



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 prescribing 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)

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|---|--|
| 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 m ² . | |
| 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/1.73m ² | | | | |
| 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)

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|--|--|
| 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/m ²) | | | | |
| arithmetic mean (standard deviation) | -6.578 (± | -2.015 (± | | |

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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

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|-----------------------|--|
| 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 occurrences (all) | 4 / 51 (7.84%) 5 | 1 / 21 (4.76%) 1 | |
| PROCEDURAL PAIN subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 2 / 21 (9.52%) 3 | |
| Cardiac disorders PALPITATIONS subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 7 | 1 / 21 (4.76%) 1 | |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 12 | 2 / 21 (9.52%) 3 | |
| HEADACHE subjects affected / exposed occurrences (all) | 16 / 51 (31.37%) 23 | 6 / 21 (28.57%) 6 | |
| NEURALGIA subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 4 | 1 / 21 (4.76%) 1 | |
| PARAESTHESIA subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 8 | 0 / 21 (0.00%) 0 | |
| TREMOR subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 4 | 0 / 21 (0.00%) 0 | |
| General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 4 | 1 / 21 (4.76%) 1 | |
| INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 0 / 21 (0.00%) 0 | |
| OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 3 | 2 / 21 (9.52%) 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 occurrences (all) | 8 / 51 (15.69%) 10 | 2 / 21 (9.52%) 2 | |
| TOOTHACHE subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 5 | 0 / 21 (0.00%) 0 | |
| VOMITING subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 9 | 3 / 21 (14.29%) 4 | |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 8 | 5 / 21 (23.81%) 5 | |
| OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 5 | 0 / 21 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders HYPERHIDROSIS subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 0 / 21 (0.00%) 0 | |
| Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 4 | 1 / 21 (4.76%) 2 | |
| INSOMNIA subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 0 / 21 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) | 6 / 51 (11.76%) 12 | 2 / 21 (9.52%) 2 | |
| BACK PAIN subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 6 | 4 / 21 (19.05%) 4 | |
| MUSCLE SPASMS subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 5 | 0 / 21 (0.00%) 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 | <ul style="list-style-type: none">• 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 $\geq 80\%$ 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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