



Clinical trial results:

A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late-onset Pompe Disease Compared With Alglucosidase Alfa/Placebo

Summary

EudraCT number	2018-000755-40
Trial protocol	DE DK GB SE HU BE SK ES NL BG SI GR AT IT
Global end of trial date	15 December 2020

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	ATB200-03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03729362
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amicus Therapeutics, Inc.
Sponsor organisation address	3675 Market Street, Philadelphia, PA , United States, 19104
Public contact	Patient advocacy, Amicus Therapeutics, Inc., 001 6096622000, clinicaltrials@amicusrx.com
Scientific contact	Patient advocacy, Amicus Therapeutics, Inc., 001 6096622000, clinicaltrials@amicusrx.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	10 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2020
Global end of trial reached?	Yes
Global end of trial date	15 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to assess the efficacy of ATB200 (also known as cipaglucoasidase alfa)/AT2221 (also known as miglustat) co-administration on ambulatory function, as measured by the 6-Minute Walk Test (6MWT), compared with alglucosidase alfa/placebo co-administration.

Following completion of Study ATB200-03, participants had the option to enroll in a long-term extension study (Study ATB200-07, EudraCT Number: 2019-000954-67) and receive cipaglucoasidase alfa/miglustat treatment until regulatory approval, marketing authorization, commercialization, or study termination.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 3

Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Worldwide total number of subjects	123
EEA total number of subjects	44

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)	109
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 123 participants were enrolled in the study and dosed at 62 clinical sites across 24 countries. Two participants were randomly assigned to the alglucosidase alfa/placebo group but never dosed because genotyping did not confirm diagnosis of Pompe disease.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Cipaglucosidase Alfa/Miglustat

Arm description:

Cipaglucosidase alfa co-administered with miglustat every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Cipaglucosidase Alfa
Investigational medicinal product code	
Other name	ATB200
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 milligram (mg)/kilogram (kg) intravenous (IV) infusion over a 4-hour duration every 2 weeks.

Investigational medicinal product name	Miglustat
Investigational medicinal product code	
Other name	AT2221
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Weight-based doses of 195 or 260 mg 1 hour prior to cipaglucosidase alfa infusion every 2 weeks.

Arm title	Alglucosidase Alfa/Placebo
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Arm description:

Alglucosidase alfa co-administered with placebo every 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Alglucosidase Alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg IV infusion over a 4-hour duration every 2 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Miglustat matching placebo was administered 1 hour prior to alglucosidase alfa infusion every 2 weeks.

Number of subjects in period 1	Cipaglucosidase Alfa/Miglustat	Alglucosidase Alfa/Placebo
Started	85	38
Received at Least 1 Dose of Study Drug	85	38
Completed	80	37
Not completed	5	1
COVID-19 pandemic	1	-
Discontinued due to COVID-19-related pneumonia	1	-
Consent withdrawn by subject	2	-
Investigator's decision	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cipagluco­sidase Alfa/Miglustat
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Reporting group description:

Cipagluco­sidase alfa co-administered with miglustat every 2 weeks.

Reporting group title	Algluco­sidase Alfa/Placebo
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Reporting group description:

Algluco­sidase alfa co-administered with placebo every 2 weeks.

Reporting group values	Cipagluco­sidase Alfa/Miglustat	Algluco­sidase Alfa/Placebo	Total
Number of subjects	85	38	123
Age categorical			
Units: Subjects			
≥ 18 to < 35 years	17	10	27
≥ 35 to < 50 years	27	13	40
≥ 50 to < 65 years	30	12	42
≥ 65 years	11	3	14
Age continuous			
Units: years			
arithmetic mean	47.6	45.1	
standard deviation	± 13.25	± 13.30	-
Gender categorical			
Units: Subjects			
Female	49	18	67
Male	36	20	56
Race			
Units: Subjects			
Asian	3	1	4
Japanese	2	4	6
American Indian or Alaska Native	0	1	1
Black or African American	0	1	1
Native Hawaiian or other Pacific Islander	1	0	1
White	74	30	104
Other	5	1	6

End points

End points reporting groups

Reporting group title	Cipagluco­sidase Alfa/Miglustat
Reporting group description: Cipagluco­sidase alfa co-administered with miglustat every 2 weeks.	
Reporting group title	Algluco­sidase Alfa/Placebo
Reporting group description: Algluco­sidase alfa co-administered with placebo every 2 weeks.	
Subject analysis set title	Cipagluco­sidase Alfa/Miglustat
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received at least 1 dose of study drug (cipagluco­sidase alfa/miglustat).	
Subject analysis set title	Algluco­sidase Alfa/Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received at least 1 dose of study drug (algluco­sidase alfa/placebo).	
Subject analysis set title	Cipagluco­sidase Alfa/Miglustat (ITT-OBS)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT)-observed (OBS) population consisted of all randomized participants who received at least 1 dose of study drug. Analyses used all available, observed data without imputation for missing post-baseline data. That is, missing data at Week 52 and at other visits were not replaced. An outlier participant was identified in the algluco­sidase alfa/placebo group. Analysis excluding this participant was considered the primary analysis. All efficacy results in the ITT Population are presented excluding the 1 outlier participant.	
Subject analysis set title	Algluco­sidase Alfa/Placebo (ITT-OBS)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT-OBS population consisted of all randomized participants who received at least 1 dose of study drug. Analyses used all available, observed data without imputation for missing post-baseline data. That is, missing data at Week 52 and at other visits were not replaced. An outlier participant was identified in the algluco­sidase alfa/placebo group. Analysis excluding this participant was considered the primary analysis. All efficacy results in the ITT Population are presented excluding the 1 outlier participant.	
Subject analysis set title	Cipagluco­sidase Alfa/Miglustat (ITT-LOCF)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT-Last Observation Carried Forward (ITT-LOCF) population consisted of all randomized participants who received at least 1 dose of study drug. Analyses used the LOCF method to replace missing data. An outlier participant was identified in the algluco­sidase alfa/placebo group. Analysis excluding this participant was considered the primary analysis. All efficacy results in the ITT Population are presented excluding the 1 outlier participant.	
Subject analysis set title	Algluco­sidase Alfa/Placebo (ITT-LOCF)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT-Last Observation Carried Forward (ITT-LOCF) population consisted of all randomized participants who received at least 1 dose of study drug. Analyses used the LOCF method to replace missing data. An outlier participant was identified in the algluco­sidase alfa/placebo group. Analysis excluding this participant was considered the primary analysis. All efficacy results in the ITT Population are presented excluding the 1 outlier participant.	
Subject analysis set title	Cipagluco­sidase Alfa
Subject analysis set type	Full analysis
Subject analysis set description: Pharmacokinetic (PK) Population: Participants who were exposed to at least 1 dose of cipagluco­sidase alfa and had at least 1 PK assessment.	
Subject analysis set title	Algluco­sidase Alfa

Subject analysis set type	Full analysis
Subject analysis set description:	
PK Population: Participants who were exposed to at least 1 dose of alglucosidase alfa and had at least 1 PK assessment.	
Subject analysis set title	Miglustat
Subject analysis set type	Full analysis
Subject analysis set description:	
PK Population: Participants who were exposed to at least 1 dose of miglustat and had at least 1 PK assessment.	
Subject analysis set title	Cipaglucosidase Alfa
Subject analysis set type	Full analysis
Subject analysis set description:	
Immunogenicity Population: All participants who received at least 1 dose of cipaglucosidase alfa.	
Subject analysis set title	Alglucosidase Alfa
Subject analysis set type	Full analysis
Subject analysis set description:	
Immunogenicity Population: All participants who received at least 1 dose of alglucosidase alfa.	

Primary: Change From Baseline To Week 52 In 6 Minute Walk Distance (6MWD)

End point title	Change From Baseline To Week 52 In 6 Minute Walk Distance (6MWD)
End point description:	
The efficacy of cipaglucosidase alfa/miglustat co-administration on ambulatory function was measured by the 6MWT. The 6MWD, measured in meters, is the distance walked on the 6MWT. A greater distance indicated greater endurance. An increase from baseline indicated improvement.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-OBS)	Alglucosidase Alfa/Placebo (ITT-OBS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	36		
Units: meter				
least squares mean (standard error)	21.31 (\pm 11.56)	7.10 (\pm 7.043)		

Statistical analyses

Statistical analysis title	Change From Baseline (CFBL) To Week 52 In 6MWD
Statistical analysis description:	
The primary and key secondary endpoints were tested in a hierarchical order as follows: The test for the primary endpoint was conducted first at the 1-sided 0.025 significance level, and if significant, the ordered key secondary endpoints were similarly tested. If at any point the null hypothesis for superiority failed to be rejected, then that comparison and any other comparison below it could not be claimed as successful and would be considered nominal.	
Comparison groups	Cipaglucosidase Alfa/Miglustat (ITT-OBS) v Alglucosidase Alfa/Placebo (ITT-OBS)

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.048 ^[2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	14.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	31.02
Variability estimate	Standard error of the mean
Dispersion value	8.481

Notes:

[1] - Analysis used mixed-effect model for repeated measures (MMRM). The model included terms for treatment, baseline 6MWD, age, height, weight (all as continuous covariates), enzyme replacement therapy (ERT) status (ERT-naïve versus ERT-experienced), gender, time, and treatment-by-time interaction. Time was used as a repeated measure, and an unstructured covariance approach was applied.

[2] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 52 In Sitting Forced Vital Capacity (FVC; % predicted)

End point title	Change From Baseline To Week 52 In Sitting Forced Vital Capacity (FVC; % predicted)
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End point description:

The efficacy of cipaglugosidase alfa/miglustat co-administration on pulmonary function was measured by sitting FVC (% predicted). FVC is a standard pulmonary function test used to quantify respiratory muscle weakness.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglugosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: score				
least squares mean (standard error)	-1.04 (± 0.624)	-3.70 (± 0.953)		

Statistical analyses

Statistical analysis title	CFBL To Week 52 In Sitting FVC (% predicted)
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Statistical analysis description:

Change from baseline to Week 52 in sitting FVC was the first of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.

Comparison groups	Cipaglugosidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase
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	Alfa/Placebo (ITT-LOCF)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.012 ^[4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	4.95
Variability estimate	Standard error of the mean
Dispersion value	1.156

Notes:

[3] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[4] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 52 In The Manual Muscle Test (MMT) Score For The Lower Extremities

End point title	Change From Baseline To Week 52 In The Manual Muscle Test (MMT) Score For The Lower Extremities
End point description:	
The total score for the MMT lower extremity strength included the following 8 body parts: right/left hip flexion, right/left hip abduction, right/left knee flexion, and right/left knee extension. The MMT lower extremity score ranged from 0 to 40, with lower scores indicating weaker muscle strength. An increase from baseline indicated increased muscle strength.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	34		
Units: score on a scale				
least squares mean (standard error)	1.64 (± 0.388)	0.68 (± 0.603)		

Statistical analyses

Statistical analysis title	CFBL To Week 52 In MMT Lower Extremity
Statistical analysis description:	
Change from baseline to Week 52 in the MMT score for the lower extremities was the second of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.	
Comparison groups	Cipaglucosidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase Alfa/Placebo (ITT-LOCF)

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.095 ^[6]
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	0.727

Notes:

[5] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[6] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 26 In 6MWD

End point title	Change From Baseline To Week 26 In 6MWD
End point description:	The 6MWD, measured in meters, is the distance walked on the 6MWT.
End point type	Secondary
End point timeframe:	Baseline, Week 26

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: meter				
least squares mean (standard error)	16.45 (± 3.360)	8.28 (± 5.168)		

Statistical analyses

Statistical analysis title	CFBL To Week 26 In 6MWD
Statistical analysis description:	Change from baseline to Week 26 in 6MWD was the third of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.
Comparison groups	Cipaglucosidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase Alfa/Placebo (ITT-LOCF)

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.097 ^[8]
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	8.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.24
upper limit	20.57
Variability estimate	Standard error of the mean
Dispersion value	6.261

Notes:

[7] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[8] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 52 In The Total Score For The Patient-Reported Outcomes Measurement Information System (PROMIS®) – Physical Function

End point title	Change From Baseline To Week 52 In The Total Score For The Patient-Reported Outcomes Measurement Information System (PROMIS®) – Physical Function
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End point description:

Physical Function Short Form 20a (v2.0) consisted of 20 questions. The first 14 questions were each scored on a scale from 1 to 5 as follows: 1 = unable to do; 2 = with much difficulty; 3 = with some difficulty; 4 = with a little difficulty; 5 = without any difficulty; the next 6 questions were each scored on a scale from 1 to 5 as follows: 1 = cannot do; 2 = quite a lot; 3 = somewhat; 4 = very little; 5 = not at all. The total score was calculated by summing up scores (1 to 5) across all items. A higher score represented better outcome.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidas e Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: score on a scale				
least squares mean (standard error)	1.98 (± 0.921)	0.11 (± 1.406)		

Statistical analyses

Statistical analysis title	CFBL To Week 52 In PROMIS® – Physical Function
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Statistical analysis description:

Change from baseline to Week 52 in the total score for the PROMIS® – Physical Function was the fourth

of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.

Comparison groups	Cipaglicosidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase Alfa/Placebo (ITT-LOCF)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.138 ^[10]
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	5.25
Variability estimate	Standard error of the mean
Dispersion value	1.706

Notes:

[9] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[10] - 1-sided significance level of 0.025

Secondary: Change From Baseline To Week 52 In The Total Score For The PROMIS® – Fatigue

End point title	Change From Baseline To Week 52 In The Total Score For The PROMIS® – Fatigue
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End point description:

Fatigue Short Form 8a consisted of 6 questions, each scored on a scale from 1 to 5 as follows: 1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; 5 = very much; and 2 questions, each scored on a scale from 1 to 5 as follows: 1 = never; 2 = rarely; 3 = sometimes; 4 = often; 5 = always. The total score was calculated by summing up scores (1 to 5) across all items. A lower score represented lower fatigue symptoms.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglicosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: score on a scale				
least squares mean (standard error)	-1.90 (± 0.585)	-1.94 (± 0.901)		

Statistical analyses

Statistical analysis title	CFBL To Week 52 In PROMIS® – Fatigue
Statistical analysis description:	
Change from baseline to Week 52 in the total score for the PROMIS® – Fatigue was the fifth of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.	
Comparison groups	Cipaglicosidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase Alfa/Placebo (ITT-LOCF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.515 ^[12]
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	1.092

Notes:

[11] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[12] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 52 In The Total Score For The Gait, Stairs, Gowers' Maneuver, And Chair (GSGC)

End point title	Change From Baseline To Week 52 In The Total Score For The Gait, Stairs, Gowers' Maneuver, And Chair (GSGC)
End point description:	
The GSGC consisted of a 10-meter walk for evaluation of gait, a 4-stair climb, Gowers' maneuver, and arising from a chair. Results of the GSGC included the time required to complete the individual tests, individual scores for each of the tests (1 to 7 points for each of gait, 4-stair climb, and Gowers' maneuver and 1 to 6 points for arising from a chair), and a total score. GSGC total score was the sum of the component scores from the 4 functional tests. The total score ranged from a minimum of 4 points (normal performance) to a maximum of 27 points (worst performance).	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglicosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	30		
Units: score on a scale				
least squares mean (standard error)	-0.567 (± 0.280)	0.847 (± 0.440)		

Statistical analyses

Statistical analysis title	CFBL To Week 52 In GSGC Total Score
Statistical analysis description: Change from baseline to Week 52 in the total score for the GSGC was the sixth of 6 key secondary efficacy endpoints, which were analyzed according to a hierarchical order.	
Comparison groups	Cipaglusidase Alfa/Miglustat (ITT-LOCF) v Alglucosidase Alfa/Placebo (ITT-LOCF)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.004 ^[14]
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.414
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.463
upper limit	-0.364
Variability estimate	Standard error of the mean
Dispersion value	0.528

Notes:

[13] - The analysis used an ANCOVA model adjusted for the baseline value (as a continuous covariate) and ERT status (ERT-naïve versus ERT-experienced), as well as baseline age, gender, baseline height, and baseline weight.

[14] - 1-sided significance level of 0.025.

Secondary: Change From Baseline To Week 52 In % Predicted 6MWD

End point title	Change From Baseline To Week 52 In % Predicted 6MWD
End point description: The % predicted 6MWD = (actual 6MWD / predicted 6MWD) * 100. The predicted values were calculated using Enright And Sherrill 1998 Reference Equations.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglusidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: percentage				
least squares mean (standard error)	4.039 (± 0.716)	1.655 (± 1.102)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants Improving On Both 6MWD And % Predicted FVC

End point title	Number Of Participants Improving On Both 6MWD And % Predicted FVC
End point description: A composite subject-level response of the 2 relevant clinical outcomes, 6MWD and FVC (% predicted), was assessed. Prespecified thresholds were used for assessment of improvement consistent with published minimal clinically important difference values for comparable instruments in similar disease.	
End point type	Secondary
End point timeframe: Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-OBS)	Alglucosidase Alfa/Placebo (ITT-OBS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: participants	14	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In the Time to Complete Individual GSGC Component Tests And Timed Up And Go (TUG) Test At Week 52

End point title	Change From Baseline In the Time to Complete Individual GSGC Component Tests And Timed Up And Go (TUG) Test At Week 52
End point description: Motor function test assessed the time to complete individual GSGC component tests (10-meter walk, 4-stair climb, Gowers' maneuver, and arise from a chair) and the TUG test. The TUG test assessed the time a subject needed to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: seconds				
least squares mean (standard error)				
Time to complete the 10-meter walk	-0.60 (± 0.631)	2.06 (± 0.967)		
Time to complete the 4-stair climb	-6.75 (± 0.851)	-3.61 (± 1.308)		

Time to complete the Gowers' maneuver	-0.36 (± 0.799)	-1.95 (± 1.281)		
Time to arise from a chair	-7.57 (± 0.409)	-6.75 (± 0.643)		
Time to complete the timed up and go test	-0.39 (± 0.768)	0.09 (± 1.217)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In The Quantitative Muscle Test (QMT) Values (Kg)

End point title	Change From Baseline To Week 52 In The Quantitative Muscle Test (QMT) Values (Kg)
End point description: QMT was measured using the hand-held dynamometer. Larger values (in kg) indicated greater muscle strength.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustate (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: kilogram				
least squares mean (standard error)				
QMT Value for the Upper Extremities	1.839 (± 2.098)	-0.553 (± 3.195)		
QMT Value for the Lower Extremities	6.496 (± 3.185)	5.265 (± 4.854)		
QMT Total Value	8.195 (± 5.079)	5.198 (± 7.746)		
QMT Value for the Proximal Muscle Group	3.401 (± 2.920)	0.945 (± 4.477)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Other MMT Scores

End point title	Change From Baseline To Week 52 In Other MMT Scores
End point description: Each manual muscle test was evaluated on a scoring scale from 0 to 5, as follows: 0 = no muscle movement; 1 = visible muscle movement, but no movement at the joint; 2 = movement at the joint, but not against gravity; 3 = movement against gravity, but not against added resistance; 4 =	

movement against resistance, but less than normal; 5 = normal strength. Upper extremity score was the sum of scores for right/left shoulder abduction, right/left shoulder adduction, right/left elbow extension, and right/left elbow flexion, with the total score ranging from 0 to 40. Proximal muscle group score was the sum of scores for right/left hip flexion, right/left hip abduction, right/left shoulder abduction, and right/left shoulder adduction, with the total score ranging from 0 to 40. MMT total score was the sum of the lower and upper extremity scores, and ranged from 0 to 80. Lower scores indicated lower overall muscle strength. An increase from baseline indicated improvement in muscle strength.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustatin (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: Score on a scale				
least squares mean (standard error)				
MMT Upper Extremity Score	1.54 (± 0.323)	0.60 (± 0.491)		
MMT Total Score	3.24 (± 0.622)	1.02 (± 0.966)		
MMT Proximal Muscle Group Score	1.82 (± 0.393)	0.70 (± 0.599)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Sitting Slow Vital Capacity (SVC) % Predicted

End point title	Change From Baseline To Week 52 In Sitting Slow Vital Capacity (SVC) % Predicted
End point description:	
SVC is a standard pulmonary function test used to quantify respiratory muscle weakness.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustatin (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	35		
Units: percentage				
least squares mean (standard error)				
Sitting % predicted SVC	-2.527 (± 0.977)	-5.368 (± 1.527)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Maximum Vital Capacity (Maximum VC) % Predicted

End point title	Change From Baseline To Week 52 In Maximum Vital Capacity (Maximum VC) % Predicted
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End point description:

Maximum VC is the greater of the two VC values (FVC or SVC).

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidase Alfa/Miglustate (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: percentage				
least squares mean (standard error)				
% predicted maximum VC	-1.286 (\pm 0.613)	-3.695 (\pm 0.936)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Maximal Inspiratory Pressure (MIP) % Predicted

End point title	Change From Baseline To Week 52 In Maximal Inspiratory Pressure (MIP) % Predicted
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End point description:

The percent predicted values of MIP were calculated as: % predicted = (actual result / predicted result) * 100, where the predicted results were obtained using the reference equations from Uldry and Fitting (1995).

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: percentage				
least squares mean (standard error)				
% predicted MIP	1.89 (± 2.079)	-2.31 (± 3.178)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Maximal Expiratory Pressure (MEP) % Predicted

End point title	Change From Baseline To Week 52 In Maximal Expiratory Pressure (MEP) % Predicted
End point description: The percent predicted values of MEP were calculated as: % predicted = (actual result / predicted result) * 100, where the predicted results were obtained using the reference equations from Uldry and Fitting (1995).	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: percentage				
least squares mean (standard error)				
% predicted MEP	0.51 (± 1.996)	-1.35 (± 3.052)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Sniff Nasal Inspiratory Pressure (SNIP) % Predicted

End point title	Change From Baseline To Week 52 In Sniff Nasal Inspiratory
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End point description:

The percent predicted values of SNIP were calculated as: % predicted = (actual result / predicted result) * 100, where the predicted results were obtained using the reference equations from Evans and Whitelaw (2009).

End point type

Secondary

End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidas e Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	37		
Units: percentage				
least squares mean (standard error)				
% predicted SNIP	1.40 (± 1.918)	4.53 (± 2.929)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In PROMIS-Dyspnea And Upper Extremities Total Scores

End point title

Change From Baseline To Week 52 In PROMIS-Dyspnea And Upper Extremities Total Scores

End point description:

The Upper Extremities Short Form 7a consisted of 7 items each scored on a decreasing scale from 1 to 5 as follows: 1 = unable to do; 2 = with much difficulty; 3 = with some difficulty; 4 = with a little difficulty; 5 = without any difficulty.

Dyspnea Severity Short Form 10a consisted of 10 items each scored on a scale from 0 to 3 as follows: 0 = no shortness of breath; 1 = mildly short of breath; 2 = moderately short of breath; 3 = severely short of breath.

A total score was generated for each instrument by adding up each item. A higher score for upper extremities represented improvement in symptoms. A lower score for dyspnea severity represented improvement in symptoms.

End point type

Secondary

End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidas e Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: Score on a scale				
least squares mean (standard error)				

PROMIS-Dyspnea Total Score	-0.41 (\pm 0.426)	-1.50 (\pm 0.652)		
PROMIS-Upper Extremities Total Score	0.97 (\pm 0.545)	0.87 (\pm 0.833)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline To Week 52 In Rasch-Built Pompe-Specific Activity (R-PAct) Total Score

End point title	Change from Baseline To Week 52 In Rasch-Built Pompe-Specific Activity (R-PAct) Total Score
End point description: The R-PAct scale was an 18-item questionnaire to measure limitations in activities and restriction in social participation. Possible responses to questions were as follows: unable to perform, able to perform, but with difficulty, and able to perform without difficulty. The total score was calculated by summing up the observed scores across the 18 items and it ranged from 0 to 36, with higher values representing lower level of disease impact on the muscles.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	33		
Units: Score on a scale				
least squares mean (standard error)	0.04 (\pm 0.387)	0.51 (\pm 0.567)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In European Quality Of Life-5 Dimensions 5 Response Levels (EQ-5D-5L) Based On The EuroQol Visual Analogue Scale (EQ VAS) Quantitative Score

End point title	Change From Baseline To Week 52 In European Quality Of Life-5 Dimensions 5 Response Levels (EQ-5D-5L) Based On The EuroQol Visual Analogue Scale (EQ VAS) Quantitative Score
End point description: The EQ-5D-5L consisted of the EQ-5D descriptive system and the EQ VAS. Each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) had 5 categorical responses/levels of perceived problems coded as follows: Level 1 = indicating no problem; Level 2 = indicating slight problems; Level 3 = indicating moderate problems; Level 4 = indicating severe problems; Level 5 = indicating extreme problems (for pain and anxiety) or indicating unable to (for mobility, self-care, and activity). The EQ VAS was a quantitative measure of health outcome that reflected the	

participants' own judgement. A lower score represented lower levels of perceived problems.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Cipaglicosidas e Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	36		
Units: Score on a scale				
least squares mean (standard error)	0.03 (± 1.542)	3.61 (± 2.400)		

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Impression Of Change (PGIC) Overall Status

End point title	Physician's Global Impression Of Change (PGIC) Overall Status
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End point description:

Physician's Global Impression of Change is based on a single item that is scored on a 7-point rating scale ranging from 1 "very much worse" to 7 "very much improved".

A tertiary response variable (improving, declining, stable) was defined as follows: "Improving", which consisted of improved, moderately improved, and very much improved; "Declining", which consisted of worse, moderately worse, and very much worse; and "Stable", which equaled to no change.

End point type	Secondary
End point timeframe:	
Week 52	

End point values	Cipaglicosidas e Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	36		
Units: participants				
number (not applicable)				
Improving	31	10		
Stable	38	16		
Declining	11	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Global Impression Of Change (SGIC)

End point title	Subject's Global Impression Of Change (SGIC)
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End point description:

The SGIC is designed to record the participants' impression of their functional status since starting study drug using a 7-point scale ranging from 1 "very much worse" to 7 "very much improved".

A tertiary response variable (improving, declining, stable) was defined as follows: "Improving", which consisted of improved, moderately improved, and very much improved; "Declining", which consisted of worse, moderately worse, and very much worse; and "Stable", which equaled to no change.

End point type	Secondary
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End point timeframe:

Week 52

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	36		
Units: participants				
number (not applicable)				
Improving	36	13		
Stable	33	12		
Declining	12	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Serum Creatine Kinase (CK) Level

End point title	Change From Baseline To Week 52 In Serum Creatine Kinase (CK) Level
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End point description:

CK levels were measured as part of the serum chemistry panel.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: U/L				
arithmetic mean (standard deviation)	-130.5 (± 231.18)	60.2 (± 159.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To Week 52 In Urinary Hexose Tetrasaccharide (Hex4) Level

End point title	Change From Baseline To Week 52 In Urinary Hexose Tetrasaccharide (Hex4) Level
End point description: Levels of urinary Hex4, a biomarker of disease substrate, were measured. The assay specifically targeted Hex4, the glucose tetrasaccharide Glc4, which was a biomarker of glycogen storage.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	Cipaglucosidase Alfa/Miglustat (ITT-LOCF)	Alglucosidase Alfa/Placebo (ITT-LOCF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	37		
Units: mmol/mol creatinine				
arithmetic mean (standard deviation)	-1.88 (± 2.380)	1.22 (± 4.432)		

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetics (PK): Maximum Observed Concentration (Cmax) Of Cipaglucosidase Alfa And Alglucosidase Alfa In ERT-Experienced Participants Using Plasma Total GAA Protein Level By Signature Peptide Assay And Plasma Miglustat Concentration

End point title	Population Pharmacokinetics (PK): Maximum Observed Concentration (Cmax) Of Cipaglucosidase Alfa And Alglucosidase Alfa In ERT-Experienced Participants Using Plasma Total GAA Protein Level By Signature Peptide Assay And Plasma Miglustat Concentration
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis in ERT-experienced

participants at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional.

End point type	Secondary
End point timeframe:	
Days 1 and 364 (Week 52)	

End point values	Cipaglicosidas e Alfa	Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56 ^[15]	26 ^[16]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Day 1	280 (± 18.5)	289 (± 13.2)		
Day 364	293 (± 19.9)	283 (± 17.6)		

Notes:

[15] - Day 1: n=56

Day 364: n=44

[16] - Day 1: n=26

Day 364: n=21

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK: Area Under The Concentration-Time Curve (AUC) Of Cipaglicosidase Alfa And Alglucosidase Alfa In ERT-Experienced Participants Using Plasma Total GAA Protein Level By Signature Peptide Assay And Plasma Miglustat Concentration

End point title	Population PK: Area Under The Concentration-Time Curve (AUC) Of Cipaglicosidase Alfa And Alglucosidase Alfa In ERT-Experienced Participants Using Plasma Total GAA Protein Level By Signature Peptide Assay And Plasma Miglustat Concentration
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis in ERT-experienced participants at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional.

End point type	Secondary
End point timeframe:	
Days 1 and 364 (Week 52)	

End point values	Cipaglicosidas e Alfa	Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56 ^[17]	26 ^[18]		
Units: µg·h/mL				
geometric mean (geometric coefficient of variation)				
Day 1	1395 (± 21.5)	1700 (± 17.6)		
Day 364	1476 (± 21.8)	1688 (± 23.9)		

Notes:

[17] - Day 1: n=56

Day 364: n=26

[18] - Day 1: n=26

Day 364: n=21

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK: Cmax Of CipaglucoSIdase Alfa And AlglucoSIdase Alfa In ERT-Naïve Subjects

End point title	Population PK: Cmax Of CipaglucoSIdase Alfa And AlglucoSIdase Alfa In ERT-Naïve Subjects
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis in ERT-naïve participants at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional.

End point type	Secondary
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End point timeframe:

Days 1 and 364 (Week 52)

End point values	CipaglucoSIdas e Alfa	AlglucoSIdase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[19]	7 ^[20]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Day 1	273 (± 18.1)	342 (± 31.0)		
Day 364	290 (± 17.4)	359 (± 28.1)		

Notes:

[19] - Day 1: n=18

Day 364: n=16

[20] - Day 1: n=7

Day 364 n=7

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK: AUC Of CipaglucoSIdase Alfa And AlglucoSIdase Alfa In ERT-Naïve Subjects

End point title	Population PK: AUC Of CipaglucoSIdase Alfa And AlglucoSIdase Alfa In ERT-Naïve Subjects
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis in ERT-naïve participants at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional.

End point type	Secondary
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End point timeframe:

Days 1 and 364 (Week 52)

End point values	Cipaglucosidase Alfa	Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[21]	7 ^[22]		
Units: µg·h/mL				
geometric mean (geometric coefficient of variation)				
Day 1	1343 (± 25.7)	1859 (± 22.4)		
Day 364	1457 (± 19.2)	1964 (± 26.8)		

Notes:

[21] - Day 1: n=18

Day 364: n=16

[22] - Day 1: n=7

Day 364: n=7

Statistical analyses

No statistical analyses for this end point

Secondary: Noncompartmental Analysis: Cmax Of Plasma Total GAA Protein By Signature Peptide T09 in ERT-Naïve Subjects

End point title	Noncompartmental Analysis: Cmax Of Plasma Total GAA Protein By Signature Peptide T09 in ERT-Naïve Subjects
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End point description:

A noncompartmental analysis was performed on ERT-naïve subjects, who underwent serial PK sampling during the study. On Day 1, serial blood samples were collected for ERT-naïve participants just prior to initiation of cipaglucosidase alfa/alglucosidase alfa infusion (time 0) and at 1, 2, 3, 3.5, 4, 4.5, 6, 8, 10, and 24 hours after the start of cipaglucosidase alfa/alglucosidase alfa infusion for plasma total human acid α-glucosidase (GAA) protein signature peptide T09 and plasma miglustat determinations.

End point type	Secondary
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End point timeframe:

Day 1

End point values	Cipaglucosidase Alfa	Alglucosidase Alfa	Miglustat	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	4	12	
Units: µg/mL				
geometric mean (geometric coefficient of variation)	260 (± 18.4)	364 (± 66.7)	2768 (± 30.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Noncompartmental Analysis: AUC From Time 0 (Predose) To The Time Of Last Quantifiable Concentration Of Plasma Total GAA Protein By Signature Peptide T09 In ERT-Naïve Subjects

End point title	Noncompartmental Analysis: AUC From Time 0 (Predose) To The Time Of Last Quantifiable Concentration Of Plasma Total GAA Protein By Signature Peptide T09 In ERT-Naïve Subjects
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End point description:

A noncompartmental analysis was performed on ERT-naïve subjects, who underwent serial PK sampling during the study. On Day 1, serial blood samples were collected for ERT-naïve participants just prior to initiation of cipaglucosidase alfa/alglucosidase alfa infusion (time 0) and at 1, 2, 3, 3.5, 4, 4.5, 6, 8, 10, and 24 hours after the start of cipaglucosidase alfa/alglucosidase alfa infusion for plasma total GAA protein signature peptide T09 and plasma miglustat determinations.

End point type	Secondary
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End point timeframe:

Day 1

End point values	Cipaglucosidase Alfa	Alglucosidase Alfa	Miglustat	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	4	12	
Units: µg·h/mL				
geometric mean (geometric coefficient of variation)	1264 (± 28.9)	1656 (± 28.9)	20588 (± 36.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison Of Cmax Of Cipaglucosidase Alfa In ERT-Experienced And ERT-Naïve Populations

End point title	Comparison Of Cmax Of Cipaglucosidase Alfa In ERT-Experienced And ERT-Naïve Populations
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional. Data were combined for Days 1 and 364 (Week 52) and analyzed using ANOVA. Ratio of geometric LS mean (%) of the test (ERT-naïve) to the reference (ERT-experienced) and 90% confidence interval (CI) were calculated to assess bioequivalence. Bioequivalence criteria was met if the upper- and lower-bound 90% CIs were within 80% and 125%.

End point type	Secondary
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End point timeframe:

Days 1 and 364 (Week 52)

End point values	Cipaglucosidas e Alfa			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: Ratio of geometric LS mean				
number (confidence interval 90%)	98.0 (90.5 to 106.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison Of AUC Of Cipaglucosidase Alfa In ERT- Experienced And ERT-Naïve Populations

End point title	Comparison Of AUC Of Cipaglucosidase Alfa In ERT- Experienced And ERT-Naïve Populations
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End point description:

On Days 1 and 364 (Week 52), sparse blood samples were collected for PK analysis at 0, 1, 4, 6, 12, and 24 hours post-dose. Collection of the 12-hour sample was optional. Data were combined for Days 1 and 364 (Week 52) and analyzed using ANOVA. Ratio of geometric LS mean (%) of the test (ERT-naïve) to the reference (ERT-experienced) and 90% CI were calculated to assess bioequivalence. Bioequivalence criteria was met if the upper- and lower-bound 90% CIs were within 80% and 125%.

End point type	Secondary
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End point timeframe:

Days 1 and 364 (Week 52)

End point values	Cipaglucosidas e Alfa			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: Ratio of geometric LS mean				
number (confidence interval 90%)	97.3 (88.1 to 106.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Anti-Drug Antibodies (ADAs)

End point title	Number of Participants With Treatment-Emergent Anti-Drug Antibodies (ADAs)
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End point description:

Treatment-emergent ADAs were defined as participants who had seroconverted or boosted their preexisting ADA during the study period.

End point type	Secondary
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End point timeframe:
Baseline up to Week 52

End point values	Cipaglicosidas e Alfa	Alglucosidase Alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65 ^[23]	38 ^[24]		
Units: participants				
number (not applicable)				
ERT-experienced: Treatment-emergent ADAs	31	5		
ERT-naïve: Treatment-emergent ADAs	19	8		

Notes:

[23] - ERT-experienced: n=65

ERT-naïve: n=20

[24] - ERT-experienced: n=30

ERT-naïve: n=8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (after dosing) through Week 52 and follow-up (30 days after last dose).

Adverse event reporting additional description:

All participants who received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Cipaglicosidase Alfa/Miglustat
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Reporting group description: -

Reporting group title	Alglucosidase Alfa/Placebo
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Reporting group description: -

Serious adverse events	Cipaglicosidase Alfa/Miglustat	Alglucosidase Alfa/Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 85 (9.41%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Removal of internal fixation			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 85 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral myositis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cipaglucosidase Alfa/Miglustat	Alglucosidase Alfa/Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 85 (81.18%)	32 / 38 (84.21%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 85 (5.88%)	3 / 38 (7.89%)	
occurrences (all)	10	6	
Fall			
subjects affected / exposed	25 / 85 (29.41%)	15 / 38 (39.47%)	
occurrences (all)	70	31	
Limb injury			
subjects affected / exposed	3 / 85 (3.53%)	2 / 38 (5.26%)	
occurrences (all)	4	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 85 (5.88%)	3 / 38 (7.89%)	
occurrences (all)	7	3	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 85 (1.18%)	2 / 38 (5.26%)	
occurrences (all)	1	3	
Dizziness			
subjects affected / exposed	8 / 85 (9.41%)	3 / 38 (7.89%)	
occurrences (all)	10	4	
Headache			

subjects affected / exposed occurrences (all)	20 / 85 (23.53%) 49	9 / 38 (23.68%) 15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 85 (1.18%)	4 / 38 (10.53%)	
occurrences (all)	2	4	
Fatigue			
subjects affected / exposed	8 / 85 (9.41%)	5 / 38 (13.16%)	
occurrences (all)	10	7	
Infusion site bruising			
subjects affected / exposed	1 / 85 (1.18%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Infusion site erythema			
subjects affected / exposed	0 / 85 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Pain			
subjects affected / exposed	6 / 85 (7.06%)	1 / 38 (2.63%)	
occurrences (all)	7	1	
Pyrexia			
subjects affected / exposed	6 / 85 (7.06%)	1 / 38 (2.63%)	
occurrences (all)	9	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 85 (5.88%)	2 / 38 (5.26%)	
occurrences (all)	7	2	
Abdominal pain			
subjects affected / exposed	2 / 85 (2.35%)	3 / 38 (7.89%)	
occurrences (all)	2	3	
Abdominal pain upper			
subjects affected / exposed	4 / 85 (4.71%)	3 / 38 (7.89%)	
occurrences (all)	11	4	
Constipation			
subjects affected / exposed	2 / 85 (2.35%)	3 / 38 (7.89%)	
occurrences (all)	3	3	
Diarrhoea			

subjects affected / exposed occurrences (all)	11 / 85 (12.94%) 18	4 / 38 (10.53%) 4	
Dyspepsia subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	2 / 38 (5.26%) 2	
Flatulence subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 3	2 / 38 (5.26%) 2	
Nausea subjects affected / exposed occurrences (all)	10 / 85 (11.76%) 14	8 / 38 (21.05%) 9	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	6 / 85 (7.06%) 9	1 / 38 (2.63%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	5 / 85 (5.88%) 6	2 / 38 (5.26%) 2	
Oropharyngeal pain subjects affected / exposed occurrences (all)	10 / 85 (11.76%) 13	2 / 38 (5.26%) 2	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 6	3 / 38 (7.89%) 3	
Rash subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 4	3 / 38 (7.89%) 3	
Skin lesion subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	2 / 38 (5.26%) 2	
Psychiatric disorders Panic attack subjects affected / exposed occurrences (all)	2 / 85 (2.35%) 2	2 / 38 (5.26%) 2	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 85 (15.29%)	5 / 38 (13.16%)	
occurrences (all)	17	6	
Back pain			
subjects affected / exposed	9 / 85 (10.59%)	7 / 38 (18.42%)	
occurrences (all)	13	8	
Groin pain			
subjects affected / exposed	1 / 85 (1.18%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	8 / 85 (9.41%)	1 / 38 (2.63%)	
occurrences (all)	10	1	
Muscular weakness			
subjects affected / exposed	3 / 85 (3.53%)	5 / 38 (13.16%)	
occurrences (all)	4	5	
Musculoskeletal pain			
subjects affected / exposed	10 / 85 (11.76%)	2 / 38 (5.26%)	
occurrences (all)	10	2	
Myalgia			
subjects affected / exposed	14 / 85 (16.47%)	5 / 38 (13.16%)	
occurrences (all)	14	9	
Pain in extremity			
subjects affected / exposed	11 / 85 (12.94%)	2 / 38 (5.26%)	
occurrences (all)	11	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 85 (22.35%)	3 / 38 (7.89%)	
occurrences (all)	28	3	
Pharyngitis			
subjects affected / exposed	1 / 85 (1.18%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	6 / 85 (7.06%)	2 / 38 (5.26%)	
occurrences (all)	8	3	
Sinusitis			

subjects affected / exposed	4 / 85 (4.71%)	3 / 38 (7.89%)	
occurrences (all)	4	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 85 (3.53%)	6 / 38 (15.79%)	
occurrences (all)	3	6	
Urinary tract infection			
subjects affected / exposed	12 / 85 (14.12%)	2 / 38 (5.26%)	
occurrences (all)	15	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2018	<ul style="list-style-type: none">• added sites and ERT-naïve participants to increase sample size and support an indication in all patients with LOPD• clarified the strength and number of capsules of miglustat and amount of cipaglucosidase alfa per vial• increased the duration of treatment• added the number of placebo capsules and amount of alglucosidase alfa per vial• updated interim statistical analyses to reflect changes in study design• changed the primary analysis from an intrasubject comparison to a between-group comparison per advice of the Food and Drug Administration (FDA)• identified key secondary objectives for hierarchical testing• updated results from Study ATB200-02• revised primary objective to reflect change in study design• clarified definition of the final analysis• removed upper limit of the age restriction• broadened the FVC inclusion criterion• modified the screening criterion for 6MWD to be broader and less restrictive• updated other exclusion criteria, including the exclusion of previous gene therapy• clarified contraception guidance with respect to participants in the UK• clarified study drug storage criteria for global studies• removed restriction for registered pharmacist• allowed for an additional day to complete assessments• clarified assessments at infusions visits• separated ET visit from follow-up visit• clarified assessments during the follow-up period• specified collection of historical results for 6MWT, MMT, and FVC as available during the 5 years before the study• added body temperature assessment• replaced the FSS with EQ-5D-5L and added the PROMIS instrument for upper extremity• added MEP assessment• clarified that videotaping is optional• provided details about analysis of key secondary endpoints• updated study conduct considerations

25 January 2019	<ul style="list-style-type: none"> • changed the order of endpoints at the request of the FDA • added a PK substudy in ERT-naïve participants • increased the minimum number of ERT-naïve participants at the request of the FDA • reduced the minimum weight for inclusion • introduced new miglustat dosing guidelines based on participant weight • excluded participants with hypersensitivity to any of the excipients in cipaglucosidase alfa, alglucosidase alfa, or miglustat excluded participants without documentation of Pompe disease and who refused to undergo genetic testing • removed early study stopping and sample size re-estimation provisions in response to comments from the FDA • added the option for home infusions for participants meeting additional criteria • extended the follow-up period for immunogenicity at the request of the FDA • added criteria for the termination of the study at the request of the National Agency for the Safety of Medicines and Health Products (ANSM) • added monitoring of participants during and after the first 3 infusions at the request of the Danish Medicines Agency (DMA) • added sections on randomization, blinding, and unblinding at the request of the DMA and other European agencies • adjusted the collection of immunogenicity samples at the request of the FDA • adjusted scheduling of the Day -15 Screening Visit • revised the contraceptive requirements to align with Clinical Trial Facilitating Group recommendations • updated the severity ratings for AEs • revised which analyses will use the ITT and mITT Populations in response to comments from the FDA • updated the document to reflect additional data
17 August 2020	<ul style="list-style-type: none"> • updated the schedule of Screening Visits • added text due to COVID-19 • updated an exclusion criterion • revised acceptable contraception wording • revised study drug storage temperatures • removed incorrect text regarding ATB200 excipients • added footnote to the Schedule of Assessments to expand upon Week 52/ET visit details • updated schedule of screening visits • revised weeks for collection of blood samples for presence of rhGAA antibodies • revised text for doses based on body weight • defined fasting • revised the collection schedule for blood samples to test for presence of rhGAA Abs • updated the text on rescreening • modified the home infusion criteria to add eligibility for participants whose mild IAR could be controlled with medication • added windows for PK sample collection • revised and updated information regarding blood samples for genotyping for participant randomization • revised informed consent text

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: