Clinical trial results:
A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients With Gaucher Disease Type 1 Who Have Reached Therapeutic Goals With Enzyme Replacement Therapy (ENCORE)

Summary

EudraCT number	2008-005223-28
Trial protocol	NL GB FR DE ES CZ IT
Global end of trial date	02 June 2015

Results information

Result version number	v2 (current)
This version publication date	27 October 2016
First version publication date	02 June 2016
Version creation reason	• Correction of full data set Correction of subjects disposition data
Summary attachment (see zip file)	GZGD02607 (2008-005223-28_GZGD02607.pdf)

Trial information

Trial identification

Sponsor protocol code	GZGD02607/EFC12812

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00943111
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: ENCORE

Notes:

Sponsors

Sponsor organisation name	Genzyme, a Sanofi Company
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of eliglustat compared with Cerezyme® (imiglucerase) after 52 weeks of treatment in subjects with Gaucher disease type 1 (GD1) who had reached therapeutic goals with enzyme replacement therapy (ERT).

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.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	10 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Egypt: 5
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	United States: 68

Worldwide total number of subjects	159
EEA total number of subjects	18

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)	157
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 209 subjects were screened of which 46 subjects were screen failure and 3 subjects withdrew prior to randomization. A total of 160 subjects were enrolled in this study.

Pre-assignment

Screening details:

All enrolled subjects received eliglustat or imiglucerase in 52 week primary analysis period (PAP). After 52- weeks PAP, all subjects who remained on-study received eliglustat in the long-term treatment period (LTTP) for up to 5 years. One subject randomized to imiglucerase group but did not receive treatment.

Period 1

Period 1 title	52-Weeks Primary Analysis Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Eliglustat: PAP

Arm description:

Eliglustat tartrate (Genz-112638) 50 mg twice daily (BID) from Day 1 to Week 4 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 8, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to Week 52.

Arm type	Experimental
Investigational medicinal product name	Eliglustat tartrate
Investigational medicinal product code	Genz-112638/GZ385660
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The dose adjustments after Week 4 and Week 8 were based on Genz-99067 (active moiety of eliglustat tartrate in plasma) trough plasma concentrations. If Genz-99067 trough plasma concentration was < 5 ng/mL, the next higher dose was administered whereas if the Genz-99067 trough plasma concentration was >= 5 ng/mL, the same dose was continued. The pharmacokinetic (PK) assessment at Week 2 and Week 6 were used for dose adjustment after Week 4 and Week 8, respectively.

Arm title	Imiglucerase: PAP

Arm description:

Imiglucerase every other week (q2w) up to Week 52 in doses equivalent to subject’s past ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change.

Arm type	Active comparator
Investigational medicinal product name	Imiglucerase
Investigational medicinal product code	
Other name	Cerezyme®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imiglucerase intravenous infusion q2w up to Week 52.

Number of subjects in period 1	Eliglustat: PAP	Imiglucerase: PAP
Started	106	53
Completed	104	52
Not completed	2	1
Adverse Event	2	1

Period 2

Period 2 title	5 Years Long-term Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eliglustat: LTTP

Arm description:

Subjects from both the arms of PAP who completed PAP were included in this arm of LTTP.
Subjects originally randomized to eliglustat in PAP continued to receive eliglustat dose, based on their Genz 99067 plasma trough concentration at Week 6.
Subjects originally randomized to imiglucerase received eliglustat tartrate 50 mg BID from Week 52+1 Day to Week 56 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 60, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to 5 years.

Arm type	Experimental
Investigational medicinal product name	Eliglustat tartrate
Investigational medicinal product code	Genz-112638/GZ385660
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The dose adjustments after Week 56 and Week 60 were based on Genz-99067 (active moiety of eliglustat tartrate in plasma) trough plasma concentrations. If Genz-99067 trough plasma concentration was <5 ng/mL next higher dose was administered whereas if the Genz-99067 trough plasma concentration was >=5 ng/mL the same dose was continued. PK assessment at Week 54 and Week 58 were used for dose adjustment after Week 56 and Week 60, respectively.

Number of subjects in period 2[1]	Eliglustat: LTTP
Started	152
Completed	77
Not completed	75
Adverse Event	9
Pregnancy	4
Transition to commercial eliglustat	51
Other than specified	2

Withdrawal by Subject	8
Lost to follow-up	1

Notes:

[1] - 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: Subjects from both the arms of PAP who completed PAP and remained on-study.

Baseline characteristics

Reporting groups	
Reporting group title	Eliglustat: PAP
Reporting group description:	
Eliglustat tartrate (Genz-112638) 50 mg twice daily (BID) from Day 1 to Week 4 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 8, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to Week 52.	
Reporting group title	Imiglucerase: PAP
Reporting group description:	
Imiglucerase every other week (q2w) up to Week 52 in doses equivalent to subject's past ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change.	

Reporting group values	Eliglustat: PAP	Imiglucerase: PAP	Total
Number of subjects	106	53	159
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	37.6	37.5	
standard deviation	± 14.17	± 14.92	-
Gender categorical			
Units: Subjects			
Female	59	28	87
Male	47	25	72
Race			
Units: Subjects			
White	98	48	146
Black or African American	6	4	10
Asian	1	1	2
White/American Indian	1	0	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	42	19	61
Not Hispanic or Latino	64	34	98
Body Mass Index (BMI)			
BMI was calculated as ([weight in kg] divided by [height in cm multiplied by 0.01]^2).			
Units: kg/m^2			
arithmetic mean	25.2	24.5	
standard deviation	± 5.24	± 4.51	-
Weight			
Units: kg			
arithmetic mean	70.8	67.8	
standard deviation	± 16.82	± 14.44	-
Height			
Units: cm			
arithmetic mean	167.6	166.2	
standard deviation	± 9.92	± 9.56	-

End points

End points reporting groups

Reporting group title	Eliglustat: PAP

Reporting group description:

Eliglustat tartrate (Genz-112638) 50 mg twice daily (BID) from Day 1 to Week 4 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 8, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to Week 52.

Reporting group title	Imiglucerase: PAP

Reporting group description:

Imiglucerase every other week (q2w) up to Week 52 in doses equivalent to subject's past ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change.

Reporting group title	Eliglustat: LTTP

Reporting group description:

Subjects from both the arms of PAP who completed PAP were included in this arm of LTTP.
Subjects originally randomized to eliglustat in PAP continued to receive eliglustat dose, based on their Genz 99067 plasma trough concentration at Week 6.
Subjects originally randomized to imiglucerase received eliglustat tartrate 50 mg BID from Week 52+1 Day to Week 56 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 60, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to 5 years.

Primary: Percentage of Subjects Who Remained Stable for 52 Weeks During the Primary Analysis Period

End point title	Percentage of Subjects Who Remained Stable for 52 Weeks During the Primary Analysis Period

End point description:

For a subject to be classified as stable, the subject must have remained stable in hematological parameters (hemoglobin levels and platelet counts) and organ volumes (spleen, when applicable, and liver volumes in multiples of normal [MN]). Stable hematological parameters were defined as hemoglobin level did not decrease >1.5 g/dL from baseline and platelet count did not decrease >25% from baseline. Stable organ volumes were defined as spleen volume (in MN) did not increase >25% from baseline, if applicable, and liver volume (in MN) did not increase >20% from baseline. Analysis was performed on per protocol population for PAP included subjects who were at least 80% compliant with treatment during PAP, had no major protocol deviations, and did not exhibit hematological decline as a result of medically determined etiologies other than Gaucher disease.

End point type	Primary

End point timeframe:

Baseline up to Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	47		
Units: percentage of subjects				
number (confidence interval 95%)	84.8 (76.2 to 91.3)	93.6 (82.5 to 98.7)		

Statistical analyses

Statistical analysis title	Eliglustat: PAP vs. Imiglucerase: PAP
Comparison groups	Eliglustat: PAP v Imiglucerase: PAP
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in Percentage Stable
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	4.2

Notes:

[1] - The sample size for study was based on expected stability rates of 95% for the Imiglucerase group and 85% for the Eliglustat group, power of 85%, a one-sided significance level of 0.025, a non-inferiority margin of 25%, and a 20% non-evaluable/dropout rate. Eliglustat was declared non-inferior to Imiglucerase if the lower-bound of the 95% confidence interval for the difference was within the non inferiority margin of 25%.

Primary: Percentage of Subjects Remaining Stable Annually for 4 Years During the LTTP

End point title	Percentage of Subjects Remaining Stable Annually for 4 Years During the LTTP[2]

End point description:

For a subject to be classified as stable, the subject must have remained stable in hematological parameters (hemoglobin levels and platelet counts) and organ volumes (spleen, when applicable, and liver volumes in MN). Stable hematological parameters were defined as hemoglobin level did not decrease >1.5 g/dL from baseline and platelet count did not decrease >25% from baseline. Stable organ volumes were defined as spleen volume (in MN) did not increase >25% from baseline, if applicable, and liver volume did not increase >20% from baseline. Analysis was performed on FAS population for LTTP: included all subjects who received at least 1 dose of eliglustat in the extension study period. Number of subjects analyzed= subjects at risk at specified time-points. Here 'n' signifies number of subjects with available data for specified time-points.

End point type	Primary

End point timeframe:

Week 52 up to Week 208

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: Due to EudraCT system constraint, the statistical analysis could not be provided for single arm.

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: percentage of subjects				
number (not applicable)				
Year 1 (n=127)	83.6			
Year 2 (n= 115)	75.65			
Year 3 (n= 92)	60.53			
Year 4 (n= 41)	26.97			

Statistical analyses

No statistical analyses for this end point

Secondary: Total T-Scores for Bone Mineral Density

End point title	Total T-Scores for Bone Mineral Density

End point description:

Images of the spine and bilateral femur were obtained by dual-energy X-ray absorptiometry (DXA) to determine T-score for each bone area and total bone mineral density. T-score compares subject's bone density with that of healthy young subject. The T-score bone density categories are: normal (score >-1), osteopenia (score -2.5 to <=-1), and osteoporosis (score <=-2.5). Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with baseline T-score assessment. Here, 'n' signifies subjects with baseline T-score assessment for specified bone area.

End point type	Secondary

End point timeframe:

Baseline

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	38		
Units: T-score				
arithmetic mean (standard deviation)				
Lumbar Spine T-Score (n=81, 38)	-0.56 (± 1.309)	-0.33 (± 1.169)		
Femur T-Score (n=80, 37)	-0.11 (± 1.08)	-0.47 (± 1.293)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total T-Scores for Bone Mineral Density at Week 52

End point title	Absolute Change From Baseline in Total T-Scores for Bone Mineral Density at Week 52

End point description:

Images of the spine and bilateral femur were obtained by DXA to determine T-score for each bone area and total bone mineral density. T-score compares subject's bone density with that of healthy young subject. The T-score bone density categories are: normal (score >-1), osteopenia (score -2.5 to <=-1), and osteoporosis (score <= -2.5). Absolute change = T-score at Week 52 minus T-score at baseline. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 T-score assessment. Here, 'n' signifies subjects with both baseline and Week 52 T-score assessment for specified bone area. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	38		
Units: T-score				
least squares mean (standard error)				
Change in Lumbar Spine T-Score (n=81, 38)	0.04 (± 0.03)	0.03 (± 0.05)		
Change in Femur T-Score (n=80, 37)	0 (± 0.02)	-0.03 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Z-Scores for Bone Mineral Density

End point title	Total Z-Scores for Bone Mineral Density

End point description:

Images of the spine and bilateral femur were obtained by DXA to determine Z-score for each bone area and total bone mineral density. The Z-score bone density categories are: normal (score >-2) and below normal (score <=-2). Per protocol population for PAP. Number of subjects analyzed = subjects with baseline Z-score assessment. Here, 'n' signifies subjects with baseline Z-score assessment for specified bone area.

End point type	Secondary

End point timeframe:

Baseline

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	45		
Units: Z-score				
arithmetic mean (standard deviation)				
Lumbar Spine Z-Score (n=94, 45)	-0.35 (± 1.26)	-0.14 (± 1.108)		
Femur Z-Score (n=93, 44)	0.09 (± 1.02)	-0.18 (± 1.122)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total Z-Scores for Bone Mineral Density at Week 52

End point title	Absolute Change From Baseline in Total Z-Scores for Bone Mineral Density at Week 52

End point description:

Images of the spine and bilateral femur were obtained by DXA to determine Z-score for each bone area and total bone mineral density. The Z-score bone density categories are: normal (score >-2) and below normal (score <=-2). Absolute change = Z-score at Week 52 minus Z-score at baseline. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 Z-score assessment. Here, 'n' signifies subjects with both baseline and Week 52 Z-score assessment for specified bone area. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	45		
Units: Z-score				
least squares mean (standard error)				
Change in Lumbar Spine Z-Score (n=94, 45)	0.06 (± 0.03)	0.06 (± 0.04)		
Change in Femur Z-Score (n=93, 44)	0.03 (± 0.02)	0.02 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin Level

End point title	Hemoglobin Level

End point description:

Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with baseline hemoglobin assessment.

End point type	Secondary

End point timeframe:

Baseline

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	47		
Units: g/dL				
arithmetic mean (standard deviation)				
Hemoglobin Level	13.592 (± 1.2467)	13.797 (± 1.2234)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Hemoglobin Levels at Week 52

End point title	Absolute Change From Baseline in Hemoglobin Levels at Week 52

End point description:

Absolute change = hemoglobin level at Week 52 minus hemoglobin level at baseline. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 hemoglobin assessment. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	47		
Units: g/dL				
least squares mean (standard error)	-0.22 (± 0.07)	0.05 (± 0.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Platelet Counts at Week 52

End point title	Percent Change From Baseline in Platelet Counts at Week 52

End point description:

Percent change in platelet counts = ([platelet count at Week 52 minus platelet count at baseline] divided by [platelet count at baseline]) multiplied by 100. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 platelet assessment. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	47		
Units: percent change				
least squares mean (standard error)	3.93 (± 1.71)	2.63 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen Volume (in MN) at Week 52

End point title	Percent Change From Baseline in Spleen Volume (in MN) at Week 52

End point description:

Percent change in spleen volume = ([spleen volume at Week 52 minus spleen volume at baseline] divided by [spleen volume at baseline]) multiplied by 100, where all volumes are in MN. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 spleen volume assessment. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	39		
Units: percent change				
least squares mean (standard error)	-6.05 (± 1.57)	-3.22 (± 2.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Liver Volume (in MN) at Week 52

End point title	Percent Change From Baseline in Liver Volume (in MN) at Week 52

End point description:

Percent change in liver volume = ([liver volume at Week 52 minus liver volume at baseline] divided by [liver volume at baseline]) multiplied by 100, where all volumes are in multiples of normal. Analysis was performed on per protocol population for PAP. Number of subjects analyzed = subjects with both baseline and Week 52 liver volume assessment. Eliglustat subjects switching to imiglucerase were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eliglustat: PAP	Imiglucerase: PAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	47		
Units: percent change				
least squares mean (standard error)	1.99 (± 0.94)	3.13 (± 1.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total T-Scores for Bone Mineral Density at Week 208

End point title	Absolute Change From Baseline in Total T-Scores for Bone Mineral Density at Week 208

End point description:

Images of the spine and bilateral femur were obtained by DXA to determine T-score for each bone area and total bone mineral density. T-score compares subject's bone density with that of healthy young subject. The T-score bone density categories are: normal (score >-1), osteopenia (score -2.5 to <=-1), and osteoporosis (score <= -2.5). Absolute change = T-score at Week 208 minus T-score at baseline. Number of subjects analyzed = subjects with both baseline and Week 208 T-score assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: T-Score				
arithmetic mean (standard deviation)				
Total Spine Total Femur	0.22 (± 0.405) -0.03 (± 0.345)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total Z-Scores for Bone Mineral Density at Week 208

End point title	Absolute Change From Baseline in Total Z-Scores for Bone Mineral Density at Week 208

End point description:

Images of the spine and bilateral femur were obtained by DXA to determine Z-score for each bone area and total bone mineral density. The Z-score bone density categories are: normal (score >-2) and below normal (score <=-2). Absolute change = Z-score at Week 208 minus Z-score at baseline. Analysis was performed on FAS population for LTTP. Number of subjects analyzed = subjects with both baseline and Week 208 Z-score assessment. Here, 'n' signifies subjects with both baseline and Week 208 Z-score assessment for specified bone area.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Z-score				
arithmetic mean (standard deviation)				
Total Spine	0.29 (± 0.358)			
Total Femur	0.03 (± 0.381)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Hemoglobin Levels at Week 208

End point title	Absolute Change From Baseline in Hemoglobin Levels at Week 208

End point description:

Absolute change = hemoglobin level at Week 208 minus hemoglobin level at baseline. Analysis was performed on FAS population for LTTP. Number of subjects analyzed = subjects with both baseline and Week 208 hemoglobin assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: g/dL				
arithmetic mean (standard deviation)	0.297 (± 0.7472)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Platelet Counts at Week 208

End point title	Percent Change From Baseline in Platelet Counts at Week 208

End point description:

Percent change in platelet counts = ([platelet count at Week 208 minus platelet count at baseline] divided by [platelet count at baseline]) multiplied by 100. Analysis was performed on FAS population for LTTP. Number of subjects analyzed = subjects with both baseline and Week 208 platelet assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percent change				
arithmetic mean (standard deviation)	6.99 (± 20.4382)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spleen Volume (in MN) at Week 208

End point title	Percent Change From Baseline in Spleen Volume (in MN) at Week 208

End point description:

Percent change in spleen volume = ([spleen volume at Week 208 minus spleen volume at baseline] divided by [spleen volume at baseline]) multiplied by 100, where all volumes are in MN. Analysis was performed on FAS population for LTTP. Number of subjects analyzed = subjects with both baseline and Week 208 spleen volume assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent change				
arithmetic mean (standard deviation)	-14.768 (± 17.9435)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Liver Volume (in MN) at Week 208

End point title	Percent Change From Baseline in Liver Volume (in MN) at Week 208

End point description:

Percent change in liver volume = ([liver volume at Week 208 minus liver volume at baseline] divided by [liver volume at baseline]) multiplied by 100, where all volumes are in multiples of normal. Analysis was performed on FAS population for LTTP. Number of subjects analyzed = subjects with both baseline and Week 208 liver volume assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 208

End point values	Eliglustat: LTTP			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: percent change				
arithmetic mean (standard deviation)	-2.345 (± 12.8795)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent up to 30-37 days after the last dose of treatment (last dose = up to Week 104)

Adverse event reporting additional description:

Safety set included all subjects who received at least 1 dose of study drug (Eliglustat or Imiglucerase). In the event a single subject experienced both serious and non-serious forms of same adverse events (AE), individual was included in numerator (number of subjects affected) of each AE table.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Imiglucerase

Reporting group description:

PAP: Imiglucerase q2w up to Week 52 in doses equivalent to subject's past ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change. LTTP: Subjects originally randomized to imiglucerase received eliglustat tartrate 50 mg BID from Week 52+1 Day to Week 56 followed by eliglustat tartrate 50 mg or 100 mg BID up to Week 60, and then eliglustat tartrate 50 mg or 100 mg or 150 mg BID up to 5 years. The dose adjustments after Week 56 and Week 60 were based on Genz-99067 (active moiety of eliglustat tartrate in plasma) trough plasma concentrations.

Reporting group title	Eliglustat

Reporting group description:

PAP: Eliglustat tartrate 50 mg BID from Day 1 to Week 4, followed by eliglustat tartrate 50, 100 or 150 mg BID up to Week 52. Dose adjustments after Week 4 and Week 8 were based on Genz-99067 (active moiety of eliglustat tartrate in plasma) trough plasma concentrations. LTTP: Subjects originally randomized to eliglustat in PAP continued to receive eliglustat dose, based on their Genz 99067 plasma trough concentration at Week 6.

Serious adverse events	Imiglucerase	Eliglustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 53 (13.21%)	18 / 106 (16.98%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Ovarian Tumour			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Renal Cell Carcinoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine Leiomyoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (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			
Injury			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy Peripheral			

subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	3 / 106 (2.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Polycythaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 106 (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			
Device Malfunction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal Obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
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			
Epistaxis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Septum Deviation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imiglucerase	Eliglustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 53 (71.70%)	91 / 106 (85.85%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 53 (1.89%)	6 / 106 (5.66%)	
occurrences (all)	1	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 53 (1.89%)	10 / 106 (9.43%)	
occurrences (all)	1	10	
Chest Pain			
subjects affected / exposed	1 / 53 (1.89%)	9 / 106 (8.49%)	
occurrences (all)	1	9	
Fatigue			
subjects affected / exposed	7 / 53 (13.21%)	20 / 106 (18.87%)	
occurrences (all)	7	20	
Pain			
subjects affected / exposed	3 / 53 (5.66%)	6 / 106 (5.66%)	
occurrences (all)	3	6	
Peripheral Swelling			
subjects affected / exposed	1 / 53 (1.89%)	6 / 106 (5.66%)	
occurrences (all)	1	6	
Pyrexia			
subjects affected / exposed	3 / 53 (5.66%)	2 / 106 (1.89%)	
occurrences (all)	3	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 53 (3.77%)	11 / 106 (10.38%)	
occurrences (all)	2	11	
Epistaxis			
subjects affected / exposed	1 / 53 (1.89%)	7 / 106 (6.60%)	
occurrences (all)	1	7	
Oropharyngeal Pain			
subjects affected / exposed	3 / 53 (5.66%)	7 / 106 (6.60%)	
occurrences (all)	3	7	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 53 (1.89%)	10 / 106 (9.43%)	
occurrences (all)	1	10	
Depression			
subjects affected / exposed	3 / 53 (5.66%)	3 / 106 (2.83%)	
occurrences (all)	3	3	
Investigations			
Mean Cell Volume Abnormal			
subjects affected / exposed	3 / 53 (5.66%)	0 / 106 (0.00%)	
occurrences (all)	3	0	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	3 / 53 (5.66%)	16 / 106 (15.09%)	
occurrences (all)	3	16	
Nerve Conduction Studies Abnormal			
subjects affected / exposed	3 / 53 (5.66%)	7 / 106 (6.60%)	
occurrences (all)	3	7	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 53 (3.77%)	7 / 106 (6.60%)	
occurrences (all)	2	7	
Laceration			
subjects affected / exposed	1 / 53 (1.89%)	7 / 106 (6.60%)	
occurrences (all)	1	7	
Ligament Sprain			
subjects affected / exposed	0 / 53 (0.00%)	8 / 106 (7.55%)	
occurrences (all)	0	8	
Limb Injury			
subjects affected / exposed	0 / 53 (0.00%)	6 / 106 (5.66%)	
occurrences (all)	0	6	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 53 (5.66%)	8 / 106 (7.55%)	
occurrences (all)	3	8	
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 53 (7.55%)	18 / 106 (16.98%)	
occurrences (all)	4	18	
Headache			
subjects affected / exposed	9 / 53 (16.98%)	26 / 106 (24.53%)	
occurrences (all)	9	26	
Paraesthesia			
subjects affected / exposed	1 / 53 (1.89%)	7 / 106 (6.60%)	
occurrences (all)	1	7	
Hypoaesthesia			
subjects affected / exposed	1 / 53 (1.89%)	6 / 106 (5.66%)	
occurrences (all)	1	6	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	6 / 53 (11.32%)	14 / 106 (13.21%)	
occurrences (all)	6	14	
Abdominal Pain Lower			
subjects affected / exposed	0 / 53 (0.00%)	6 / 106 (5.66%)	
occurrences (all)	0	6	
Abdominal Pain Upper			
subjects affected / exposed	3 / 53 (5.66%)	26 / 106 (24.53%)	
occurrences (all)	3	26	
Constipation			
subjects affected / exposed	6 / 53 (11.32%)	10 / 106 (9.43%)	
occurrences (all)	6	10	
Diarrhoea			
subjects affected / exposed	2 / 53 (3.77%)	20 / 106 (18.87%)	
occurrences (all)	2	20	
Gastritis			
subjects affected / exposed	5 / 53 (9.43%)	6 / 106 (5.66%)	
occurrences (all)	5	6	
Dyspepsia			
subjects affected / exposed	4 / 53 (7.55%)	15 / 106 (14.15%)	
occurrences (all)	4	15	
Gastrooesophageal Reflux Disease			

subjects affected / exposed	2 / 53 (3.77%)	13 / 106 (12.26%)	
occurrences (all)	2	13	
Nausea			
subjects affected / exposed	7 / 53 (13.21%)	18 / 106 (16.98%)	
occurrences (all)	7	18	
Toothache			
subjects affected / exposed	3 / 53 (5.66%)	7 / 106 (6.60%)	
occurrences (all)	3	7	
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	10 / 106 (9.43%)	
occurrences (all)	0	10	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	3 / 53 (5.66%)	5 / 106 (4.72%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	4 / 53 (7.55%)	5 / 106 (4.72%)	
occurrences (all)	4	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 53 (24.53%)	38 / 106 (35.85%)	
occurrences (all)	13	38	
Back Pain			
subjects affected / exposed	6 / 53 (11.32%)	23 / 106 (21.70%)	
occurrences (all)	6	23	
Bone Pain			
subjects affected / exposed	3 / 53 (5.66%)	9 / 106 (8.49%)	
occurrences (all)	3	9	
Muscle Spasms			
subjects affected / exposed	1 / 53 (1.89%)	6 / 106 (5.66%)	
occurrences (all)	1	6	
Musculoskeletal Pain			
subjects affected / exposed	3 / 53 (5.66%)	8 / 106 (7.55%)	
occurrences (all)	3	8	
Myalgia			

subjects affected / exposed	2 / 53 (3.77%)	6 / 106 (5.66%)	
occurrences (all)	2	6	
Pain In Extremity			
subjects affected / exposed	5 / 53 (9.43%)	21 / 106 (19.81%)	
occurrences (all)	5	21	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 53 (3.77%)	8 / 106 (7.55%)	
occurrences (all)	2	8	
Gastroenteritis			
subjects affected / exposed	2 / 53 (3.77%)	11 / 106 (10.38%)	
occurrences (all)	2	11	
Influenza			
subjects affected / exposed	6 / 53 (11.32%)	20 / 106 (18.87%)	
occurrences (all)	6	20	
Nasopharyngitis			
subjects affected / exposed	10 / 53 (18.87%)	28 / 106 (26.42%)	
occurrences (all)	10	28	
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 53 (13.21%)	21 / 106 (19.81%)	
occurrences (all)	7	21	
Sinusitis			
subjects affected / exposed	3 / 53 (5.66%)	20 / 106 (18.87%)	
occurrences (all)	3	20	
Urinary Tract Infection			
subjects affected / exposed	3 / 53 (5.66%)	16 / 106 (15.09%)	
occurrences (all)	3	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2009	- Treatment duration for the PAP was increased to 52 weeks in response to regulatory agency feedback. - Changed to a non-inferiority study design (versus Cerezyme) in response to regulatory agency feedback. - Nerve conduction assessments and analysis were added to the safety analyses. - Inclusion/exclusion criteria were modified to ensure study conduct in subjects receiving long-term Cerezyme treatment. - An Independent Adjudication Board (IAB) was added to confirm whether failure to meet the primary endpoint during the 52-week PAP could be attributed to a decline in GD. - Prior and concomitant medication guidelines were revised, including the following: added restrictions for cytochrome P450 (CYP) 3A4 inducers and CYP3A4 strong inhibitors in all subjects.
05 May 2010	- The duration of study participation was extended for individual subjects. - Enrollment to a broader subject population was expanded based on subject age, including subjects who were >65 years of age, and prior ERT therapy; i.e, subjects previously receiving Cerezyme or velaglucerase were eligible for the study. - Prior and concomitant medication guidelines were revised, including the following: Restrictions related to ingestion of grapefruit or grapefruit juice 72 hours prior to the first dose of study medication; Inducers of CYP3A4 were prohibited in all subjects; Strong CYP3A4 inhibitors were prohibited in subjects who were CYP2D6 poor metabolizers; An exception was added for temporary use of CYP3A4 inducers and strong inhibitors of CYP2D6 and CYP3A4 after completion of dose adjustment in each treatment period, and an exception for new chronic use of these medications after completion of dose adjustment in the LTTP.
29 November 2010	- The exclusion of subjects who received ERT therapy with taliglucerase was removed based on preliminary data indicating subjects were able to maintain GD therapeutic goals on taliglucerase. - Subjects without historical X-ray or magnetic resonance imaging (MRI) scans but whose screening images confirmed that any bone findings were not acute in origin were eligible for inclusion in the study. - The analysis of organ volume measurements in subjects who had a repeat measurement was modified such that only the repeat measurement was to be used in statistical analyses, rather than the average of the original and repeat measurements. This change was made because the original percent increase in organ volume could potentially be due to a transient condition unrelated to GD or treatment response.
06 July 2011	- It included the implementation of additional monitoring in subjects with a peak plasma concentration ≥150 ng/mL. - Planned enrollment was reduced from 186 subjects to 132 subjects. The underlying sample size assumptions were unchanged, and the study remained adequately powered for the primary efficacy endpoint (80% power for 132 subjects compared with a previous estimate of 90% power for 186 subjects) and all secondary endpoints. - US Food and Drug Administration (FDA)-recommended efficacy endpoint was added for the non-inferiority analysis as the percentage change in spleen volume (in MN) from baseline to Week 52. - Prior and concomitant medication guidelines were revised, including the following: Grapefruit products were added to the list of restricted medications prior to first dose of treatment; An exception was added for temporary use of medications known to prolong QTc interval, after completion of the dose adjustment in either treatment period.

13 March 2012	- Sample size, which had been adjusted downward to 132 subjects in previous amendment, was reverted to 150 subjects. - Clarified the length of time subjects randomized to eliglustat were to be followed in the study after any clinical decline requiring Cerezyme therapy. - Prior and concomitant medication guidelines were revised, including the following: A definition of concomitant medications was added; Requirements were added to notify the Sponsor's Medical Monitor in the event of temporary use of a CYP3A4 inducer and to interrupt the dose of eliglustat during temporary use of strong inhibitors of CYP2D6 or CYP3A4. - A statement about the potential for eliglustat to increase the exposure of P-glycoprotein substrate drugs was added. - Clarified that CYP2D6 non-poor metabolizer subjects could be on chronic therapy with a strong inhibitor of CYP2D6 or CYP3A4 (but not both) when entering the LTTP. Chronic therapy with strong CYP3A4 inhibitors remained prohibited in CYP2D6 poor metabolizers.
31 January 2013	- Added text was updated to include moderate CYP2D6 and CYP3A4 inhibitors. - Text was added to include specific PK sampling points for subjects who started or changed current chronic treatment of these medications. - Information on taliglucerase was added. - The eliglustat benefits/risk summary was updated to include results of the metropol study. - Added text was revised to include effects of Genz-112638 on CYP2D6 substrates. - Updated yexy was added to provide guidance regarding use of concomitant medications as of the date of this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported