



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients With Gaucher Disease Type 1 (ENGAGE)

#### Summary

EudraCT number	2008-005222-37
Trial protocol	NL GB BG
Global end of trial date	21 January 2016

#### Results information

Result version number	v3 (current)
This version publication date	13 April 2017
First version publication date	01 June 2016
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Clarification of analysis population descriptions and correction of subjects disposition data

#### Trial information

##### Trial identification

Sponsor protocol code	GZGD02507
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00891202
WHO universal trial number (UTN)	-
Other trial identifiers	Study name: ENGAGE

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	03 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To confirm the efficacy and safety of Genz-112638 after 39 weeks of treatment in subjects with Gaucher disease type 1.

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	05 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Lebanon: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Tunisia: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	40
EEA total number of subjects	3

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	38
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 72 subjects were screened between 5 November 2009 and 29 July 2011, of which 32 subjects were screen failure. Overall 40 subjects were enrolled and the study was conducted in 18 centers in 12 countries.

### Pre-assignment

Screening details:

The 40 subjects who met inclusion criteria received placebo or Genz-112638 (eliglustat tartrate) during 39 weeks primary analysis period (PAP). After Week 39 of the PAP, all subjects who remained in the study received eliglustat tartrate in the long-term treatment period (LTP) for up to Week 312.

### Period 1

Period 1 title	PAP (Up To Week 39)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	PAP: Placebo

Arm description:

Matching placebo capsule once daily on Day 1 followed by matching placebo capsule twice daily (BID) from Day 2 through Week 39.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to eliglustat tartrate was given to subjects up to Week 39.

<b>Arm title</b>	PAP: Eliglustat
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Arm description:

Eliglustat tartrate capsule as a single 50 mg dose on Day 1 followed by eliglustat tartrate 50 mg capsule BID from Day 2 to Week 4, and then either eliglustat tartrate 50 mg capsule BID (in subjects who had a Genz-99067 [active moiety of eliglustat tartrate in plasma] trough plasma concentration  $\geq 5$  ng/mL) or eliglustat tartrate 100 mg capsule BID (in subjects who had a Genz-99067 trough plasma concentration  $< 5$  ng/mL), up to Week 39. The pharmacokinetic (PK) assessment at Week 2 was used for dose adjustment after Week 4.

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

Dosage and administration details:

Eliglustat tartrate capsule single 50 mg dose on Day 1 followed by eliglustat tartrate 50 mg capsule BID

from Day 2 to Week 4. Depending upon Genz-99067 plasma trough concentration of < 5 ng/mL or  $\geq$  5 ng/mL at Week 2, subjects received eliglustat tartrate 50 mg or 100 mg BID from Week 4 to Week 39 respectively.

Number of subjects in period 1	PAP: Placebo	PAP: Eliglustat
Started	20	20
Completed	20	19
Not completed	0	1
Consent withdrawn by subject	-	1

## Period 2

Period 2 title	LTTP (Post-Week 39 up to Week 312)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LTTP: Eliglustat (Originally on Placebo)

### Arm description:

Subjects of the placebo arm in PAP who completed PAP were included in LTTP and received eliglustat tartrate from Day 1 (post Week 39) up to Week 312. Day 1 (post Week 39) was considered as baseline of LTTP for this arm. On Day 1, subjects received eliglustat tartrate capsule 50 mg BID orally until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration <5 ng/mL: next higher dose administered; if  $\geq$ 5 ng/mL: same dose continued) at Week 41 & Week 45, respectively.

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

### Dosage and administration details:

Subjects received eliglustat tartrate capsule 50 mg BID orally until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration <5 ng/mL: next higher dose administered; if  $\geq$ 5 ng/mL: same dose continued) at Week 41 & Week 45, respectively.

<b>Arm title</b>	LTTP: Eliglustat (Originally on Eliglustat)
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### Arm description:

Subjects of the eliglustat arm in PAP who completed PAP were included in LTTP and received eliglustat

tartrate capsule 50 mg BID orally from Day 1 (post Week 39) until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration <5 ng/mL: next higher dose administered; if ≥5 ng/mL: same dose continued) at Week 41 & Week 45, respectively.

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

**Dosage and administration details:**

Subjects received eliglustat tartrate capsule 50 mg BID orally from Day 1 (post Week 39) until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration <5 ng/mL: next higher dose administered; if ≥5 ng/mL: same dose continued) at Week 41 & Week 45, respectively.

<b>Number of subjects in period 2</b>	LTPP: Eliglustat (Originally on Placebo)	LTPP: Eliglustat (Originally on Eliglustat)
Started	20	19
Completed	15	12
Not completed	5	7
Transitioned to commercial eliglustat	5	2
Consent withdrawn by subject	-	4
Pregnancy	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	PAP: Placebo
Reporting group description: Matching placebo capsule once daily on Day 1 followed by matching placebo capsule twice daily (BID) from Day 2 through Week 39.	
Reporting group title	PAP: Eliglustat
Reporting group description: Eliglustat tartrate capsule as a single 50 mg dose on Day 1 followed by eliglustat tartrate 50 mg capsule BID from Day 2 to Week 4, and then either eliglustat tartrate 50 mg capsule BID (in subjects who had a Genz-99067 [active moiety of eliglustat tartrate in plasma] trough plasma concentration $\geq 5$ ng/mL) or eliglustat tartrate 100 mg capsule BID (in subjects who had a Genz-99067 trough plasma concentration $< 5$ ng/mL), up to Week 39. The pharmacokinetic (PK) assessment at Week 2 was used for dose adjustment after Week 4.	

Reporting group values	PAP: Placebo	PAP: Eliglustat	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	32.1 $\pm 11.26$	31.6 $\pm 11.55$	-
Gender categorical Units: Subjects			
Female	8	12	20
Male	12	8	20
Race Units: Subjects			
White	20	19	39
Asian	0	1	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	20	18	38
Hispanic or Latino	0	2	2
Body Mass Index (BMI)			
BMI was calculated as ([weight in kg] divided by [height in cm multiplied by 0.01] <sup>2</sup> ).			
Units: kg/m <sup>2</sup> arithmetic mean standard deviation	23.4 $\pm 3.54$	23.3 $\pm 2.74$	-
Weight Units: kg arithmetic mean standard deviation	68.6 $\pm 17.17$	64.8 $\pm 11.74$	-
Height Units: cm arithmetic mean	170	166.2	

standard deviation	$\pm 12.02$	$\pm 9.91$	-
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## End points

### End points reporting groups

Reporting group title	PAP: Placebo
Reporting group description: Matching placebo capsule once daily on Day 1 followed by matching placebo capsule twice daily (BID) from Day 2 through Week 39.	
Reporting group title	PAP: Eliglustat
Reporting group description: Eliglustat tartrate capsule as a single 50 mg dose on Day 1 followed by eliglustat tartrate 50 mg capsule BID from Day 2 to Week 4, and then either eliglustat tartrate 50 mg capsule BID (in subjects who had a Genz-99067 [active moiety of eliglustat tartrate in plasma] trough plasma concentration $\geq 5$ ng/mL) or eliglustat tartrate 100 mg capsule BID (in subjects who had a Genz-99067 trough plasma concentration $< 5$ ng/mL), up to Week 39. The pharmacokinetic (PK) assessment at Week 2 was used for dose adjustment after Week 4.	
Reporting group title	LTTP: Eliglustat (Originally on Placebo)
Reporting group description: Subjects of the placebo arm in PAP who completed PAP were included in LTTP and received eliglustat tartrate from Day 1 (post Week 39) up to Week 312. Day 1 (post Week 39) was considered as baseline of LTTP for this arm. On Day 1, subjects received eliglustat tartrate capsule 50 mg BID orally until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration $< 5$ ng/mL: next higher dose administered; if $\geq 5$ ng/mL: same dose continued) at Week 41 & Week 45, respectively.	
Reporting group title	LTTP: Eliglustat (Originally on Eliglustat)
Reporting group description: Subjects of the eliglustat arm in PAP who completed PAP were included in LTTP and received eliglustat tartrate capsule 50 mg BID orally from Day 1 (post Week 39) until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration $< 5$ ng/mL: next higher dose administered; if $\geq 5$ ng/mL: same dose continued) at Week 41 & Week 45, respectively.	

### Primary: PAP: Percent Change From Baseline in Spleen Volume (in multiples of normal [MN]) at Week 39 With Eliglustat Tartrate Treatment as Compared to Placebo

End point title	PAP: Percent Change From Baseline in Spleen Volume (in multiples of normal [MN]) at Week 39 With Eliglustat Tartrate Treatment as Compared to Placebo
End point description: Percent change in spleen volume = ([spleen volume at Week 39 minus spleen volume at baseline] divided by [spleen volume at baseline]) multiplied by 100, where all volumes were in MN. Analysis was performed on full analysis set (FAS) for PAP which included all subjects who signed informed consent and received at least one dose of study drug (placebo or eliglustat).	
End point type	Primary
End point timeframe: PAP Baseline (Day 1), Week 39	

End point values	PAP: Placebo	PAP: Eliglustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent change				
least squares mean (standard error)	2.26 ( $\pm$ 2.37)	-27.77 ( $\pm$ 2.37)		

## Statistical analyses

Statistical analysis title	Placebo vs Genz-112638
Statistical analysis description:	
Analysis was performed using analysis of covariance (ANCOVA) model fitted with treatment and baseline spleen severity (low spleen severity: spleen volume $\leq$ 20 multiples of normal spleen volume, high spleen severity: spleen volume $>$ 20 multiples of normal spleen volume).	
Comparison groups	PAP: Eliglustat v PAP: Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$< 0.0001$
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-30.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.82
upper limit	-23.24
Variability estimate	Standard error of the mean
Dispersion value	3.35

## Secondary: PAP: Hemoglobin Level at Baseline

End point title	PAP: Hemoglobin Level at Baseline
End point description:	
Analysis was performed on FAS for PAP which included all subjects who signed informed consent and received at least one dose of study drug (placebo or eliglustat).	
End point type	Secondary
End point timeframe:	
PAP Baseline (Day 1)	

End point values	PAP: Placebo	PAP: Eliglustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: g/dL				
arithmetic mean (standard deviation)	12.75 ( $\pm$ 1.629)	12.05 ( $\pm$ 1.816)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PAP: Absolute Change From Baseline in Hemoglobin Level at Week 39

End point title	PAP: Absolute Change From Baseline in Hemoglobin Level at Week 39
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End point description:

Absolute change = hemoglobin level at Week 39 minus hemoglobin level at baseline. Analysis was performed on FAS for PAP which included all subjects who signed informed consent and received at least one dose of study drug (placebo or eliglustat).

End point type	Secondary
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End point timeframe:

PAP Baseline (Day 1), Week 39

End point values	PAP: Placebo	PAP: Eliglustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: g/dL				
least squares mean (standard error)	-0.54 ( $\pm$ 0.23)	0.69 ( $\pm$ 0.23)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PAP: Percent Change From Baseline in Liver Volume (in MN) at Week 39

End point title	PAP: Percent Change From Baseline in Liver Volume (in MN) at Week 39
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End point description:

Percent change in liver volume = ([liver volume at Week 39 minus liver volume at baseline] divided by [liver volume at baseline]) multiplied by 100, where all volumes are in MN. Analysis was performed on FAS for PAP which included all subjects who signed informed consent and received at least one dose of study drug (placebo or eliglustat).

End point type	Secondary
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End point timeframe:

PAP Baseline (Day 1), Week 39

End point values	PAP: Placebo	PAP: Eliglustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent change				
least squares mean (standard error)	1.44 ( $\pm$ 1.64)	-5.2 ( $\pm$ 1.64)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: PAP: Percent Change From Baseline in Platelet Counts at Week 39

End point title	PAP: Percent Change From Baseline in Platelet Counts at Week 39
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End point description:

Percent change in platelet count = ([platelet count at Week 39 minus platelet count at baseline] divided by [platelet count at baseline]) multiplied by 100. Analysis was performed on FAS for PAP which included all subjects who signed informed consent and received at least one dose of study drug (placebo or eliglustat).

End point type	Secondary
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End point timeframe:

PAP Baseline (Day 1), Week 39

End point values	PAP: Placebo	PAP: Eliglustat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent change				
least squares mean (standard error)	-9.06 ( $\pm$ 5.95)	32 ( $\pm$ 5.95)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: LTTP: Percent Change From Baseline in Spleen Volume (in MN) at Week 234

End point title	LTTP: Percent Change From Baseline in Spleen Volume (in MN) at Week 234
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End point description:

Percent change in spleen volume = ([spleen volume at Week 234 minus spleen volume at baseline] divided by [spleen volume at baseline]) multiplied by 100, where all volumes are in MN. Baseline values for the original placebo subjects refer to Day 1 of LTTP and baseline values for the original eliglustat

subjects refer to the Day 1 of PAP. Analysis was performed on Intent-to-treat (ITT) population for LTTP which included all subjects who received at least 1 dose of eliglustat in LTTP period. Number of subjects analyzed= subjects evaluable for this endpoint and had available data for baseline and Week 234 spleen volume assessment.

End point type	Secondary
End point timeframe:	
PAP Baseline for Eliglustat (Originally on Eliglustat) arm, LTTP Baseline for Eliglustat (Originally on Placebo) arm, Week 234	

End point values	LTTP: Eliglustat (Originally on Placebo)	LTTP: Eliglustat (Originally on Eliglustat)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Percent Change				
arithmetic mean (standard deviation)	-64 (± 6.43)	-66.9 (± 8.45)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: LTTP: Absolute Change from Baseline in Hemoglobin Level at Week 234

End point title	LTTP: Absolute Change from Baseline in Hemoglobin Level at Week 234
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End point description:

Baseline values for the original placebo subjects refer to Day 1 of LTTP and baseline values for the original eliglustat subjects refer to the Day 1 of PAP. Analysis was performed on ITT population for LTTP which included all subjects who received at least 1 dose of eliglustat in LTTP period. Number of subjects analyzed= subjects evaluable for this endpoint and had available data for baseline and Week 234 hemoglobin level assessment.

End point type	Secondary
End point timeframe:	
PAP Baseline for Eliglustat (Originally on Eliglustat) arm, LTTP Baseline for Eliglustat (Originally on Placebo) arm, Week 234	

End point values	LTTP: Eliglustat (Originally on Placebo)	LTTP: Eliglustat (Originally on Eliglustat)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: g/dL				
arithmetic mean (standard deviation)	1.9 (± 1.88)	1.1 (± 0.65)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: LTTP: Percent Change From Baseline in Liver Volume (in MN) at Week 234

End point title	LTTP: Percent Change From Baseline in Liver Volume (in MN) at Week 234
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End point description:

Percent change in liver volume = ([liver volume at Week 234 minus liver volume at baseline] divided by [liver volume at baseline]) multiplied by 100, where all volumes are in MN. Baseline values for the original placebo subjects refer to Day 1 of LTTP and baseline values for the original eliglustat subjects refer to the Day 1 of PAP. Analysis was performed on ITT population for LTTP which included all subjects who received at least 1 dose of eliglustat in LTTP period. Number of subjects analyzed= subjects evaluable for this endpoint and had available data for baseline and Week 234 liver volume assessment.

End point type	Secondary
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End point timeframe:

PAP Baseline for Eliglustat (Originally on Eliglustat) arm, LTTP Baseline for Eliglustat (Originally on Placebo) arm, Week 234

End point values	LTTP: Eliglustat (Originally on Placebo)	LTTP: Eliglustat (Originally on Eliglustat)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: percent change				
arithmetic mean (standard deviation)	-22.4 (± 10.77)	-24.3 (± 11.21)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: LTTP: Percent Change From Baseline in Platelet Counts at Week 234

End point title	LTTP: Percent Change From Baseline in Platelet Counts at Week 234
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End point description:

Percent change in platelet count = ([platelet count at Week 234 minus platelet count at baseline] divided by [platelet count at baseline]) multiplied by 100. Baseline values for the original placebo subjects refer to Day 1 of LTTP and baseline values for the original eliglustat subjects refer to the Day 1 of PAP. Analysis was performed on ITT population for LTTP which included all subjects who received at least 1 dose of eliglustat in LTTP period. Number of subjects analyzed= subjects evaluable for this endpoint and had available data for baseline and Week 234 platelet count assessment.

End point type	Secondary
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End point timeframe:

PAP Baseline for Eliglustat (Originally on Eliglustat) arm, LTTP Baseline for Eliglustat (Originally on Placebo) arm, Week 234

<b>End point values</b>	LTPP: Eliglustat (Originally on Placebo)	LTPP: Eliglustat (Originally on Eliglustat)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Percent Change				
arithmetic mean (standard deviation)	100.1 (± 80.69)	77.3 (± 28.17)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from the signature of the Informed Consent Form through the follow-up period (30-37 days after the last visit, which was Week 312).

Adverse event reporting additional description:

Reported adverse events and death are treatment-emergent that is AEs that developed/worsened and death that occurred during the 'on treatment period' (first dose of eliglustat to end of follow-up period).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Eliglustat
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Reporting group description:

PAP: Eliglustat tartrate capsule 50 mg orally on Day 1 followed by eliglustat tartrate 50 mg capsule BID from Day 2 to Week 4, then either eliglustat tartrate 50 mg capsule BID (subjects with Genz-99067 trough plasma concentration  $\geq 5$  ng/mL) or eliglustat tartrate 100 mg capsule BID (subjects with Genz-99067 trough plasma concentration  $< 5$  ng/mL), up to Week 39. PK assessment at Week 2 used for dose adjustment after Week 4. LTTP: Subjects of the eliglustat arm in PAP who completed PAP were included in LTTP & received eliglustat tartrate capsule 50 mg BID orally from Day 1 (post Week 39) until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 & Week 47 were based on Genz-99067 trough plasma Concentrations (if trough plasma concentration  $< 5$  ng/mL: next higher dose administered; if  $\geq 5$  ng/mL: same dose continued) at Week 41 & Week 45, respectively.

Reporting group title	Placebo
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Reporting group description:

PAP: Matching placebo capsule once daily on Day 1 followed by matching placebo capsule BID from Day 2 through Week 39. LTTP: Subjects of the placebo arm in PAP who completed PAP were included in LTTP and received eliglustat tartrate from Day 1 (post Week 39) up to Week 312. Day 1 (post Week 39) was considered as baseline for LTTP. On Day 1, subjects received eliglustat tartrate capsule 50 mg BID orally until Week 43 followed by eliglustat tartrate 50 mg or 100 mg capsule BID up to Week 47, then eliglustat tartrate 50 mg or 100 mg or 150 mg capsule BID up to Week 312. Dose adjustments at Week 43 and Week 47 were based on Genz-99067 trough plasma concentrations (if trough plasma concentration  $< 5$  ng/mL: next higher dose administered; if  $\geq 5$  ng/mL: same dose continued) at Week 41 & Week 45, respectively.

Serious adverse events	Eliglustat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	3 / 20 (15.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrioventricular Block			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	



Atrioventricular Block Second Degree			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Eliglustat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	14 / 20 (70.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Fatigue			

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	
Oedema Peripheral subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	
Immune system disorders Seasonal Allergy subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 20 (10.00%) 2	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Epistaxis subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Nasal Obstruction subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Nasal Congestion subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Oropharyngeal Pain subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	
Investigations Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all)  Bone Density Decreased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  0 / 20 (0.00%) 0	2 / 20 (10.00%) 2  2 / 20 (10.00%) 2	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)  Ligament Sprain subjects affected / exposed occurrences (all)  Thermal Burn subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2  0 / 20 (0.00%) 0  0 / 20 (0.00%) 0	0 / 20 (0.00%) 0  2 / 20 (10.00%) 2  2 / 20 (10.00%) 2	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	3 / 20 (15.00%) 3	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Migraine subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  11 / 20 (55.00%) 11  3 / 20 (15.00%) 3	3 / 20 (15.00%) 3  7 / 20 (35.00%) 7  0 / 20 (0.00%) 0	
Blood and lymphatic system disorders			

Iron Deficiency Anaemia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Eye disorders Eye Irritation subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Gastrointestinal disorders Abdominal Distension subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	0 / 20 (0.00%) 0	
Abdominal Pain subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	2 / 20 (10.00%) 2	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	4 / 20 (20.00%) 4	
Diarrhoea subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5	1 / 20 (5.00%) 1	
Dry Mouth subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 20 (10.00%) 2	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	2 / 20 (10.00%) 2	
Gastritis subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	4 / 20 (20.00%) 4	
Nausea subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	2 / 20 (10.00%) 2	
Toothache			

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 20 (10.00%) 2	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Alopecia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	3 / 20 (15.00%) 3	
Skin Lesion subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 20 (10.00%) 2	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5	2 / 20 (10.00%) 2	
Arthralgia subjects affected / exposed occurrences (all)	11 / 20 (55.00%) 11	4 / 20 (20.00%) 4	
Bone Pain subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	
Joint Stiffness subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Musculoskeletal Pain			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	2 / 20 (10.00%) 2	
Myalgia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Pain In Extremity subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	4 / 20 (20.00%) 4	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Hordeolum subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 20 (10.00%) 2	
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	3 / 20 (15.00%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5	2 / 20 (10.00%) 2	
Otitis Media subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	2 / 20 (10.00%) 2	
Tonsillitis subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	3 / 20 (15.00%) 3	
Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 20 (5.00%) 1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2009	<ul style="list-style-type: none"><li>- Changes to study eligibility: pregnancy test results and use of medications known to inhibit CYP2D6 were to be evaluated prior to randomisation, and not prior to dosing; pathological bone involvement was to be evaluated in consultation with the central bone reviewer; acid glucosidase activity was to be evaluated in leukocytes, and not whole blood; documentation of anemia due to causes other than GD1 was to be based on folate, iron, and vitamin B-12 only, and not RBC.</li><li>- A T2-weighted MRI of the femur was to be obtained, and not short T1 inversion recovery (STIR). Bone disease assessments were also added to the safety endpoints and safety analyses for completeness.</li></ul>
25 February 2010	<ul style="list-style-type: none"><li>- Listed duration of each subjects in study. Updated risk/benefit &amp; dose rationale information. Extension in screening period. Opened enrollment of broader subject population, including subjects who were &gt;65 years of age, had received ERT more recently or had a prior history of cancer.</li><li>- Removed contraception requirement for male subjects &amp; allowed use of certain hormonal contraceptives in female subjects.</li><li>- Modified restriction of CYP2D6 inhibitors use, temporary use of CYP3A4 inducers &amp; strong inhibitors of CYP2D6 &amp; CYP3A4 after completion of dose adjustment in each treatment period &amp; exception for chronic medications after completion of dose adjustment in LTTP. Outlined specific actions were taken during temporary use based on type of concomitant medication, subject's CYP2D6 phenotype &amp; treatment period.</li><li>- Added second dose adjustment to 150 mg BID LTTP for subjects not achieved target trough conc. &gt;5 ng/mL.</li><li>- Added serial PK sampling after second dose adjustment, with 24-hour sampling for subjects receiving 150 mg BID.</li><li>-Reduced PK sampling after single 50-mg dose on Day 1 &amp; during study periods when subjects had received 50 mg BID or 100 mg BID.</li><li>-Added and updated PK sampling in concomitant medications that had potential to alter Genz-112638 exposure based on revised PK sampling scheme.</li><li>-Moved Wk 43 clinical laboratory tests &amp; ECGs to Wk 45 &amp; Wk 47, to better align with timing of second dose adjustment.</li><li>-Added optional blood collection for pharmacogenetics analyses, to permit evaluation of emerging clinical issues.</li><li>-Added GM3 as an exploratory marker to confirm lack of inhibition of the GL-1 pathway. Revised time points for biomarkers &amp; exploratory biomarkers to reduce total number of measurements.</li><li>-Added measurement of spleen &amp; liver volume of subjects withdrew prior Week 26 &amp; missing data was handled for subjects withdrew prior to Week 39.</li><li>-Changed AE causality assessment as per National Cancer Institute Common Toxicology Criteria for Adverse Events.</li></ul>



10 November 2010	<ul style="list-style-type: none"> <li>- Planned enrollment was reduced from 36 subjects to 28 subjects. Underlying sample size assumptions were unchanged, and study remained adequately powered for primary efficacy endpoint (85% power for 28 subjects compared with a previous estimate of 92% power for 36 subjects) and all secondary endpoints.</li> <li>- Broadened target subject population to included following subjects, as data from the Phase 2 study (GZGD00304) and/or Gaucher Registry (for subjects on Cerezyme) suggested that such subjects might benefit from eliglustat therapy: Spleen volume as low as 6 MN (previously 8 MN) Platelet count as high as 130,000/mm<sup>3</sup> (previously 100,000/mm<sup>3</sup>)</li> <li>- Radiological evidence of bone involvement in the absence of clinical symptoms (previously any documented bone involvement was an exclusion)</li> <li>- The analysis of organ volume measurements in subjects who had a repeat measurement (due to a &gt;30% increase in volume on the original 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 &gt;30% increase in organ volume could potentially be due to a transient condition unrelated to Gaucher disease or treatment response.</li> <li>- Study visits in the LTTP were scheduled relative to the start of that study period, and not relative to the start of the Primary Analysis Period, given the duration of time required to complete specified assessments between study periods.</li> <li>- A PK sample was to be obtained at the Early Withdrawal visit only for subjects who withdrew due to an AE.</li> </ul>
12 July 2011	<ul style="list-style-type: none"> <li>- The principal change was the implementation of additional monitoring in subjects with a peak plasma concentration <math>\geq 150</math> ng/mL. In such subjects, the dose of eliglustat was to be temporarily interrupted while the subject returned to the site for further evaluations. The nature of these evaluations and any subsequent dose modifications were dependent on the subject's observed peak plasma concentration and the treatment period in which it occurred, any concurrent safety findings, and the feasibility of adjusting any concomitant medications. Management of subjects with peak plasma concentrations <math>\geq 150</math> ng/mL.</li> <li>- Added 2-hour post-dose PK sampling at additional study visits.</li> <li>- Added a secondary analysis of within-subject changes in spleen volume, hemoglobin, liver volume, and platelet count for all randomised subjects with 39 weeks of treatment on eliglustat in the Primary Analysis Period (eliglustat group) or LTTP (placebo group).</li> <li>- Added an exception for temporary use of medications known to prolong QTc interval, after completion of the dose adjustment in either treatment period.</li> <li>- Clarified that, for the purpose of concomitant medication management, CYP2D6 indeterminate metabolizers would be considered poor metabolizers if neither allele was known to be active and non-poor metabolizer if 1 allele was known to be active.</li> <li>- Expanded the definition of MEOIs to include syncope from any cause, and not just syncope that may be a result of arrhythmia. Clarified that MEOIs occurring prior to initiation of study treatment were not required to be reported.</li> <li>- Clarified which assessments were required to be repeated during re-screening.</li> </ul>

27 March 2012	<ul style="list-style-type: none"> <li>- Sample size, which had been adjusted downward to 28 subjects, was reverted to 36 subjects.</li> <li>- Extended the total study duration (due to the delay in enrollment).</li> <li>- Added an exploratory analysis of bone biomarkers (to investigate the role of impaired bone formation vs. accelerated bone resorption in the pathophysiology of Gaucher-related osteopenia and the mechanism of eliglustat effects on bone).</li> <li>- Updated / clarified concomitant medication guidance:</li> <li>- Added a definition of concomitant medications.</li> <li>- Added requirements to (1) notify the Sponsor's Medical Monitor in the event of temporary use of a CYP3A4 inducer and (2) interrupt the dose of eliglustat during temporary use of strong inhibitors of CYP2D6 or CYP3A4.</li> <li>- Added a statement about the potential for eliglustat to increase the exposure of P gp substrate drugs.</li> <li>- Clarified that the only subjects who should be on chronic therapy when entering the Long-term Treatment Period are CYP2D6 non-poor metabolizers, and that chronic therapy in these subjects is limited to a strong inhibitor of CYP2D6 or CYP3A4 (but not both).</li> <li>- Clarified that PK samples would be collected only in the event of changes in chronic use (not temporary use) of strong inhibitors of CYP2D6 or CYP3A4 or inducers of CYP3A4, and further clarified that discontinuation of a chronic medication would necessitate such PK sampling.</li> <li>- Added annual neurological examinations from Week 78 through the end of study, to allow detection of clinical signs or symptoms suggestive of nerve conduction abnormalities during LTTP.</li> <li>- Reduced the frequency of ECGs to every 6 months (previously every 3 months) during the Long-term Treatment Period, as this is deemed sufficient to monitor cardiac safety and will reduce the burden on subjects.</li> <li>- Updated risk/benefit information based on recently completed clinical studies.</li> </ul>
05 February 2013	<ul style="list-style-type: none"> <li>- Updated concomitant medication guidance as based on the information provided in the investigator letter.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/9605861>