



## Clinical trial results:

### A Cross-sectional Study of Renal Function in Treatment-naïve, Young Male Patients with Fabry Disease

#### Summary

EudraCT number	2012-001966-14
Trial protocol	ES
Global end of trial date	17 August 2016

#### Results information

Result version number	v1 (current)
This version publication date	02 March 2017
First version publication date	02 March 2017

#### Trial information

##### Trial identification

Sponsor protocol code	AGAL19110
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01839526
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact- US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact- US@sanofi.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?	Yes

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	02 November 2016
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	17 August 2016
Was the trial ended prematurely?	Yes

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Notes:

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**General information about the trial**

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Main objective of the trial:

To document renal function and other Fabry disease manifestations across age in treatment-naïve, young male subjects with Fabry disease.

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Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

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Background therapy: -

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Evidence for comparator: -

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Actual start date of recruitment	13 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	39
EEA total number of subjects	23

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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)	16
Adolescents (12-17 years)	12
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 19 centers in 13 countries between 13 May 2013 and 17 August 2016. A total of 45 subjects were screened, of whom 6 were screen failures. Screen failures were due to failure to meet inclusion criteria.

### Pre-assignment

Screening details:

Out of 45 screened subjects, 39 subjects were enrolled in the study.

### Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Fabry Disease - All Subjects
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Arm description:

All male subjects, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.

Arm type	No intervention
Investigational medicinal product name	Non interventional medicinal product (NIMP): Iohexol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Small dose of iohexol was administered for determining glomerular filtration rate (GFR).

<b>Number of subjects in period 1</b>	Fabry Disease - All Subjects
Started	39
Completed	39

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Period
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Reporting group description:

All male subjects, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.

Reporting group values	Overall Period	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	13.6 ± 6.3	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	39	39	

## End points

### End points reporting groups

Reporting group title	Fabry Disease - All Subjects
Reporting group description:	
All male subjects, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.	

### Primary: Fabry Disease Parameter: GFR Estimated from Serum Creatinine (eGFR)

End point title	Fabry Disease Parameter: GFR Estimated from Serum Creatinine (eGFR) <sup>[1]</sup>
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#### End point description:

GFR was assessed by estimation from serum creatinine level (eGFR) using an age-appropriate method based on the subject's age at the screening visit (for the purpose of determining a subject's eligibility for measurement of iohexol glomerular filtration rate [iGFR]) and at the clinical investigational visit (for use in statistical analyses). For subjects <18 years old, the Bedside Schwartz equation was used to calculate eGFR, while for subjects >18 years old, the CKD-EPI equation was used. Analysis was performed on safety population which included all subjects who signed the informed consent and deemed eligible to enroll based on screening assessments. Number of subjects analyzed = subjects with available data for this point. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Primary
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#### End point timeframe:

Screening, Day 1

#### 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: mL/minute/1.73m <sup>2</sup>				
arithmetic mean (standard deviation)				
Screening (n=39)	113.9 (± 20.1)			
Day 1 (n=37)	115.8 (± 22.7)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Fabry Disease Parameter: Glomerular Filtration Rate (GFR) Measured Using Plasma Iohexol Clearance (iGFR)

End point title	Fabry Disease Parameter: Glomerular Filtration Rate (GFR) Measured Using Plasma Iohexol Clearance (iGFR) <sup>[2]</sup>
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#### End point description:

GFR was calculated by plasma iohexol clearance after the required medication washout. Analysis was performed on safety population. Number of subjects analyzed = subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

Day 1 onwards up to safety follow-up phone contact (up to Day 28)

Notes:

[2] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: mL/min/1.73 <sup>2</sup>				
arithmetic mean (standard deviation)	105.3 (± 21.5)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Fabry Disease Parameter: Protein Excretion Assessed from Three First-Morning Urine Voids

End point title	Fabry Disease Parameter: Protein Excretion Assessed from Three First-Morning Urine Voids <sup>[3]</sup>
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End point description:

Protein excretion was evaluated from the 3 first morning urine voids, each obtained at least 1 week apart and not more than 2 weeks apart. Mean value for each parameter was calculated and reported. Parameters determined for each urine sample were albumin; total protein; creatinine (for calculation of albumin:creatinine ratio [ACR] and protein-creatinine ratio [PCR]); retinol binding protein (RBP); and Beta-2 microglobulin. Analysis was performed on safety population. Number of subjects analyzed = subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

Day 1 after the medication washout up to follow-up phone contact (Day28)

Notes:

[3] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: specified in categories				
arithmetic mean (standard deviation)				
Albumin (mg/dL)	4.6 (± 18.3)			
Albumin/Creatinine (mg/g)	56.3 (± 270.9)			
Beta-2 microglobulin (mg/L)	0.1 (± 0.2)			
Creatinine (mmol/L)	10.4 (± 4.7)			
Protein (mg/dL)	9.6 (± 20.9)			
Protien/Creatinine (mg/g)	98.2 (± 294.6)			
Retinol binding protein (ug/L)	110.1 (± 72.9)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Fabry Disease Parameter: Electrocardiogram (ECG) Parameters

End point title	Fabry Disease Parameter: Electrocardiogram (ECG) Parameters
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End point description:

ECG parameters included heart rate, PR interval, QRS interval, QT interval, RR interval, QTcB interval and QTcF interval. PR interval is the time on ECG tracing from the start of the P wave to the start of the R wave. PR interval represents the time from the onset of atrial depolarization until the onset of ventricular depolarization. QRS interval is the time from the start of the Q wave to the end of S wave. QRS interval represents depolarization of the ventricular myocardium. QT interval is a measure of the time between the start of the Q wave and the end of the T wave and represents electrical depolarization and repolarization of the ventricles. The QTcB includes a Bazett's correction factor for changes in heart rate and QTcF includes a Fredericia's correction factor for changes in heart rate. The RR interval is the time between QRS complexes. Analysis was performed on safety population. Number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Day 1 onwards up to safety follow-up phone contact (up to Day 28)

End point values	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: specified in the categories				
arithmetic mean (standard deviation)				
Heart rate (beats/minute)	71.06 ( $\pm$ 13.57)			
PR interval (msec)	137.66 ( $\pm$ 21.65)			
QRS interval (msec)	83.77 ( $\pm$ 9.16)			
QT interval (msec)	367.89 ( $\pm$ 31.77)			
RR interval (msec)	873.94 ( $\pm$ 166.25)			
QTcB interval (msec)	396.46 ( $\pm$ 26.36)			
QTcF interval (msec)	386.31 ( $\pm$ 23.02)			

## Statistical analyses

No statistical analyses for this end point



**Secondary: Fabry Disease Parameter: Number of Subjects with Clinically Significant Echocardiogram Findings**

End point title	Fabry Disease Parameter: Number of Subjects with Clinically Significant Echocardiogram Findings
End point description: Analysis was performed on safety population.	
End point type	Secondary
End point timeframe: Day 1 onwards up to safety follow-up phone contact (up to Day 28)	

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
Normal	34			
Abnormal, but not clinically significant	3			
Abnormal, Clinically significant	1			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Fabry Disease Parameter: Number of Subjects with Gastrointestinal (GI) Symptoms at Screening**

End point title	Fabry Disease Parameter: Number of Subjects with Gastrointestinal (GI) Symptoms at Screening
End point description: GI symptoms were collected at the screening visit by asking the subject-specific questions about the following GI symptoms: abdominal pain; diarrhea; nausea; vomiting (subjects who answered "yes" were reported); maximum number of bowel movements per day in the past week; stool consistency on average in the past week; severity of abdominal pain on average in the past week; severity of bloating on average in the past week. Analysis was performed on safety population.	
End point type	Secondary
End point timeframe: At screening	

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
Abdominal pain	20			
Diarrhea	17			
Nausea	8			
Vomiting	7			

Number of bowel movements per day (1-2)	26			
Number of bowel movements per day (3-4)	2			
Number of bowel movements per day (5-7)	3			
Number of bowel movements per day (8-10)	0			
Number of bowel movements per day (>10)	0			
Number of bowel movements per day (unknown)	8			
Stool consistency on average (very hard)	0			
Stool consistency on average (hard)	1			
Stool consistency on average (formed)	28			
Stool consistency on average (loose)	7			
Stool consistency on average (watery)	0			
Stool consistency on average (unknown)	3			
Severity of abdominal pain on average (mild)	4			
Severity of abdominal pain on average (moderate)	5			
Severity of abdominal pain on average (severe)	0			
Severity of abdominal pain on average (extreme)	1			
Severity of abdominal pain on average (unknown)	1			
Severity of abdominal pain on average (none)	28			
Severity of bloating on average (mild)	3			
Severity of bloating on average (moderate)	4			
Severity of bloating on average (severe)	2			
Severity of bloating on average (extreme)	0			
Severity of bloating on average (unknown)	2			
Severity of bloating on average (none)	28			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Fabry Disease Parameter: Quality of Life assessed by Pediatric Pain Questionnaire (PedsQL) Scores

End point title	Fabry Disease Parameter: Quality of Life assessed by Pediatric Pain Questionnaire (PedsQL) Scores
End point description:	
PedsQL completed by subjects between 5 and 17 years of age. It comprises of 2 questions: 'How do you feel now' and 'Worst pain this week', each measured on a 0-10 cm VAS scale (0=no pain; 10=severe pain). Analysis was performed on safety population. Number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Secondary

End point timeframe:

At screening

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: milimeters				
median (full range (min-max))				
How you feel now	0 (0 to 42)			
Worst pain this week	1.5 (0 to 83)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fabry Disease Parameter: Quality of Life assessed by Brief Pain Inventory Short Form (BPI [SF]) Scores

End point title	Fabry Disease Parameter: Quality of Life assessed by Brief Pain Inventory Short Form (BPI [SF]) Scores
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End point description:

BPI [SF] was completed by subjects  $\geq 18$  years of age. BPI (SF) comprises of 2 dimensions of pain: severity/intensity (4 items: worst, least, average and now pain) and interference with daily function (7 items: pain interference with general activity, walking, work, mood, enjoyment of life, relations with others and sleep). Each item was rated by subject on a scale ranges from 0-10, where lower scores indicated less pain. In this endpoint, average pain reported by subjects in last 24 hours along with the mean pain interference was reported. Analysis was performed on safety population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

At screening

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: units on a scale				
arithmetic mean (standard deviation)				
BPI (SF): Average pain in last 24 hours	2.5 ( $\pm$ 2)			
BPI (SF): Mean pain interfered	0.909 ( $\pm$ 1.344)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fabry Disease Parameter: Plasma Globotriaosylceramide (GL-3) Concentrations

End point title	Fabry Disease Parameter: Plasma Globotriaosylceramide (GL-3) Concentrations
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End point description:

Accumulation of Globotriaosylceramide in blood was evaluated by measuring levels of total GL-3 and lyso-GL-3 using tandem mass spectrometry. Blood samples were collected for all subjects and obtained either before or after the medication washout. Analysis was performed on safety population.

End point type	Secondary
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End point timeframe:

Day 1 onwards up to safety follow-up phone contact (up to Day 28)

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: units specified in the categories				
arithmetic mean (standard deviation)				
GL-3 (microgram/mL)	13.5 (± 6.8)			
Lyso-GL-3 (nanogram/mL)	144.2 (± 97.7)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fabry Disease Parameter: Urine Globotriaosylceramide (GL-3) Concentrations

End point title	Fabry Disease Parameter: Urine Globotriaosylceramide (GL-3) Concentrations
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End point description:

Accumulation of Globotriaosylceramide concentration in urine was evaluated by measuring levels of total GL-3 and lyso-GL-3 using tandem mass spectrometry. Urine samples were obtained either before or after the medication washout. Analysis was performed on safety population.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 28 (Before or after the medication washout)

<b>End point values</b>	Fabry Disease - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: units specified in the categories				
arithmetic mean (standard deviation)				
GL-3 (miligram/milimoles Cr)	0.34 (± 0.27)			

Lyso-GL-3 (nanogram/milimoles Cr)	83.9 ( $\pm$ 107.1)			
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## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 28) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

AEs in the study subject population would be expected to be related to Fabry or concomitant diseases, or related to procedures (i.e., iohexol). All subjects were observed for approximately 4 weeks after iohexol administration. All AEs from the time of written informed consent through completion of the safety follow-up phone contact were reported.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	ed 19.0
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### Reporting groups

Reporting group title	All Subjects: Age range (5 to <12 years)
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Reporting group description:

All male subjects in the age range of 5 to <12 years, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.

Reporting group title	All Subjects: Age range ( $\geq 18$ years)
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Reporting group description:

All male subjects in the age of  $\geq 18$  years, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.

Reporting group title	All Subjects: Age range (12 to <18 years)
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Reporting group description:

All male subjects in the age range of 12 to <18 years, with Fabry disease and who had not received any interventional treatment for the disease within 30 days of screening. They were observed in this cross-sectional study.

Serious adverse events	All Subjects: Age range (5 to <12 years)	All Subjects: Age range ( $\geq 18$ years)	All Subjects: Age range (12 to <18 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All Subjects: Age range (5 to <12 years)	All Subjects: Age range ( $\geq 18$ years)	All Subjects: Age range (12 to <18 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	2 / 11 (18.18%)	4 / 12 (33.33%)

Cardiac disorders			
Dilatation Ventricular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Left Atrial Dilatation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 11 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	0 / 11 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 11 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	0 / 11 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Musculoskeletal and connective tissue disorders Pain In Extremity subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Infections and infestations Ear Infection Fungal subjects affected / exposed occurrences (all)  Sinusitis subjects affected / exposed occurrences (all)  Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)  Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0  1 / 16 (6.25%) 1  0 / 16 (0.00%) 0  0 / 16 (0.00%) 0	1 / 11 (9.09%) 1  0 / 11 (0.00%) 0  1 / 11 (9.09%) 1  0 / 11 (0.00%) 0	0 / 12 (0.00%) 0  0 / 12 (0.00%) 0  0 / 12 (0.00%) 0  1 / 12 (8.33%) 1
Metabolism and nutrition disorders Vitamin D Deficiency subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2012	-Clarified that both a medical/surgical history and a Fabry specific history was required in the subjects. -Added a physical examination at the clinical investigation visit and clarified that the physical examination at screening include an assessment of angiokeratomas and Tanner stage. -Added respiratory rate and temperature to the vital signs assessment. -Clarified that laboratory samples were collected at the screening visit. -Added a table describing the Tanner Stages for reference. -Reflected changes in company ownership, study team changes and department name changes.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Enrollment period not extended and screening stopped for slow recruitment and in accordance with provisions of the protocol. Not linked to any safety concern.

Notes: