



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 (LTP) 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 (\pm 1.309) | -0.33 (\pm 1.169) | | |
| Femur T-Score (n=80, 37) | -0.11 (\pm 1.08) | -0.47 (\pm 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 (\pm 0.07) | 0.05 (\pm 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 (\pm 1.71) | 2.63 (\pm 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 (\pm 1.57) | -3.22 (\pm 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 (\pm 0.94) | 3.13 (\pm 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 | 0.22 (\pm 0.405) | | | |
| Total Femur | -0.03 (\pm 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 occurrences (all) | 2 / 53 (3.77%) 2 | 13 / 106 (12.26%) 13 | |
| Nausea subjects affected / exposed occurrences (all) | 7 / 53 (13.21%) 7 | 18 / 106 (16.98%) 18 | |
| Toothache subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 7 / 106 (6.60%) 7 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 10 / 106 (9.43%) 10 | |
| Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 5 / 106 (4.72%) 5 | |
| Skin and subcutaneous tissue disorders Dry Skin subjects affected / exposed occurrences (all) | 4 / 53 (7.55%) 4 | 5 / 106 (4.72%) 5 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 13 / 53 (24.53%) 13 | 38 / 106 (35.85%) 38 | |
| Back Pain subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 6 | 23 / 106 (21.70%) 23 | |
| Bone Pain subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 9 / 106 (8.49%) 9 | |
| Muscle Spasms subjects affected / exposed occurrences (all) | 1 / 53 (1.89%) 1 | 6 / 106 (5.66%) 6 | |
| Musculoskeletal Pain subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 8 / 106 (7.55%) 8 | |
| Myalgia | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 05 October 2009 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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. |

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|-----------------|---|
| 13 March 2012 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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