6.82%)	5 / 52 (9.62%)
occurrences (all)	5	4	7
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 51 (1.96%)	1 / 44 (2.27%)	3 / 52 (5.77%)
occurrences (all)	1	1	12
Syncope			
subjects affected / exposed	0 / 51 (0.00%)	0 / 44 (0.00%)	3 / 52 (5.77%)
occurrences (all)	0	0	3
Paraesthesia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 44 (4.55%)	0 / 52 (0.00%)
occurrences (all)	3	2	0
Dizziness			
subjects affected / exposed	5 / 51 (9.80%)	3 / 44 (6.82%)	6 / 52 (11.54%)
occurrences (all)	6	4	8
Headache			
subjects affected / exposed	11 / 51 (21.57%)	17 / 44 (38.64%)	12 / 52 (23.08%)
occurrences (all)	32	220	42
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	3 / 52 (5.77%)
occurrences (all)	0	3	3
Eye disorders			
Conjunctival Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	0 / 52 (0.00%)
occurrences (all)	0	4	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 44 (0.00%)	3 / 52 (5.77%)
occurrences (all)	3	0	4
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 51 (1.96%)	4 / 44 (9.09%)	5 / 52 (9.62%)
occurrences (all)	1	6	8
Abdominal Pain Upper			
subjects affected / exposed	2 / 51 (3.92%)	3 / 44 (6.82%)	3 / 52 (5.77%)
occurrences (all)	4	4	6
Diarrhoea			

subjects affected / exposed	6 / 51 (11.76%)	14 / 44 (31.82%)	7 / 52 (13.46%)
occurrences (all)	9	19	15
Dyspepsia			
subjects affected / exposed	3 / 51 (5.88%)	3 / 44 (6.82%)	2 / 52 (3.85%)
occurrences (all)	9	9	2
Nausea			
subjects affected / exposed	6 / 51 (11.76%)	7 / 44 (15.91%)	12 / 52 (23.08%)
occurrences (all)	8	22	16
Toothache			
subjects affected / exposed	1 / 51 (1.96%)	4 / 44 (9.09%)	2 / 52 (3.85%)
occurrences (all)	2	5	3
Vomiting			
subjects affected / exposed	4 / 51 (7.84%)	6 / 44 (13.64%)	3 / 52 (5.77%)
occurrences (all)	5	7	4
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 51 (5.88%)	5 / 44 (11.36%)	3 / 52 (5.77%)
occurrences (all)	4	7	4
Pruritus			
subjects affected / exposed	4 / 51 (7.84%)	11 / 44 (25.00%)	3 / 52 (5.77%)
occurrences (all)	5	51	3
Rash			
subjects affected / exposed	2 / 51 (3.92%)	8 / 44 (18.18%)	4 / 52 (7.69%)
occurrences (all)	11	16	8
Urticaria			
subjects affected / exposed	3 / 51 (5.88%)	4 / 44 (9.09%)	5 / 52 (9.62%)
occurrences (all)	4	9	12
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 51 (3.92%)	3 / 44 (6.82%)	0 / 52 (0.00%)
occurrences (all)	4	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 51 (11.76%)	13 / 44 (29.55%)	13 / 52 (25.00%)
occurrences (all)	7	29	27
Back Pain			

subjects affected / exposed	12 / 51 (23.53%)	10 / 44 (22.73%)	11 / 52 (21.15%)
occurrences (all)	15	20	13
Muscle Spasms			
subjects affected / exposed	3 / 51 (5.88%)	5 / 44 (11.36%)	4 / 52 (7.69%)
occurrences (all)	3	8	7
Muscular Weakness			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	5	1
Musculoskeletal Pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	3 / 52 (5.77%)
occurrences (all)	0	117	3
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	4	1
Myalgia			
subjects affected / exposed	5 / 51 (9.80%)	10 / 44 (22.73%)	6 / 52 (11.54%)
occurrences (all)	15	22	12
Neck Pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	3 / 52 (5.77%)
occurrences (all)	0	3	4
Pain In Extremity			
subjects affected / exposed	8 / 51 (15.69%)	9 / 44 (20.45%)	10 / 52 (19.23%)
occurrences (all)	9	19	29
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	2 / 51 (3.92%)	3 / 44 (6.82%)	8 / 52 (15.38%)
occurrences (all)	3	9	10
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 51 (7.84%)	8 / 44 (18.18%)	3 / 52 (5.77%)
occurrences (all)	5	10	4
Sinusitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 44 (2.27%)	3 / 52 (5.77%)
occurrences (all)	0	1	5
Pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	4	1

Nasopharyngitis			
subjects affected / exposed	12 / 51 (23.53%)	13 / 44 (29.55%)	15 / 52 (28.85%)
occurrences (all)	15	27	23
Influenza			
subjects affected / exposed	10 / 51 (19.61%)	4 / 44 (9.09%)	4 / 52 (7.69%)
occurrences (all)	11	5	4
Cystitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 44 (0.00%)	2 / 52 (3.85%)
occurrences (all)	4	0	2
Covid-19			
subjects affected / exposed	0 / 51 (0.00%)	9 / 44 (20.45%)	16 / 52 (30.77%)
occurrences (all)	0	9	17
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)	4 / 44 (9.09%)	3 / 52 (5.77%)
occurrences (all)	0	4	3
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 51 (0.00%)	3 / 44 (6.82%)	1 / 52 (1.92%)
occurrences (all)	0	4	2
Vitamin D Deficiency			
subjects affected / exposed	2 / 51 (3.92%)	2 / 44 (4.55%)	5 / 52 (9.62%)
occurrences (all)	2	2	5

Non-serious adverse events	PAP: Alglucosidase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 49 (89.80%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	5		
Flushing			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chills			

subjects affected / exposed occurrences (all) Chest Discomfort subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all) Infusion Site Extravasation subjects affected / exposed occurrences (all) Influenza Like Illness subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Peripheral Swelling subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 6 0 / 49 (0.00%) 0 4 / 49 (8.16%) 4 5 / 49 (10.20%) 13 3 / 49 (6.12%) 3 3 / 49 (6.12%) 3 0 / 49 (0.00%) 0 7 / 49 (14.29%) 27 3 / 49 (6.12%) 3		
Immune system disorders Seasonal Allergy subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Nasal Congestion subjects affected / exposed occurrences (all) Dyspnoea	5 / 49 (10.20%) 5		

subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Oropharyngeal Pain			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	8		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Blood Pressure Increased			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Post-Traumatic Pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Joint Injury			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Fall			

subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	13		
Contusion			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	16 / 49 (32.65%)		
occurrences (all)	102		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Eye disorders			
Conjunctival Haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Ocular Hyperaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Abdominal Pain Upper			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2 8 / 49 (16.33%) 9 3 / 49 (6.12%) 5 7 / 49 (14.29%) 15 0 / 49 (0.00%) 0 3 / 49 (6.12%) 3		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 7 4 / 49 (8.16%) 11 4 / 49 (8.16%) 4 1 / 49 (2.04%) 5		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	 0 / 49 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	11		
Back Pain			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	7		
Muscle Spasms			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Muscular Weakness			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	6		
Musculoskeletal Pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	12		
Neck Pain			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	5		
Pain In Extremity			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	15		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	4		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Sinusitis			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	12 / 49 (24.49%)		
occurrences (all)	17		
Influenza			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Cystitis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Covid-19			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Vitamin D Deficiency			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2016	Following changes were made: • Change to the inclusion/exclusion criteria. Inclusion criterion 1 and exclusion criterion 8 were reworded in order to comply with local requirements regarding age of minors and adults. Exclusion criterion 6 was modified to allow more severely compromised subjects into the study by reducing the lower cut-off for % predicted FVC from 40% to 30%. • Change to the sample size. Sample size was increased from approximately 86 to approximately 96 as a result of modification to the exclusion criteria for % predicted FVC (the primary endpoint) and using a more conservative 10% estimate for missing data.
18 July 2017	Following changes were made: • Minor editorial: spelling, punctuation, grammar and syntax. • Updated: abbreviations, table of contents, table footnotes and references. • Updated flow charts to reflect study procedures and to clarify that AEs and concomitant medication use information were to be collected at each visit to assure that information was kept up to date. • Renumbered: sections, table footnotes and citations and references. • Reformatted tables. • Extended screening period: screening phase (time from signing of informed consent form [ICF] to start of study treatment) should not exceed 14 days, but could be extended to a maximum of 8 weeks in pre-specified situations. • Added re-screening details: Subjects re-screened once when clinical condition changed. Subjects who were screen failed because FVC% predicted was >85% might be re-screened only if clinically relevant worsening respiratory condition related to Pompe Disease and not related to intercurrent illness as assessed by Investigator occurs. In rescreening, subject would be first screened failed in interactive voice/web response system, would sign new written ICF and new subject number would be provided. All screening assessments/procedures would had to be performed again, except GAA genotyping. • PFT details updated: Subjects might repeat assessment once up to 3 times within Screening Visit time window in case of failed quality as determined by central laboratory. • Clarified ADA tests: Subjects in neoGAA treatment arm would be tested for anti-neoGAA antibodies and subjects in glucosidase alfa treatment arm would be tested for anti-alglucosidase alfa antibodies. In open label follow-up phase, subjects from alglucosidase alfa treatment arm who had switched to neoGAA would be tested for both anti-alglucosidase alfa antibodies and anti-neoGAA antibodies. Subjects who were +ve for anti-neoGAA antibodies would be tested to determine if antibodies cross-react with alglucosidase alfa.

10 April 2019	Following changes were done: • In order to allow study subjects to continue to receive study drug after Week 145, study was extended to an additional period of up to 144 weeks (or until avalglucosidase alfa was approved in subject's country, whichever came first). • Enrollment of subjects aged 3 to <18 years had been challenging, mainly due to exclusion criterion related to respiratory function (requirements that FVC% predicted less than or equal to 85%). At end of recruitment, if <4 subjects 3 to <18 years were enrolled, in order to comply with Health Authority requirements to enroll a certain number of paediatric subjects, up to 2 additional paediatric subjects were to be enrolled directly in open-label avalglucosidase alfa long-term follow-up phase where they received avalglucosidase alfa. • In permitted countries, home infusion of avalglucosidase alfa in extension period was allowed. • Language was added in 'randomisation code-breaking during study' section, to document that an unblinded programmer prepared dataset for population pharmacokinetic analysis. • Updated statistical section: removed noninferiority test of 6MWT from testing order and used superiority instead for secondary endpoint of 6MWT in accordance with feedback from regulatory agency. Added superiority test of MEP to hierarchical testing and updated safety population definition. • Removed messenger ribonucleic acid test since it test was not performed. • Clarified conditions for temporary study drug discontinuation with Data Monitoring Committee consultation (eg, in case of abnormal liver function test). • HHD not required in Canadian sites. • Home infusion did not apply in France. • In the UK: updated extended open-label avalglucosidase alfa long-term follow-up period as 'up to 144 weeks after last subject had been enrolled in study'.
21 December 2020	Following changes were done: • To include the recommendations that were developed for the coronavirus disease 2019 pandemic period and shared with the sites/Investigators. These recommendations will remain applicable after the end of the pandemic, especially the information regarding the post-infusion surveillance period. • To revise the text as per the current Sanofi protocol template to use the most updated wordings that are compliant with general guidance, including monitoring techniques. • To update the details regarding home infusion, to harmonize this text across the different studies included in the avalglucosidase alfa development program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported