Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of AT1001 in Patients with Fabry Disease and AT1001-Responsive GLA Mutations

Summary

EudraCT number	2009-013459-31
Trial protocol	GB FR DE NL BE ES IT DK
Global end of trial date	29 January 2014

Results information

Result version number	v1 (current)
This version publication date	12 August 2016
First version publication date	12 August 2016

Trial information

Trial identification

Sponsor protocol code	AT1001-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00925301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amicus Therapeutics, Inc.
Sponsor organisation address	1 Cedarbrook Drive, Cranbury, United States, NJ 08512
Public contact	Medical Information, Amicus Therapeutics, Inc., MedInfo_Amicus@quintiles.com
Scientific contact	Medical Information, Amicus Therapeutics, Inc., MedInfo_Amicus@quintiles.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	29 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2014
Global end of trial reached?	Yes
Global end of trial date	29 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of migalastat hydrochloride (migalastat HCl) versus placebo on kidney globotriaosylceramide (GL-3) as assessed by histological scoring of the number of inclusions in interstitial capillaries (ICs) in subjects with Fabry disease with a mutation in alpha galactosidase A gene (GLA) that was responsive to migalastat.

Protection of trial subjects:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice, as required by the major regulatory authorities and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2009
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	Argentina: 11
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Egypt: 14
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	180
EEA total number of subjects	48

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)	5
Adults (18-64 years)	168
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

180 subjects enrolled (signed informed consent) & attended 36 study centers in 16 countries. First subject randomized: 23 Oct 2009. Last subject completed: 29 Jan 2014. Period 1 was a 6-month double-blind randomized treatment period. Period 2 was a 6-month OL treatment period. There was an optional 12-month OLE for subjects completing both periods.

Pre-assignment

Screening details:

67 subjects with Fabry disease, naïve to enzyme replacement therapy (ERT) or had not received ERT for at least 6 months and met all eligibility criteria (including having a migalastat-responsive GLA mutation based on the Clinical Trial HEK assay) were randomized to treatment groups in Period 1, 34 Migalastat; 33 Placebo.

Pre-assignment period milestones

Number of subjects started	180
Number of subjects completed	67

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 113

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Migalastat - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Arm type	Experimental
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	Migalastat
Other name	AT1001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of migalastat HCl was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat.

Arm title	Placebo - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and

2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules were identical in appearance to migalastat capsules and contained magnesium stearate and pregelatinized starch. Placebo was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each placebo capsule.

Number of subjects in period 1[1]	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population
Started	34	33
Completed	34	30
Not completed	0	3
Consent withdrawn by subject	-	2
Pregnancy	-	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: The number of subjects starting the baseline period includes all subjects who met the eligibility criteria for the study and is equivalent to the number of subjects completing the pre-assignment period.

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Migalastat - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Arm type	Experimental
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	Migalastat
Other name	AT1001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of migalastat HCl was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat.

Arm title	Placebo - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Arm type	Placebo
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	Migalastat
Other name	AT1001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of migalastat HCl was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat.

Number of subjects in period 2[2]	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population
Started	33	30
Completed	31	29
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 1 subject who completed Period 1 in the Migalastat - Migalastat arm withdrew consent before starting Period 2. As such, in the Migalastat - Migalastat arm 34 subjects completed Period 1 and 33 subjects started Period 2.

Period 3

Period 3 title	Open-Label Extension
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Migalastat - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Arm type	Experimental
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	Migalastat
Other name	AT1001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of migalastat HCl was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat.

Arm title	Placebo - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Arm type	Placebo
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	Migalastat
Other name	AT1001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of migalastat HCl was administered orally QOD at approximately the same time each day. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat.

Number of subjects in period 3[3]	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population
Started	29	28
Completed	27	27
Not completed	2	1
Consent withdrawn by subject	-	1
Pregnancy	1	-
Lost to follow-up	1	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Period 3 of the Study was an optional 12-month open-label extension. As such not all subjects who completed the preceding Period 2 entered the open-label extension.

Baseline characteristics

Reporting groups

Reporting group title	Migalastat - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Reporting group title	Placebo - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group values	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population	Total
Number of subjects	34	33	67
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	0	2
Adults (18-64 years)	31	33	64
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	40	44.5	
standard deviation	± 13.29	± 10.18	-
Gender categorical Units: Subjects			
Male	12	12	24
Female	22	21	43

End points

End points reporting groups

Reporting group title	Migalastat - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Reporting group title	Placebo - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group title	Migalastat - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Reporting group title	Placebo - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group title	Migalastat - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 millgram (mg) orally every other day (QOD) at approximately the same time. During Period 2 (6-month open-label [OL] treatment period) all subjects received migalastat HCl 150 mg orally QOD. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month open-label extension (OLE) phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose. Inactive reminder capsules were taken on alternate days during each treatment period.

Reporting group title	Placebo - Migalastat ITT Population

Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received a matching placebo orally QOD. During Period 2 (6-month OL treatment period) all subjects received migalastat HCl 150 mg orally QOD. Inactive reminder capsules were taken on alternate days. Subjects completing both Periods 1 and 2 were eligible to participate in a 12-month OLE phase and continued to take migalastat HCl 150 mg QOD for up to 12 months. Subjects were required to fast 2 hours before and 2 hours after each dose.

Subject analysis set title	Migalastat-Migalastat ITT Population (amenable GLA mutations)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Migalastat - Migalastat ITT population with amenable GLA mutations includes subjects in the Intent-to-Treat (ITT) population who were randomized to receive migalastat in Period 1 and who had amenable mutations based on the Good Laboratory Practice (GLP) Human Embryonic Kidney (HEK) assay.

Subject analysis set title	Placebo-Migalastat ITT Population (amenable GLA mutations)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Placebo - Migalastat ITT population with amenable GLA mutations includes subjects in the ITT population who were randomized to receive placebo in Period 1 and who had amenable mutations based on the GLP HEK assay.

Subject analysis set title	OLE Population with amenable GLA mutations
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The OLE population includes all randomized subjects included in the OLE population with amenable mutations based on the GLP HEK assay.

Subject analysis set title	Migalastat Safety Population (24-month analyses)
Subject analysis set type	Safety analysis

Subject analysis set description:

The migalastat safety population (24-month analyses) includes all subjects in the ITT population who received at least 1 dose of migalastat during Periods 1, 2 and 3.

Subject analysis set title	Placebo Safety Population (6-month analyses)
Subject analysis set type	Safety analysis

Subject analysis set description:

The placebo safety population (6-month analyses) includes all subjects in the ITT population who received at least 1 dose of placebo during Period 1.

Primary: IC GL-3 Responder Analysis

End point title	IC GL-3 Responder Analysis

End point description:

A subject was described as a responder if the average number of IC GL-3 inclusions at Month 6 (Visit 4) had been reduced by at least 50% from the average number of inclusions at Baseline (Visit 1). The percentage of subjects meeting this definition is presented. The full ITT Population was used for this analysis and included all randomized subjects regardless of mutation status in the GLP HEK assay.

End point type	Primary

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	33		
Units: Responder rate (percentage responders)				
number (not applicable)				
IC GL-3 Responder Analysis	40.6	28.1		

Statistical analyses

Statistical analysis title	Rate Difference (Migalastat minus Placebo)

Statistical analysis description:

The proportion of successes (i.e. ≥50% reduction from Baseline to Month 6 in the average number of IC GL-3 inclusions) in each treatment group was compared using the exact Cochran-Mantel-Haenszel test stratified by sex. The difference of the proportion of successes between the 2 groups and its exact 95% confidence interval was calculated.

Comparison groups	Migalastat - Migalastat ITT Population v Placebo - Migalastat ITT Population

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2996
Method	Cochran-Mantel-Haenszel
Parameter estimate	Responder Rate Difference
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	37.3

Secondary: IC GL-3 Inclusions Percent Change from Baseline (Visit 1)

End point title	IC GL-3 Inclusions Percent Change from Baseline (Visit 1)

End point description:

Percent changes from Baseline (Visit 1) were based on a summary of individual percent change from Baseline (Visit 1) in GL-3 inclusions. The full ITT Population was used for this analysis and included all randomized subjects regardless of mutation status in the GLP HEK assay.

End point type	Secondary

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Percentage responders				
arithmetic mean (standard deviation)				
IC GL-3 Inclusions Percent Change from Baseline	-7.948 (± 105.2736)	12.985 (± 90.5131)		

Statistical analyses

Statistical analysis title	Treatment Difference (Migalastat minus Placebo)

Statistical analysis description:

The percent change from Baseline (Visit 1) in the average number of IC GL-3 inclusions was analyzed using an analysis of covariance (ANCOVA) model based on ranked observations with covariate adjustment for the baseline value and factors for treatment group and the treatment by baseline interaction. The p-value corresponds to the least-square (LS) mean difference between migalastat-migalastat and placebo-migalastat.

Comparison groups	Migalastat - Migalastat ITT Population v Placebo - Migalastat ITT Population

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0974
Method	ANCOVA

Notes:

[1] - Non-parametric analysis

Other pre-specified: Change in Percent ICs with Zero GL-3 Inclusions

End point title	Change in Percent ICs with Zero GL-3 Inclusions

End point description:

The change from Baseline (Visit 1) to Month 6 (Visit 4) in the percent of ICs with zero GL-3 inclusions was a tertiary efficacy endpoint. The full ITT Population was used for this analysis and included all randomized subjects regardless of mutation status in the GLP HEK assay.

End point type	Other pre-specified

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat - Migalastat ITT Population	Placebo - Migalastat ITT Population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Percent ICs				
least squares mean (standard deviation)				
Change in Percent ICs with Zero GL-3 Inclusions	7.304 (± 9.7206)	1.317 (± 11.7467)		

Statistical analyses

Statistical analysis title	Treatment Difference (Migalastat minus Placebo)

Statistical analysis description:

The change from Baseline in percent of capillaries with zero GL-3 inclusions was analyzed using an ANCOVA model with covariate adjustment for the Baseline value and factors for treatment group, sex, and the treatment by Baseline interaction, sex by treatment interaction and sex by Baseline interaction. The p-value corresponds to the LS mean difference between migalastat-migalastat and placebo-migalastat.

Comparison groups	Migalastat - Migalastat ITT Population v Placebo - Migalastat ITT Population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0418
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	11.7

Notes:

[2] - Non-parametric analysis

Other pre-specified: Change in Plasma globotriaosylsphingosine (Lyso-Gb3)

End point title	Change in Plasma globotriaosylsphingosine (Lyso-Gb3)

End point description:

The change from Baseline (Visit 1) to Month 6 (Visit 4) in Plasma Lyso-Gb3 was a pre-specified exploratory endpoint. The ITT Population with amenable mutations was used for this analysis and included all randomized subjects with amenable mutations based on the GLP HEK assay.

End point type	Other pre-specified

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat-Migalastat ITT Population (amenable GLA mutations)	Placebo-Migalastat ITT Population (amenable GLA mutations)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	13		
Units: nmol/L				
least squares mean (standard deviation)				
Change in Plasma Lyso-Gb3	-10.58 (± 20.196)	0.83 (± 8.548)		

Statistical analyses

Statistical analysis title	Treatment Difference (Migalastat minus Placebo)

Statistical analysis description:

Data were analyzed using an ANCOVA model that included treatment as a factor with the Baseline value as a covariate and the treatment by Baseline interaction. The treatment effect was estimated as the difference between migalastat and placebo in the LS mean estimates for treatment.

Comparison groups	Migalastat-Migalastat ITT Population (amenable GLA mutations) v Placebo-Migalastat ITT Population (amenable GLA mutations)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0033
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-11.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	-4.1

Notes:

[3] - Non-parametric analysis

Other pre-specified: Annualized Change in Estimated Glomerular Filtration Rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR CKD-EPI)

End point title	Annualized Change in Estimated Glomerular Filtration Rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR CKD-EPI)

End point description:

The eGFR CKD-EPI is calculated as GFR=141 x min(Scr/κ,1)α x max(Scr/κ,1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. The OLE Population with amenable mutations was used for this analysis and included all randomized subjects included in the OLE with amenable mutations based on the GLP HEK assay.

End point type	Other pre-specified

End point timeframe:

Baseline (Visit 1) to Month 24 (Visit 10)

End point values	OLE Population with amenable GLA mutations			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: mL/min/1.73m2				
arithmetic mean (standard error)				
Annualized Change in eGFR CKD-EPI	-0.3 (± 0.663)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change in Average Number of IC GL-3 Inclusions

End point title	Change in Average Number of IC GL-3 Inclusions

End point description:

The change from Baseline (Visit 1) to Month 6 (Visit 4) in average number of IC GL-3 inclusions was a Post-Hoc endpoint. The ITT Population with amenable mutations was used for this analysis and included all randomized subjects with amenable mutations based on the GLP HEK assay.

End point type	Post-hoc

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat-Migalastat ITT Population (amenable GLA mutations)	Placebo-Migalastat ITT Population (amenable GLA mutations)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	20		
Units: number				
least squares mean (standard deviation)				
Change in Average Number of IC GL-3 Inclusions	-0.224 (± 0.5126)	0.106 (± 0.5627)		

Statistical analyses

Statistical analysis title	Treatment Difference (Migalastat minus Placebo)

Statistical analysis description:

The change from Baseline (Visit 1) to Month 6 (Visit 4) in the average number of inclusions per capillary was analyzed using an ANCOVA model with covariate adjustment for the Baseline value and factors for treatment group and the treatment by Baseline interaction. The p-value corresponds to the LS mean difference between migalastat-migalastat and placebo-migalastat.

Comparison groups	Migalastat-Migalastat ITT Population (amenable GLA mutations) v Placebo-Migalastat ITT Population (amenable GLA mutations)
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	other[4]
P-value	= 0.0078
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1

Notes:

[4] - Non-parametric analysis

Post-hoc: Change from Baseline (Visit 1) in the Gastrointestinal Symptom Rating Scale (GSRS) Diarrhea Subscale

End point title	Change from Baseline (Visit 1) in the Gastrointestinal Symptom Rating Scale (GSRS) Diarrhea Subscale

End point description:

The change from Baseline (Visit 1) to Month 6 (Visit 4) in the Diarrhea Subscale of the GSRS was a Post-Hoc endpoint. The ITT Population with amenable mutations was used for this analysis and included all randomized subjects with amenable mutations based on the GLP HEK assay.

End point type	Post-hoc

End point timeframe:

Baseline (Visit 1) to Month 6 (Visit 4)

End point values	Migalastat-Migalastat ITT Population (amenable GLA mutations)	Placebo-Migalastat ITT Population (amenable GLA mutations)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	19		
Units: units on a scale				
least squares mean (standard deviation)				
Change from Baseline in the GSRS Diarrhea Subscale	-0.3 (± 0.86)	0.2 (± 0.75)		

Statistical analyses

Statistical analysis title	Treatment Difference (Migalastat minus Placebo)

Statistical analysis description:

Data were analyzed using an ANCOVA model that included treatment, Baseline and treatment by Baseline interaction. The treatment effect was estimated as the difference between migalastat and placebo in the LS mean estimates for treatment.

Comparison groups	Migalastat-Migalastat ITT Population (amenable GLA mutations) v Placebo-Migalastat ITT Population (amenable GLA mutations)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	other[5]
P-value	= 0.0264
Method	ANCOVA
Parameter estimate	LS mean difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.1

Notes:

[5] - Non-parametric analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the first dose of study medication in Period 1 through to 1 month (±7 days) after the date of last study visit whether in Period 1, 2 or 3.

Adverse event reporting additional description:

AE data is reported as treatment-emergent AEs. AEs are presented for the safety population for all study periods, i.e. 24 months. Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Migalastat Safety Population (24-month analyses)

Reporting group description:

The migalastat safety population (24-month analyses) includes all subjects in the Intent-to Treat (ITT) population who received at least 1 dose of migalastat during Periods 1, 2 and 3.

Reporting group title	Placebo Safety Population (6-month analyses)

Reporting group description:

The placebo safety population (6-month analyses) includes all subjects in the ITT population who received at least 1 dose of placebo during Period 1.

Serious adverse events	Migalastat Safety Population (24-month analyses)	Placebo Safety Population (6-month analyses)	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 64 (23.44%)	4 / 33 (12.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANAPLASTIC LARGE CELL LYMPHOMA T- AND NULL-CELL TYPES	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	0 / 64 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
MULTIPLE FRACTURES	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		

subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	0 / 64 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
PALPITATIONS	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
AMYOTROPHIC LATERAL SCLEROSIS	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		

subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
FATIGUE	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		

subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN LOWER	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	2 / 64 (3.13%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
BULIMIA NERVOSA	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		

subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HYDRONEPHROSIS	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BONE CYST	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BACTERIAL INFECTION	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	0 / 64 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HELICOBACTER GASTRITIS	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	1 / 64 (1.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS VIRAL	Additional description: Reporting groups: Migalastat Safety Population (24-month analyses) (subjects received migalastat in Periods 1, 2 and 3); and Placebo Safety Population (6-month analyses) (subjects received placebo in Period 1).		
subjects affected / exposed	0 / 64 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Migalastat Safety Population (24-month analyses)	Placebo Safety Population (6-month analyses)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 64 (87.50%)	23 / 33 (69.70%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 64 (6.25%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	7 / 64 (10.94%)	4 / 33 (12.12%)	
occurrences (all)	9	4	
PYREXIA			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	9	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	5 / 64 (7.81%)	0 / 33 (0.00%)	
occurrences (all)	6	0	
EPISTAXIS			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
OROPHARYNGEAL PAIN			
subjects affected / exposed	8 / 64 (12.50%)	2 / 33 (6.06%)	
occurrences (all)	8	2	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
DEPRESSION			
subjects affected / exposed	7 / 64 (10.94%)	0 / 33 (0.00%)	
occurrences (all)	8	0	
INSOMNIA			
subjects affected / exposed	3 / 64 (4.69%)	2 / 33 (6.06%)	
occurrences (all)	3	2	
Injury, poisoning and procedural complications			

INCORRECT DOSE ADMINISTERED			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
PROCEDURAL PAIN			
subjects affected / exposed	8 / 64 (12.50%)	1 / 33 (3.03%)	
occurrences (all)	10	1	
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 64 (7.81%)	1 / 33 (3.03%)	
occurrences (all)	6	1	
HEADACHE			
subjects affected / exposed	22 / 64 (34.38%)	7 / 33 (21.21%)	
occurrences (all)	60	8	
PARAESTHESIA			
subjects affected / exposed	10 / 64 (15.63%)	4 / 33 (12.12%)	
occurrences (all)	13	4	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	5 / 64 (7.81%)	3 / 33 (9.09%)	
occurrences (all)	5	3	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	5 / 64 (7.81%)	1 / 33 (3.03%)	
occurrences (all)	6	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	6 / 64 (9.38%)	0 / 33 (0.00%)	
occurrences (all)	6	0	
CONSTIPATION			
subjects affected / exposed	5 / 64 (7.81%)	2 / 33 (6.06%)	
occurrences (all)	6	2	
DIARRHEA			
subjects affected / exposed	10 / 64 (15.63%)	1 / 33 (3.03%)	
occurrences (all)	13	1	

DRY MOUTH			
subjects affected / exposed	2 / 64 (3.13%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
NAUSEA			
subjects affected / exposed	9 / 64 (14.06%)	2 / 33 (6.06%)	
occurrences (all)	12	2	
VOMITING			
subjects affected / exposed	5 / 64 (7.81%)	2 / 33 (6.06%)	
occurrences (all)	5	2	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	4 / 64 (6.25%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
PROTEINURIA			
subjects affected / exposed	9 / 64 (14.06%)	0 / 33 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	8 / 64 (12.50%)	2 / 33 (6.06%)	
occurrences (all)	10	2	
BACK PAIN			
subjects affected / exposed	8 / 64 (12.50%)	0 / 33 (0.00%)	
occurrences (all)	9	0	
MUSCLE SPASMS			
subjects affected / exposed	4 / 64 (6.25%)	3 / 33 (9.09%)	
occurrences (all)	6	4	
MYALGIA			
subjects affected / exposed	5 / 64 (7.81%)	1 / 33 (3.03%)	
occurrences (all)	6	2	
NECK PAIN			
subjects affected / exposed	4 / 64 (6.25%)	1 / 33 (3.03%)	
occurrences (all)	11	1	
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 64 (4.69%)	4 / 33 (12.12%)	
occurrences (all)	5	6	
Infections and infestations			

BRONCHITIS			
subjects affected / exposed	8 / 64 (12.50%)	0 / 33 (0.00%)	
occurrences (all)	10	0	
INFLUENZA			
subjects affected / exposed	2 / 64 (3.13%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
NASOPHARYNGITIS			
subjects affected / exposed	12 / 64 (18.75%)	2 / 33 (6.06%)	
occurrences (all)	15	2	
SINUSITIS			
subjects affected / exposed	4 / 64 (6.25%)	0 / 33 (0.00%)	
occurrences (all)	6	0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 64 (12.50%)	3 / 33 (9.09%)	
occurrences (all)	13	4	
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 64 (14.06%)	0 / 33 (0.00%)	
occurrences (all)	11	0	
Metabolism and nutrition disorders			
VITAMIN D DEFICIENCY			
subjects affected / exposed	5 / 64 (7.81%)	1 / 33 (3.03%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2009	• Changed the stopping criterion regarding serum creatinine from a 50% increase to a 30% increase. • Removed surgical sterilization as an acceptable method of contraception for male subjects. • Clarified methods of surgical sterilization allowed as contraception for female subjects to include hysterectomy or bilateral tubal ligation, oophorectomy or salpingectomy. • Changed to not require female subjects using a diaphragm as contraception to use the diaphragm in combination with male condoms. Eliminated monthly at home pregnancy tests. • Added Levaquin and amiodarone as prohibited medications.
10 August 2010	This description includes the cummulative changes from Amendment 2 (dated 27 July 2010) and Amendment 2.1 (dated 10 August 2010): • Added details of the open-label extension • Corrected inclusion criterion #4 "from urine GL-3 greater than 4 times…" to "urine GL-3 greater than or equal to 4 times…" • Removed exclusion criterion #3, which was related to QTc at Screening • Removed Levaquin and amiodarone from the list of prohibited medications • Permitted repeat assessments at Screening and rescreening of subjects who screen failed • No longer required repeat testing of persistent clinically significant results • Added blister packaged study drug. Corrected description of the color of study drug capsules • Prior versions of the protocol stipulated that the iohexol dose was to be administered over 1 to 2 minutes; the laboratory manual specified that the iohexol dose was to be administered over 30 seconds to 1 minute. The protocol was modified to align with the laboratory manual. • Provided guidance for cases in which a subject discontinued within a short time from Baseline (Visit 1), Month 6 (Visit 4), or Month 12 (Visit 6).

20 September 2011	• Added opportunity for subjects to transition into a separate open-label extension protocol • Revised so that the Follow-Up Visit occurred after the last study treatment visit • No longer required subjects to have a Follow-Up Visit if they entered the open-label extension • Clarified method of assessing study drug compliance • Clarified which female subjects were required to undergo pregnancy testing • Clarified visit windows and standardized definition of a study month • Clarified that it may not be possible to perform all assessments at certain visits within 1 day • Allowed an Unscheduled Visit to occur at the discretion of the investigator • Described procedures to occur for subjects taking study drug after 24 months of treatment • Clarified when serum and urine pregnancy tests would be taken • Added request to repeat urinalysis if visits involving a kidney biopsy spanned a long period of time • Clarified timing of blood draws and removed requirements for visit windows for pharmacokinetic assessments • Provided guidance for evaluation of disease progression of Fabry symptoms as AEs • Changed definition of serious AEs to reflect Food and Drug Administration revisions. Clarified reporting timelines. • Clarified responsibilities of investigator and sponsor.
20 November 2012	This description includes cummulative changes from Amendment 4 (dated 1 November 2012) and Amendment 4.1 (dated 20 November 2012): • Revised description of contraception requirements • Added optional blood draw for GLA genotyping • Allowed for potential future genetic testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported