Clinical trial results:
Evaluation of Glycosphingolipid Clearance in Patients Treated With Agalsidase Alfa Who Switch to Agalsidase Beta (The INFORM Study)

Summary

EudraCT number	2015-000697-35
Trial protocol	Outside EU/EEA
Global end of trial date	15 March 2013

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	AGAL19412

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01650779
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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 June 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an exploratory study to evaluate changes in glycosphingolipid levels and other (exploratory) Fabry disease parameters in male Fabry disease subjects who were previously treated with agalsidase alfa (Replagal®) 0.2 milligram per kilogram (mg/kg) every two weeks (q2w) and who were being switched to agalsidase beta (Fabrazyme®) 1.0 mg/kg q2w.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.
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.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	30 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	15
EEA total number of subjects	0

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)	2
Adolescents (12-17 years)	2
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 6 centers in the United States of America between April 30, 2012 and March 15, 2013.

Pre-assignment

Screening details:

A total of 16 subjects were screened of which 1 subject was screen failure. A total of 15 subjects were enrolled in this study.

Period 1

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

Arms

Arm title	Agalsidase Beta

Arm description:

Commercially available agalsidase beta up to Month 6.

Arm type	Experimental
Investigational medicinal product name	Agalsidase beta
Investigational medicinal product code	
Other name	Fabrazyme®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg every two weeks (q2w).

Number of subjects in period 1	Agalsidase Beta
Started	15
Completed	14
Not completed	1
Withdrawal by Subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Agalsidase Beta
Reporting group description:	
Commercially available agalsidase beta up to Month 6.	

Reporting group values	Agalsidase Beta	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	28.5		
standard deviation	± 16.11	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	15	15	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	13	13	
Hispanic	1	1	
Other	1	1	
Duration of Fabry Disease			
Duration of Fabry disease was calculated from date of initial diagnosis of Fabry disease to date of the first study infusion. Number of subjects analyzed for this baseline measure were 14, as one subjects did not have information on date of initial diagnosis of Fabry disease.			
Units: years			
median	9.3		
full range (min-max)	2 to 19	-	

End points

End points reporting groups

Reporting group title	Agalsidase Beta
Reporting group description:	
Commercially available agalsidase beta up to Month 6.	

Primary: Percent Change From Baseline in Plasma Deacylated Globotriaosylceramide (Lyso-GL-3) at Month 2, 4 and 6

End point title	Percent Change From Baseline in Plasma Deacylated Globotriaosylceramide (Lyso-GL-3) at Month 2, 4 and 6[1]
End point description:	
Percent change from baseline = ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. For levels reported as below quantitative limit (BQL), the lower limit of quantitation (LLOQ) value was divided by 2 and used in the calculation to estimate values in samples that were BQL. The LLOQ for plasma lyso-GL-3 was 5.0 nanogram per milliliter (ng/mL). This study is exploratory because little is known about the dose-response of these biomarkers to enzyme replacement therapy (ERT) or about the clinical significance of the biomarkers. All enrolled subjects were included in the analysis. Here, 'n' signifies subjects with plasma Lyso-GL-3 assessment at the specified time point.	
End point type	Primary
End point timeframe:	
Baseline, Month 2, 4, 6	

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: Due to system limitations statistical analysis cannot be presented for Single Arm Study.

End point values	Agalsidase Beta			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent change				
arithmetic mean (standard deviation)				
Month 2 (n=14)	-31.71 (± 22.54)			
Month 4 (n=12)	-39.04 (± 22.28)			
Month 6 (n=14)	-39.54 (± 23.567)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Plasma Globotriaosylceramide (GL-3) at Month 2, 4 and 6

End point title	Percent Change From Baseline in Plasma Globotriaosylceramide (GL-3) at Month 2, 4 and 6
End point description:	
Percent change from baseline = ([post-baseline value minus baseline value] divided by [baseline value])	

multiplied by 100. For levels reported as BQL, the LLOQ value was divided by 2 and used in the calculation to estimate values in samples that were BQL. The LLOQ for plasma GL-3 was 2.0 microgram per milliliter (mcg/mL). This study is exploratory because little is known about the dose-response of these biomarkers to ERT or about the clinical significance of the biomarkers. All enrolled subjects were included in the analysis. Here, 'n' signifies subjects with plasma GL-3 assessment at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, 6

End point values	Agalsidase Beta			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent change				
arithmetic mean (standard deviation)				
Month 2 (n=12)	-10.33 (± 21.087)			
Month 4 (n=10)	-12.8 (± 23.388)			
Month 6 (n=12)	-17.89 (± 25.291)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine GL-3 at Month 2, 4, and 6

End point title	Percent Change From Baseline in Urine GL-3 at Month 2, 4, and 6

End point description:

Percent change from baseline = ([post-baseline value minus baseline value] divided by [baseline value]) multiplied by 100. For levels reported as BQL, the LLOQ value was divided by 2 and used in the calculation to estimate values in samples that were BQL. The LLOQ for urine GL-3 was 0.2 mcg/mL. The absolute values were calculated in microgram per millimole (mcg/mmol) of creatinine by dividing GL-3 (mcg/mL) by creatinine (mg/mL) and multiplying by 113.13 (mg/mmol), the molecular weight of creatinine. For levels reported BQL, the absolute values were calculated in microgram per millimole (mcg/mmol) of creatinine by dividing 0.1 (mcg/mL) by creatinine (mg/mL) and multiplying by 133.13 (mg/mmol). This study is exploratory because little is known about the dose-response of these biomarkers to ERT or about the clinical significance of the biomarkers. All enrolled subjects were included in the analysis. Here, 'n' signifies subjects with urine GL-3 assessment at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, 6

End point values	Agalsidase Beta			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent change				
median (full range (min-max))				
Month 2 (n=13)	-44.71 (-98.4 to 1068.2)			
Month 4 (n=12)	-41.49 (-96.5 to 464.9)			
Month 6 (n=12)	-33.75 (-97.1 to 1116.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Gastrointestinal (GI) Symptoms (Abdominal Pain, Abdominal Distention, and Bowel Irregularities) at Month 2, 4, and 6

End point title	Percent Change From Baseline in Gastrointestinal (GI) Symptoms (Abdominal Pain, Abdominal Distention, and Bowel Irregularities) at Month 2, 4, and 6

End point description:

Gastrointestinal symptoms (abdominal pain, abdominal distention, and irregular bowel movements) were to be assessed by a modified version of the Irritable Bowel Syndrome (IBS) Severity Scoring System. The modified IBS Severity Scoring System is a 7-item questionnaire. The severity score calculated by summing the scores of 5 of the 7 questions. Each of the 5 questions were scored on a scale of 0 to 100, leading to a total possible score range of 0 to 500, where higher scores indicate more severe gastrointestinal symptoms. The data for this outcome measure was exploratory and to be collected in individual subject listing only. Analysis of this data was planned only if baseline data was collected on a large number of enrolled subjects. This was not the case and therefore interpretation of these results were not possible.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, 6

End point values	Agalsidase Beta			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percent change				
number (not applicable)				

Notes:

[2] - Explanation is provided in measure description.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to end of study (Month 6) or early withdrawal.	
Adverse event reporting additional description:	
All enrolled subjects were included in the analysis.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Agalsidase Beta
Reporting group description:	
Commercially available agalsidase beta up to Month 6.	

Serious adverse events	Agalsidase Beta		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Agalsidase Beta		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		
General disorders and administration site conditions			
Infusion-associated reactions			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

This is considered to be an exploratory study for the following reasons: it was based on a small number of subjects and has been designed as an open-label, single-arm study as opposed to a two-arm crossover design.

Notes: