



Clinical trial results:

A Phase 2 Study to Evaluate the Safety, Pharmacodynamics, Pharmacokinetics, and Exploratory Efficacy of GZ/SAR402671 in Enzyme Replacement Therapy (ERT) Treatment-naïve Adult Male Patients Diagnosed with Fabry Disease

Summary

EudraCT number	2013-005324-41
Trial protocol	GB CZ
Global end of trial date	06 September 2016

Results information

Result version number	v1 (current)
This version publication date	21 September 2017
First version publication date	21 September 2017

Trial information

Trial identification

Sponsor protocol code	ACT13739
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02228460
WHO universal trial number (UTN)	U1111-1152-1456

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy of GZ402671/SAR402671 in enzyme replacement therapy (ERT) treatment-naïve adult male subjects diagnosed with Fabry disease (FD).

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	11 November 2014
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	Poland: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	11
EEA total number of subjects	6

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)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled in the study at 8 centers in 5 countries between 11 November 2014 and 06 September 2016. A total of 14 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 14 screened subjects, 11 subjects were enrolled and treated in the study.

Period 1

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

Arms

Arm title	GZ/SAR402671
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Arm description:

GZ/SAR402671 15 mg once daily, orally for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	GZ/SAR402671
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

GZ/SAR402671 capsule, once daily for 26 weeks.

Number of subjects in period 1	GZ/SAR402671
Started	11
Completed	9
Not completed	2
Adverse event	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	GZ/SAR402671
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Reporting group description:

GZ/SAR402671 15 mg once daily, orally for 26 weeks.

Reporting group values	GZ/SAR402671	Total	
Number of subjects	11	11	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	26.5		
standard deviation	± 7.6	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	11	11	

End points

End points reporting groups

Reporting group title	GZ/SAR402671
Reporting group description: GZ/SAR402671 15 mg once daily, orally for 26 weeks.	

Primary: Change From Baseline at Week 26 in Skin Globotriaosylceramide (GL-3) Score in Superficial Skin Capillary Endothelium: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26

End point title	Change From Baseline at Week 26 in Skin Globotriaosylceramide (GL-3) Score in Superficial Skin Capillary Endothelium: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26 ^[1]
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End point description:

Skin biopsies taken at baseline and Week 26 were analyzed for cellular GL-3 accumulation (inclusions) by light microscopy. Three independent pathologists evaluated each biopsy using an inclusion severity score of 0 (none/trace), 1 (mild), 2 (moderate), and 3 (severe). A single score per subject per time point was derived by taking the score rated by a majority of the pathologists; if a majority score could not be derived, the median score was used. Data were summarized and reported in terms of number of subjects with shift from baseline GL-3 score to Week 26 GL-3 score. Any shift category of Baseline score/Week 26 score that was not observed is not reported. Shift to lower score from baseline to Week 26 indicates less severe condition at Week 26. Analysis was performed on Full Analysis Set (FAS) that included all subjects who received at least 1 dose of study treatment. Number of subjects analyzed=subjects with available data at both baseline and Week 26.

End point type	Primary
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End point timeframe:

Baseline, Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Single arm study. A McNemar test was used to assess the treatment effect based on paired pre-treatment and post-treatment (Week 26) frequencies of skin GL-3 score grouped into categories (0 to <2; 2 to 3) at the 5% significance level. $p = 0.3173$

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects				
Baseline Score:1/Week 26 Score:1	4			
Baseline Score:1/Week 26 Score:2	1			
Baseline Score:2/Week 26 Score:1	3			
Baseline Score:2/Week 26 Score:2	1			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline at Week 26 in Skin GL-3 Score in Superficial Skin Capillary Endothelium

End point title	Mean Change From Baseline at Week 26 in Skin GL-3 Score in Superficial Skin Capillary Endothelium ^[2]
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End point description:

Skin biopsies taken at baseline and Week 26 were analyzed for cellular GL-3 accumulation (inclusions) by light microscopy. Three independent pathologists evaluated each biopsy using an inclusion severity score of 0 (none/trace), 1 (mild), 2 (moderate), and 3 (severe). A single score per subject per time point was derived by taking the score rated by a majority of the pathologists; if a majority score could not be derived, the median score was used. Change from baseline in GL-3 score was obtained by subtracting baseline value from post-baseline value at Week 26. A negative change from baseline indicates less severe condition at Week 26. Analysis was performed on FAS. Number of subjects analyzed=subjects with available data at both baseline and Week 26.

End point type	Primary
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End point timeframe:

Baseline, Week 26

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: Single arm study. A Wilcoxon signed rank test was used to assess the mean change from baseline to Week 26 in skin GL-3 score at the 5% significance level. p = 0.625

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	-0.22 (-0.73 to 0.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma GL-3 Concentration at Week 26

End point title	Change From Baseline in Plasma GL-3 Concentration at Week 26
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End point description:

Change from baseline in plasma GL-3 was obtained by subtracting baseline value from post-baseline value at Week 26. Concentration of GL-3 in plasma was determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Analysis was performed on FAS. Number of subjects analyzed = subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mcg/mL				
arithmetic mean (standard deviation)	-3.62 (± 1.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Lyso Globotriaosylceramide (Lyso-GL-3) Concentration at Week 26

End point title	Change From Baseline in Plasma Lyso Globotriaosylceramide (Lyso-GL-3) Concentration at Week 26
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End point description:

Change from baseline in plasma Lyso-GL-3 was obtained by subtracting baseline value from post-baseline value at Week 26. Concentration of lyso-GL-3 in plasma was determined using a validated LC-MS/MS method. Analysis was performed on FAS. Number of subjects analyzed = subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)	-30.99 (\pm 22.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Glucosylceramide (GL-1) Concentration at Week 26

End point title	Change From Baseline in Plasma Glucosylceramide (GL-1) Concentration at Week 26
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End point description:

Change from baseline in plasma GL-1 was obtained by subtracting baseline value from post-baseline value at Week 26. Concentration of GL-1 in plasma was determined using a validated LC-MS/MS method. Analysis was performed on FAS. Number of subjects analyzed = subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mcg/mL				
arithmetic mean (standard deviation)	-3.26 (± 1.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in Skin GL-3 Score in Deep Vessels Endothelial Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26

End point title	Change From Baseline at Week 26 in Skin GL-3 Score in Deep Vessels Endothelial Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26
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End point description:

Skin biopsies taken at baseline and Week 26 were analyzed for cellular GL-3 accumulation (inclusions) by light microscopy. Three independent pathologists evaluated each biopsy using an inclusion severity score of 0 (none/trace), 1 (mild), 2 (moderate), and 3 (severe). A single score per subject per time point was derived by taking the score rated by a majority of the pathologists; if a majority score could not be derived, the median score was used. Data were summarized and reported in terms of number of subjects with shift from baseline GL-3 score to Week 26 GL-3 score. Any shift category of Baseline score/Week 26 score that was not observed is not reported. Shift to lower score from baseline to Week 26 indicates less severe condition at Week 26. Analysis was performed on FAS. Number of subjects analyzed=subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects				
Baseline Score:1/Week 26 Score:1	1			
Baseline Score:2/Week 26 Score:1	2			
Baseline Score:2/Week 26 Score:2	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in Skin GL-3 Score in Deep Vessels Smooth Muscle Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26

End point title	Change From Baseline at Week 26 in Skin GL-3 Score in Deep Vessels Smooth Muscle Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26
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End point description:

Skin biopsies taken at baseline and Week 26 were analyzed for cellular GL-3 accumulation (inclusions) by light microscopy. Three independent pathologists evaluated each biopsy using an inclusion severity score of 0 (none/trace), 1 (mild), 2 (moderate), and 3 (severe). A single score per subject per time point was derived by taking the score rated by a majority of the pathologists; if a majority score could not be derived, the median score was used. Data were summarized and reported in terms of number of subjects with shift from baseline GL-3 score to Week 26 GL-3 score. Any shift category of Baseline score/Week 26 score that was not observed is not reported. Shift to lower score from baseline to Week 26 indicates less severe condition at Week 26. Analysis was performed on FAS. Number of subjects analyzed=subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects				
Baseline Score:1.5/Week 26 Score:1.5	2			
Baseline Score:2/Week 26 Score:2	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in Skin GL-3 Score in Perineurium Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26

End point title	Change From Baseline at Week 26 in Skin GL-3 Score in Perineurium Cells: Number of Subjects in Categories of Shift in GL-3 Score From Baseline to Week 26
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End point description:

Skin biopsies taken at baseline and Week 26 were analyzed for cellular GL-3 accumulation (inclusions) by light microscopy. Three independent pathologists evaluated each biopsy using an inclusion severity score of 0 (none/trace), 1 (mild), 2 (moderate), and 3 (severe). A single score per subject per time point was derived by taking the score rated by a majority of the pathologists; if a majority score could not be derived, the median score was used. Data were summarized and reported in terms of number of subjects with shift from baseline GL-3 score to Week 26 GL-3 score. Any shift category of Baseline score/Week 26 score that was not observed is not reported. Shift to lower score from baseline to Week 26 indicates less severe condition at Week 26. Analysis was performed on FAS. Number of subjects analyzed=subjects with available data at both baseline and Week 26.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects				
Baseline Score:1/Week 26 Score:2	1			
Baseline Score:2/Week 26 Score:2	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urine Globotriaosylceramide (GL-3) Concentration at Week 26

End point title	Change From Baseline in Urine Globotriaosylceramide (GL-3) Concentration at Week 26
End point description: Change from baseline in plasma GL-3 was obtained by subtracting baseline value from post-baseline value at Week 26. Concentration of GL-3 in urine was determined using a validated LC-MS/MS method. Analysis was performed on FAS. Number of subjects analyzed = subjects with available data at both baseline and Week 26.	
End point type	Secondary
End point timeframe: Baseline, Week 26	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mg/mmol Cr				
arithmetic mean (standard deviation)	-0.25 (± 0.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs)
End point description: Any untoward medical occurrence in a subject who received study drug was considered an adverse event (AE) without regard to possibility of causal relationship with this treatment. TEAEs were defined as AEs that developed or worsened during on-treatment period (period from the first administration of study drug through the last administration of the study drug plus 30 days or end of study participation	

for subject, whichever occurs first). Analysis was performed on safety population defined as all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
Baseline up to 212 days	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Plasma Drug Concentration (Cmax) of GZ/SAR402671

End point title	Pharmacokinetics (PK): Maximum Plasma Drug Concentration (Cmax) of GZ/SAR402671
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End point description:

Maximum plasma concentration observed for study drug was reported. Analysis was performed on PK population defined as all subjects for whom the primary PK data were considered sufficient and interpretable. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Day 1 (predose and 1, 2, 4, 8, 24 hours post-dose); Day 182 (predose and 1, 2, 4, 8, 24 hours postdose)

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=11)	24.7 (± 5.89)			
Day 182 (n=9)	192 (± 96.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Plasma Trough Concentration (Ctrough) of GZ/SAR402671

End point title	PK: Plasma Trough Concentration (Ctrough) of GZ/SAR402671
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End point description:

Ctrough was defined as the plasma concentration of study drug observed just before treatment administration during repeated dosing. Analysis was performed on PK population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Predose on Day 14, 28, 56, 84, 126 and 182

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 14 (n= 11)	152 (± 68.9)			
Day 28 (n= 11)	165 (± 66.1)			
Day 56 (n= 10)	182 (± 90.3)			
Day 84 (n= 10)	164 (± 124)			
Day 126 (n= 9)	175 (± 94.7)			
Day 182 (n= 9)	164 (± 89.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time to Reach Maximum Plasma Drug Concentration (Tmax) of GZ/SAR402671

End point title	PK: Time to Reach Maximum Plasma Drug Concentration (Tmax) of GZ/SAR402671
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End point description:

Tmax was defined as time to reach maximum plasma concentration of study drug. Analysis was performed on PK population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Day 1 (predose and 1, 2, 4, 8, 24 hours post-dose); Day 182 (predose and 1, 2, 4, 8, 24 hours postdose)

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
median (full range (min-max))				
Day 1 (n= 11)	8 (1.07 to 24)			
Day 182 (n= 9)	4 (0 to 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under Plasma Concentration Versus Time Curve From 0 to 24 Hours (AUC0-24) of GZ/SAR402671

End point title	PK: Area Under Plasma Concentration Versus Time Curve From 0 to 24 Hours (AUC0-24) of GZ/SAR402671
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End point description:

Area under the plasma concentration versus time curve of study drug from time 0 to 24 hours (AUC0-24) was calculated using the trapezoidal method over the dosing interval. Analysis was performed on PK population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Day 1 (predose and 1, 2, 4, 8, 24 hours post-dose); Day 182 (predose and 1, 2, 4, 8, 24 hours postdose)

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng*hour/mL				
arithmetic mean (standard deviation)				
Day 1 (n= 11)	476 (± 125)			
Day 182 (n= 9)	4110 (± 2090)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Terminal Half-life (t1/2z) of GZ/SAR402671

End point title	PK: Terminal Half-life (t1/2z) of GZ/SAR402671
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End point description:

Plasma t1/2z was the time measured for the plasma concentration of drug to decrease by one half. The t1/2z was estimated based on 24-hour post-dose PK. Analysis was performed on PK population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Day 1 (predose and 1, 2, 4, 8, 24 hours post-dose); Day 182 (predose and 1, 2, 4, 8, 24 hours postdose)

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
arithmetic mean (standard deviation)				
Day 1 (n= 4)	86.8 (± 39.6)			
Day 182 (n= 7)	128 (± 59)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Apparent Total Body Clearance of GZ/SAR402671 (CLss/F)

End point title	PK: Apparent Total Body Clearance of GZ/SAR402671 (CLss/F)
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End point description:

Drug clearance was a quantitative measure of the rate at which a drug substance was removed from the blood. Analysis was performed on PK population. Number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
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End point timeframe:

Predose and 1, 2, 4, 8, 24 hours post-dose on Day 182

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mL/hour				
arithmetic mean (standard deviation)	7490 (± 10900)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Apparent Volume of Distribution of GZ/SAR402671 (Vss/F) at Steady State

End point title	PK: Apparent Volume of Distribution of GZ/SAR402671 (Vss/F) at Steady State
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End point description:

Volume of distribution at steady state was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of drug. Since the percent extrapolation of AUC for all subjects was >30%, AUC could not be determined and hence, Vss/F could not be calculated.

End point type	Secondary
End point timeframe:	
Predose and 1, 2, 4, 8, 24 hours post-dose on Day 182	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[3]			
Units: Liters (L)				
arithmetic mean (standard deviation)	()			

Notes:

[3] - Since percent extrapolation of AUC for all subjects was >30%, hence Vss/F could not be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Cumulated Amount of GZ/SAR402671 Excreted in Urine From 0 to 24 Hours (Ae0-24)

End point title	PK: Cumulated Amount of GZ/SAR402671 Excreted in Urine From 0 to 24 Hours (Ae0-24)
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End point description:

Ae0-24 was the cumulated amount of study drug excreted in urine during the time interval of 0 to 24 hours. Analysis was performed on PK population. Number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
End point timeframe:	
0-24 hours on Day 182	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mcg				
arithmetic mean (standard deviation)	3210 (± 1640)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Percentage of Dose of GZ/SAR402671 Excreted in Urine From 0 to 24 Hours (fe0-24)

End point title	PK: Percentage of Dose of GZ/SAR402671 Excreted in Urine From 0 to 24 Hours (fe0-24)
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End point description:

fe0-24 was the fraction of dose excreted in urine during the time interval of 0 to 24 hours. Analysis was

performed on PK population. Number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
End point timeframe:	
0-24 hours on Day 182	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of dose				
arithmetic mean (standard deviation)	21.4 (± 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Renal Clearance of GZ/SAR402671 From 0 to 24 Hours (CLR)

End point title	PK: Renal Clearance of GZ/SAR402671 From 0 to 24 Hours (CLR)
End point description:	
Renal clearance (CLR) was calculated by dividing the cumulative amount of drug excreted in urine during the dosing interval of 0-24 hours by area under the plasma drug concentration time-curve during the dosing interval of 0-24 hours. Analysis was performed on PK population. Number of subjects analyzed = subjects with available data for this end point.	
End point type	Secondary
End point timeframe:	
0-24 hours on Day 182	

End point values	GZ/SAR402671			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mL/hour				
arithmetic mean (standard deviation)	925 (± 407)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 212 days.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs developed/worsened during "on treatment period" (from first administration through last administration of study drug + 30 days or end of study participation for subject, whichever occurs first). Analysis was performed on safety population that included all enrolled subjects who received ≥ 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	GZ/SAR402671
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Reporting group description:

GZ/SAR402671 15 mg once daily, orally for 26 weeks.

Serious adverse events	GZ/SAR402671		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depressed Mood			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Floppy Infant			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GZ/SAR402671		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Feeling Hot			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Influenza Like Illness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Oropharyngeal Pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Depressed Mood			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Investigations Electrocardiogram T Wave Abnormal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Electrocardiogram Abnormal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Nuclear Magnetic Resonance Imaging Brain Abnormal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Vibration Test Abnormal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Injury, poisoning and procedural complications Muscle Strain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Wound subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 6		
Amnesia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Headache subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 5		

Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Migraine subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Sinus Headache subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
White Matter Lesion subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Chalazion subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Eye Pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Lacrimation Increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Lenticular Opacities subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Retinal Vascular Disorder			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vision Blurred			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dry Mouth			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	6		
Oesophageal Discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Angiokeratoma			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Muscle Twitching subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 3		
Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Pain In Extremity subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Neck Pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Infections and infestations			
Ear Infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Rhinitis subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2014	Following changes were made: - Added ophthalmology exam at Week 12, as requested by the Medicines and Healthcare products Regulatory Agency; - Exclusion of the use of grapefruit, grapefruit juice, or grapefruit products for 72 hours prior to administration of first dose of study drug and for duration of 26-week treatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported