Clinical trial results:
A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients With Fabry Disease and AT1001-Responsive GLA Mutations, Who Were Previously Treated With ERT.

Summary

EudraCT number	2010-022636-37
Trial protocol	BE GB DK AT GR DE IT
Global end of trial date	28 May 2015

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	08 July 2016

Trial information

Trial identification

Sponsor protocol code	AT1001-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01218659
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	28 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2015
Global end of trial reached?	Yes
Global end of trial date	28 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to compare the efficacy and safety of migalastat hydrochloride (migalastat HCl) to ERT in subjects with Fabry disease who were currently receiving ERT and who had migalastat-responsive alpha-galactosidase A gene (GLA) mutations.

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:

Current approved therapy for Fabry disease is ERT consisting of lifelong biweekly intravenous infusion with 1 of 2 synthetic enzymes (agalsidase alfa or agalsidase beta) to treat the deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A).

Actual start date of recruitment	08 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	68
EEA total number of subjects	34

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

68 subjects were enrolled in this 2 period study. Subjects attended 25 study centres in 10 countries. First subject enrolled: 8 September 2011. Last subject completed: 28 May 2015. Period 1 was an 18-month randomized treatment period; Period 2 was an optional 12 month OLE.

Pre-assignment

Screening details:

Subjects with Fabry disease who were previously treated with ERT for at least 12 months and with known GLA mutations were enrolled. 60 subjects were randomized, 36 to the migalastat group and 24 to the ERT group (Period 1). The first dose of migalastat was given at Visit 2, 10 to 18 days after the last ERT infusion in the screening period.

Pre-assignment period milestones

Number of subjects started	68
Number of subjects completed	60

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 8

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Migalastat-Migalastat

Arm description:

During Period 1 (18-month randomized treatment period), subjects received migalastat HCl 150 milligram (mg) orally every other day (QOD) at approximately the same time. Inactive reminder capsules were taken on alternate days during each treatment period. During Period 2 (optional 12-month open-label extension [OLE]) all subjects received migalastat HCl 150 mg orally. Subjects were required to fast 2 hours before and 2 hours after each dose.

Arm type	Experimental
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	AT1001
Other name	Migalastat
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	ERT-Migalastat

Arm description:

During Period 1 (18-month randomized treatment period), subjects continued to receive at least 80% of the currently labelled dose and regimen of ERT (agalsidase alfa or agalsidase beta) as an intravenous infusion and as prescribed by the subject's treating physician. The dose level and regimen of ERT were required to be stable for the 3 months prior to the baseline visit. During Period 2 (optional 12-month OLE) all subjects received migalastat HCl 150 mg orally.

Arm type	Active comparator

Investigational medicinal product name	ERT
Investigational medicinal product code	ERT
Other name	Agalsidase
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Agalsidase alfa or agalsidase beta was administered as an intravenous infusion in accordance with the prescibing information of the treating physician. Subjects were required to fast 2 hours before and 2 hours after taking each dose.

Number of subjects in period 1[1]	Migalastat-Migalastat	ERT-Migalastat
Started	36	24
Completed	34	18
Not completed	2	6
Consent withdrawn by subject	2	6

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	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Migalastat-Migalastat

Arm description:

During Period 1 (18-month randomized treatment period), subjects received migalastat HCl 150 milligram (mg) orally every other day (QOD) at approximately the same time. Inactive reminder capsules were taken on alternate days during each treatment period. During Period 2 (optional 12-month open-label extension [OLE]) all subjects received migalastat HCl 150 mg orally. Subjects were required to fast 2 hours before and 2 hours after each dose.

Arm type	Experimental
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	AT1001
Other name	Migalastat
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	ERT-Migalastat

Arm description:

During Period 1 (18-month randomized treatment period), subjects continued to receive at least 80% of the currently labelled dose and regimen of ERT (agalsidase alfa or agalsidase beta) as an intravenous

infusion and as prescribed by the subject's treating physician. The dose level and regimen of ERT were required to be stable for the 3 months prior to the baseline visit. During Period 2 (optional 12-month OLE) all subjects received migalastat HCl 150 mg orally.

Arm type	Active comparator
Investigational medicinal product name	Migalastat HCl
Investigational medicinal product code	AT1001
Other name	Migalastat
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	ERT-Migalastat
Started	33	15
Completed	30	12
Not completed	3	3
Consent withdrawn by subject	1	1
Physician decision	-	1
Pregnancy	1	-
Lost to follow-up	-	1
Lack of efficacy	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: Period 2 of the Study was an optional 12-month open-label extension. As such not all subjects who completed Period 1 entered Period 2.

Baseline characteristics

Reporting groups

Reporting group title	Migalastat-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects received migalastat HCl 150 milligram (mg) orally every other day (QOD) at approximately the same time. Inactive reminder capsules were taken on alternate days during each treatment period. During Period 2 (optional 12-month open-label extension [OLE]) all subjects received migalastat HCl 150 mg orally. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group title	ERT-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects continued to receive at least 80% of the currently labelled dose and regimen of ERT (agalsidase alfa or agalsidase beta) as an intravenous infusion and as prescribed by the subject's treating physician. The dose level and regimen of ERT were required to be stable for the 3 months prior to the baseline visit. During Period 2 (optional 12-month OLE) all subjects received migalastat HCl 150 mg orally.

Reporting group values	Migalastat-Migalastat	ERT-Migalastat	Total
Number of subjects	36	24	60
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)	0	0	0
Adults (18-64 years)	32	21	53
From 65-84 years	4	3	7
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.5	44.9	
standard deviation	± 13.76	± 14.47	-
Gender Categorical Units: Subjects			
Male	16	10	26
Female	20	14	34

End points

End points reporting groups

Reporting group title	Migalastat-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects received migalastat HCl 150 milligram (mg) orally every other day (QOD) at approximately the same time. Inactive reminder capsules were taken on alternate days during each treatment period. During Period 2 (optional 12-month open-label extension [OLE]) all subjects received migalastat HCl 150 mg orally. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group title	ERT-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects continued to receive at least 80% of the currently labelled dose and regimen of ERT (agalsidase alfa or agalsidase beta) as an intravenous infusion and as prescribed by the subject's treating physician. The dose level and regimen of ERT were required to be stable for the 3 months prior to the baseline visit. During Period 2 (optional 12-month OLE) all subjects received migalastat HCl 150 mg orally.

Reporting group title	Migalastat-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects received migalastat HCl 150 milligram (mg) orally every other day (QOD) at approximately the same time. Inactive reminder capsules were taken on alternate days during each treatment period. During Period 2 (optional 12-month open-label extension [OLE]) all subjects received migalastat HCl 150 mg orally. Subjects were required to fast 2 hours before and 2 hours after each dose.

Reporting group title	ERT-Migalastat

Reporting group description:

During Period 1 (18-month randomized treatment period), subjects continued to receive at least 80% of the currently labelled dose and regimen of ERT (agalsidase alfa or agalsidase beta) as an intravenous infusion and as prescribed by the subject's treating physician. The dose level and regimen of ERT were required to be stable for the 3 months prior to the baseline visit. During Period 2 (optional 12-month OLE) all subjects received migalastat HCl 150 mg orally.

Subject analysis set title	Migalastat with amenable GLA mutations
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The migalastat with amenable GLA mutations modified Intent-to-Treat (mITT) population includes all randomized subjects with mutations amenable to migalastat in the Good Laboratory Practice Human Embryonic Kidney (GLP HEK) assay who received at least 1 dose of migalastat and who had relevant baseline and postbaseline efficacy measures.

Subject analysis set title	ERT with amenable GLA mutations
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The ERT with amenable GLA mutations mITT population includes all randomized subjects with mutations amenable to migalastat in the GLP HEK assay who received at least 1 dose of ERT and who had relevant baseline and postbaseline efficacy measures.

Subject analysis set title	Migalastat Safety Population (30-month analyses)
Subject analysis set type	Safety analysis

Subject analysis set description:

The migalastat safety population (30-month analyses) includes all subjects in the ITT population who received at least 1 dose of migalastat during Periods 1 and 2.

Subject analysis set title	ERT Safety Population (18-month analyses)
Subject analysis set type	Safety analysis

Subject analysis set description:

The ERT safety population (18-month analyses) includes all subjects in the ITT population who received at least 1 dose of ERT during Period 1.

Primary: Estimated glomerular filtration rate (eGFR)

End point title	Estimated glomerular filtration rate (eGFR)[1]

End point description:

The annualized rate of change in eGFR is presented for subjects who received migalastat or ERT in Period 1. This was assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR[CKD-EPI]) and was determined for subjects with GLA mutations amenable to migalastat in the validated GLP HEK assay. The calculated least squares (LS) means and confidence intervals (CIs) are based on an analysis of covariance (ANCOVA) model that includes the treatment groups, baseline eGFR[CKD-EPI], sex, age and baseline 24-hour urine protein stratification factor. The measure of comparability between migalastat and ERT in the annualized rate of change of primary efficacy parameters was defined as a >50% overlap of the 95% CIs and a difference of LS mean annualized rate of change no greater than 2.2 mL/min/1.73 m2.

End point type	Primary

End point timeframe:

Baseline to Month 18

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Study analyses were performed using descriptive statistics. No statistical inference testing was performed.

End point values	Migalastat with amenable GLA mutations	ERT with amenable GLA mutations		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	18		
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	-0.397 (-2.272 to 1.478)	-1.031 (-3.636 to 1.575)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in left ventricular mass index (LVMi)

End point title	Change from Baseline in left ventricular mass index (LVMi)

End point description:

The cardiac parameter LVMi was measured by echocardiogram (ECHO) at Visits 2, 5, 7, 9, 12 and 13, and the ECHOs were read centrally in a blinded fashion. The change from Baseline to Month 18 is presented for subjects who received migalastat or ERT in Period 1.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Migalastat with amenable GLA mutations	ERT with amenable GLA mutations		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	18		
Units: grams per square meter (g/m2)				
arithmetic mean (standard deviation)	-6.578 (±	-2.015 (±		

12.0817)	14.8569)

Statistical analyses

No statistical analyses for this end point

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 30 days after the last treatment visit whether in Period 1 or Period 2.

Adverse event reporting additional description:

AE data is reported as treatment-emergent AEs. AEs are presented for subjects in the safety population for both study periods, i.e. over 30 months. Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 and 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Migalastat Safety Population (30-month analyses)

Reporting group description:

The migalastat safety population includes all subjects in the ITT population who received at least 1 dose of migalastat during Periods 1 and 2.

Reporting group title	ERT Safety Population (18-month analyses)

Reporting group description:

The ERT safety population includes all subjects in the ITT population who received at least 1 dose of ERT during Period 1.

Serious adverse events	Migalastat Safety Population (30-month analyses)	ERT Safety Population (18-month analyses)	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 51 (31.37%)	7 / 21 (33.33%)	
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)			
PHAEOCHROMOCYTOMA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (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			
CHEST PAIN	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		

subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE MALFUNCTION	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1). Event experienced by 1 subject in separate periods.		
subjects affected / exposed	1 / 51 (1.96%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1). Event experienced by 1 subject in separate periods.		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
SUICIDAL IDEATION	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
UPPER LIMB FRACTURE	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		

subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CHRONIC	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (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			
EMBOLIC STROKE	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1). Event experienced by 1 subject in separate periods.		
subjects affected / exposed	1 / 51 (1.96%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

VERTIGO	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
VISION BLURRED	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	0 / 51 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERNIAL EVENTRATION	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1). Event experienced by 1 subject in separate periods.		
subjects affected / exposed	1 / 51 (1.96%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT STONE	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (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			
PROTEINURIA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ENDOCARDITIS	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		

subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERINEAL ABSCESS	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	1 / 51 (1.96%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
OBESITY	Additional description: Reporting groups: Migalastat Safety Population (30-month analyses) (subjects received migalastat in Periods 1 + 2) and ERT Safety Population (18-month analyses) (subjects received ERT in Period 1).		
subjects affected / exposed	2 / 51 (3.92%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Migalastat Safety Population (30-month analyses)	ERT Safety Population (18-month analyses)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 51 (96.08%)	19 / 21 (90.48%)	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	7 / 51 (13.73%)	0 / 21 (0.00%)	
occurrences (all)	8	0	
PROTEIN URINE PRESENT			
subjects affected / exposed	4 / 51 (7.84%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Injury, poisoning and procedural complications			

FALL			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
PROCEDURAL PAIN			
subjects affected / exposed	0 / 51 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	5 / 51 (9.80%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	8 / 51 (15.69%)	2 / 21 (9.52%)	
occurrences (all)	12	3	
HEADACHE			
subjects affected / exposed	16 / 51 (31.37%)	6 / 21 (28.57%)	
occurrences (all)	23	6	
NEURALGIA			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
PARAESTHESIA			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	8	0	
TREMOR			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 51 (3.92%)	2 / 21 (9.52%)	
occurrences (all)	3	2	

PAIN			
subjects affected / exposed	5 / 51 (9.80%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
PYREXIA			
subjects affected / exposed	6 / 51 (11.76%)	2 / 21 (9.52%)	
occurrences (all)	9	4	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	5 / 51 (9.80%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
VERTIGO			
subjects affected / exposed	3 / 51 (5.88%)	1 / 21 (4.76%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	7 / 51 (13.73%)	2 / 21 (9.52%)	
occurrences (all)	10	2	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 51 (5.88%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
CONSTIPATION			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
DIARRHOEA			
subjects affected / exposed	11 / 51 (21.57%)	2 / 21 (9.52%)	
occurrences (all)	13	2	
DRY MOUTH			
subjects affected / exposed	1 / 51 (1.96%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
DYSPEPSIA			
subjects affected / exposed	3 / 51 (5.88%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
GASTRITIS			
subjects affected / exposed	1 / 51 (1.96%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
NAUSEA			

subjects affected / exposed	8 / 51 (15.69%)	2 / 21 (9.52%)	
occurrences (all)	10	2	
TOOTHACHE			
subjects affected / exposed	4 / 51 (7.84%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
VOMITING			
subjects affected / exposed	8 / 51 (15.69%)	3 / 21 (14.29%)	
occurrences (all)	9	4	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	8 / 51 (15.69%)	5 / 21 (23.81%)	
occurrences (all)	8	5	
OROPHARYNGEAL PAIN			
subjects affected / exposed	4 / 51 (7.84%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	4	2	
INSOMNIA			
subjects affected / exposed	5 / 51 (9.80%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	6 / 51 (11.76%)	2 / 21 (9.52%)	
occurrences (all)	12	2	
BACK PAIN			
subjects affected / exposed	5 / 51 (9.80%)	4 / 21 (19.05%)	
occurrences (all)	6	4	
MUSCLE SPASMS			
subjects affected / exposed	4 / 51 (7.84%)	0 / 21 (0.00%)	
occurrences (all)	5	0	

MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 51 (5.88%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
MYALGIA			
subjects affected / exposed	6 / 51 (11.76%)	1 / 21 (4.76%)	
occurrences (all)	10	1	
NECK PAIN			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 51 (5.88%)	2 / 21 (9.52%)	
occurrences (all)	6	2	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	5 / 51 (9.80%)	3 / 21 (14.29%)	
occurrences (all)	6	5	
CYSTITIS			
subjects affected / exposed	4 / 51 (7.84%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
HERPES ZOSTER			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
INFLUENZA			
subjects affected / exposed	12 / 51 (23.53%)	4 / 21 (19.05%)	
occurrences (all)	15	4	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 51 (5.88%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
NASOPHARYNGITIS			
subjects affected / exposed	21 / 51 (41.18%)	7 / 21 (33.33%)	
occurrences (all)	41	11	
SINUSITIS			
subjects affected / exposed	4 / 51 (7.84%)	3 / 21 (14.29%)	
occurrences (all)	7	3	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	5 / 51 (9.80%)	2 / 21 (9.52%)	
occurrences (all)	6	2	
URINARY TRACT INFECTION			
subjects affected / exposed	6 / 51 (11.76%)	1 / 21 (4.76%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2011	• Increase in number of sites to facilitate enrollment • Change in the randomization ratio of treatment with migalastat or ERT from 1:1 to 1.5:1 • Re-defined proteinuria parameter for subject randomization stratification to <0.1 g/24 h and ≥ 0.1 g/24 h • Medical specialist to be consulted for clinical outcomes • Informed consent to be completed prior to any study related procedures • Discontinued subjects to complete assessments at last treatment visit • Subjects to receive ERT at least ≥ 80% of currently labelled dose • Migalastat treatment to begin at least 5 days after last ERT infusion • Increased number of visits during OLE period from 2 to 4.
27 November 2012	• Removal of recruitment period extension in Japan • Addition of an optional repeat GLA genotype blood draw to help validate a new genotyping test under development • Update of pregnancy language • Addition of allowance to use future exploratory analyses with retained biological samples to improve understanding of Fabry disease • Periodic updates to be provided to regulatory authorities and ethics committees responsible for suspected, unexpected, serious adverse reactions.
13 March 2013	• Addition of a mechanism for subjects to transition to a separate protocol, early access or other program after completing both study treatment periods and removal of need to complete a follow-up visit if this was the case • Addition of a telephone contact to assess study drug compliance for subjects receiving migalastat • Addition of requirement for subjects to return for an unscheduled visit to draw an additional blood sample to measure α-Gal A activity • Addition of guidance regarding use of medication that inhibited the protein renin-angiotensin system or that could affect renal perfusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported