



## 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
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##### 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:

<b>Subjects enrolled per age group</b>	
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
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### 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
<b>Arm title</b>	Migalastat - Migalastat ITT Population

#### Arm description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 milligram (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.

<b>Arm title</b>	Placebo - Migalastat ITT Population
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#### 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.

<b>Number of subjects in period 1<sup>[1]</sup></b>	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
<b>Arm title</b>	Migalastat - Migalastat ITT Population

Arm description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 milligram (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.

<b>Arm title</b>	Placebo - Migalastat ITT Population
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**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.

<b>Number of subjects in period 2<sup>[2]</sup></b>	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
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<b>Arm title</b>	Migalastat - Migalastat ITT Population
Arm description:	
During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 milligram (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.	
<b>Arm title</b>	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.	

<b>Number of subjects in period 3<sup>[3]</sup></b>	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
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Reporting group description:

During Period 1 (6-month randomized treatment period), subjects received migalastat HCl 150 milligram (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
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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 milligram (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 milligram (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 milligram (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 milligram (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
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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
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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)
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Statistical analysis description:

The proportion of successes (i.e.  $\geq 50\%$  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
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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 <sup>[1]</sup>
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
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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
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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)
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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 <sup>[2]</sup>
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)
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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
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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)
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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 <sup>[3]</sup>
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)
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End point description:

The eGFR CKD-EPI is calculated as  $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$  [if female]  $\times 1.159$  [if black], where Scr is serum creatinine,  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ $\kappa$  or 1, and max indicates the maximum of Scr/ $\kappa$  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
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End point timeframe:

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

<b>End point values</b>	OLE Population with amenable GLA mutations			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: mL/min/1.73m <sup>2</sup>				
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
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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
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End point timeframe:

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

<b>End point values</b>	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 ( $\pm$ 0.5126)	0.106 ( $\pm$ 0.5627)		

## Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[4]</sup>
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

<b>End point title</b>	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)	

<b>End point values</b>	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

<b>Statistical analysis title</b>	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 <sup>[5]</sup>
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 ( $\pm 7$  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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Migalastat Safety Population (24-month analyses)
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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)
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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	
<b>Renal and urinary disorders</b>			
<b>HYDRONEPHROSIS</b>	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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>BONE CYST</b>	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	
<b>Infections and infestations</b>			
<b>BACTERIAL INFECTION</b>	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	
<b>HELICOBACTER GASTRITIS</b>	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	
<b>MENINGITIS VIRAL</b>	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 %

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

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

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



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	<ul style="list-style-type: none"><li>• Changed the stopping criterion regarding serum creatinine from a 50% increase to a 30% increase.</li><li>• Removed surgical sterilization as an acceptable method of contraception for male subjects.</li><li>• Clarified methods of surgical sterilization allowed as contraception for female subjects to include hysterectomy or bilateral tubal ligation, oophorectomy or salpingectomy.</li><li>• 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.</li><li>• Added Levaquin and amiodarone as prohibited medications.</li></ul>
10 August 2010	<p>This description includes the cumulative changes from Amendment 2 (dated 27 July 2010) and Amendment 2.1 (dated 10 August 2010):</p> <ul style="list-style-type: none"><li>• Added details of the open-label extension</li><li>• Corrected inclusion criterion #4 "from urine GL-3 greater than 4 times..." to "urine GL-3 greater than or equal to 4 times..."</li><li>• Removed exclusion criterion #3, which was related to QTc at Screening</li><li>• Removed Levaquin and amiodarone from the list of prohibited medications</li><li>• Permitted repeat assessments at Screening and rescreening of subjects who screen failed</li><li>• No longer required repeat testing of persistent clinically significant results</li><li>• Added blister packaged study drug. Corrected description of the color of study drug capsules</li><li>• 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.</li><li>• 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).</li></ul>

20 September 2011	<ul style="list-style-type: none"> <li>• Added opportunity for subjects to transition into a separate open-label extension protocol</li> <li>• Revised so that the Follow-Up Visit occurred after the last study treatment visit</li> <li>• No longer required subjects to have a Follow-Up Visit if they entered the open-label extension</li> <li>• Clarified method of assessing study drug compliance</li> <li>• Clarified which female subjects were required to undergo pregnancy testing</li> <li>• Clarified visit windows and standardized definition of a study month</li> <li>• Clarified that it may not be possible to perform all assessments at certain visits within 1 day</li> <li>• Allowed an Unscheduled Visit to occur at the discretion of the investigator</li> <li>• Described procedures to occur for subjects taking study drug after 24 months of treatment</li> <li>• Clarified when serum and urine pregnancy tests would be taken</li> <li>• Added request to repeat urinalysis if visits involving a kidney biopsy spanned a long period of time</li> <li>• Clarified timing of blood draws and removed requirements for visit windows for pharmacokinetic assessments</li> <li>• Provided guidance for evaluation of disease progression of Fabry symptoms as AEs</li> <li>• Changed definition of serious AEs to reflect Food and Drug Administration revisions. Clarified reporting timelines.</li> <li>• Clarified responsibilities of investigator and sponsor.</li> </ul>
20 November 2012	<p>This description includes cumulative changes from Amendment 4 (dated 1 November 2012) and Amendment 4.1 (dated 20 November 2012):</p> <ul style="list-style-type: none"> <li>• Revised description of contraception requirements</li> <li>• Added optional blood draw for GLA genotyping</li> <li>• Allowed for potential future genetic testing.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported