



## Clinical trial results:

### An Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of REPLAGAL® in Treatment-naïve Chinese Subjects with Fabry Disease

#### Summary

EudraCT number	2022-004246-35
Trial protocol	Outside EU/EEA
Global end of trial date	03 January 2024

#### Results information

Result version number	v1 (current)
This version publication date	18 July 2024
First version publication date	18 July 2024

#### Trial information

##### Trial identification

Sponsor protocol code	TAK-675-3001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04974749
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to assess the safety of REPLAGAL in treatment-naïve Chinese participants with Fabry disease.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	China: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	5
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 6 investigative sites in China from 1 May 2022 to 3 January 2024.

### Pre-assignment

Screening details:

A total of 20 participants with Fabry disease were enrolled in this study to receive REPLAGAL for 52 weeks.

### Period 1

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

### Arms

Arm title	REPLAGAL
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Arm description:

Participants received REPLAGAL 0.2 milligrams per kilogram (mg/kg) body weight, intravenous (IV) infusion, every other week (EOW) from Day 1 (Week 0) up to Week 52.

Arm type	Experimental
Investigational medicinal product name	REPLAGAL
Investigational medicinal product code	
Other name	Agalsidase Alfa, TAK-675
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received REPLAGAL 0.2 mg/kg body weight, infusion, IV, EOW for 52 weeks.

Number of subjects in period 1	REPLAGAL
Started	20
Completed	17
Not completed	3
Consent withdrawn by subject	2
Gestation	1

## Baseline characteristics

### Reporting groups

Reporting group title	REPLAGAL
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Reporting group description:

Participants received REPLAGAL 0.2 milligrams per kilogram (mg/kg) body weight, intravenous (IV) infusion, every other week (EOW) from Day 1 (Week 0) up to Week 52.

Reporting group values	REPLAGAL	Total	
Number of subjects	20	20	
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	30.1		
standard deviation	± 14.90	-	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	8	8	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	20	20	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	20	20	
Unknown or Not Reported	0	0	
Height			
Units: centimeters (cm)			
arithmetic mean	160.47		
standard deviation	± 9.271	-	
Weight			
Units: kilograms (kg)			
arithmetic mean	53.88		
standard deviation	± 10.370	-	
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2]			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean	20.87		
standard deviation	± 3.674	-	



## End points

### End points reporting groups

Reporting group title	REPLAGAL
Reporting group description:	
Participants received REPLAGAL 0.2 milligrams per kilogram (mg/kg) body weight, intravenous (IV) infusion, every other week (EOW) from Day 1 (Week 0) up to Week 52.	

### Primary: Number of Participants With Serious Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Serious Treatment-emergent Adverse Events (TEAEs) <sup>[1]</sup>
End point description:	
An adverse event (AE) was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that did not necessarily have a causal relationship with this investigational product (IP) or medicinal product. Serious AE was any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital abnormality/birth defect, and was an important medical event. A TEAE was defined as any event emerging at or after the initiation of treatment with an IP or any existing event that worsened in either intensity or frequency following exposure to the IP until the end of the safety follow-up period. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.	
End point type	Primary
End point timeframe:	
From start of study drug administration up to 14 days after end of treatment (EOT) [up to Week 54]	

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: Only descriptive analysis was planned for this endpoint.

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With TEAEs

End point title	Number of Participants With TEAEs
End point description:	
An AE was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that did not necessarily have a causal relationship with this investigational product or medicinal product. A TEAE was defined as any event emerging at or after the initiation of treatment with an IP or any existing event that worsened in either intensity or frequency following exposure to the IP until the end of the safety follow-up period. Safety Analysis Set included all participants in the Intent-to-treat (ITT) Set who received at least 1 dose of REPLAGAL.	
End point type	Secondary

End point timeframe:

From start of study drug administration up to 14 days after EOT (up to Week 54)

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	20			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Infusion-related Reactions (IRRs)

End point title	Number of Participants With Infusion-related Reactions (IRRs)
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End point description:

An IRR was defined as an event that began either during or within 24 hours after the start of the infusion, and was judged as related to treatment with the IP. An IRR could be serious or non-serious. Adverse events that were considered IRRs were noted as such in the participant's source documentation. Other AEs which occurred prior to the infusion, along with AEs associated with protocol-defined testing and assessments (example, laboratory testing and physical examinations), which were performed prior to the infusion, were not considered as IRRs. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to Week 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	5			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Clinically Meaningful Changes in Laboratory Parameters

End point title	Number of Participants With Clinically Meaningful Changes in Laboratory Parameters
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End point description:

Laboratory assessment included parameters of serum chemistry, hematology, and urinalysis. Clinically meaningful laboratory parameters assessment was based on investigator interpretation. Number of participants with clinically meaningful changes in laboratory parameters were reported. Safety Analysis

Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

End point type	Secondary
End point timeframe:	
From start of study drug administration up to Week 52	

<b>End point values</b>	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in eGFR Values at Weeks 8, 16, 28, and 40

End point title	Change From Baseline in eGFR Values at Weeks 8, 16, 28, and 40
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End point description:

The eGFR was calculated by CKD-EPI formula for  $\geq 18$  years participants,  $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$  (if female)  $\times 1.159$  (if black) where: Scr is serum creatinine (mg/dL);  $\kappa$  is 0.7 for females and 0.9 for males;  $\alpha$  is -0.329 for females and -0.411 for males; min indicates the minimum of Scr/ $\kappa$  or 1; max indicates the maximum of Scr/ $\kappa$  or 1. For  $<18$  years participants, Counahan-Barratt equation was used for calculation of eGFR.  $eGFR = (0.43 \times \text{height in cm})/Scr$  where, Scr is serum creatinine (mg/dL). mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. 'n' denotes the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 8, 16, 28, and 40	

<b>End point values</b>	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard deviation)				
Week 8 (n=18)	-1.2 ( $\pm$ 15.66)			
Week 16 (n=18)	-0.4 ( $\pm$ 13.67)			
Week 28 (n=17)	5.1 ( $\pm$ 11.25)			
Week 40 (n=16)	0.3 ( $\pm$ 13.17)			

## Statistical analyses



No statistical analyses for this end point

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**Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) to REPLAGAL**

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End point title	Number of Participants With Positive Anti-drug Antibodies (ADA) to REPLAGAL
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End point description:

Number of participants with positive ADA to REPLAGAL were reported. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

End point type	Secondary
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End point timeframe:

Baseline up to Week 52

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End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	6			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of Participants With Clinically Meaningful Changes in Vital Signs**

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End point title	Number of Participants With Clinically Meaningful Changes in Vital Signs
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End point description:

Vital sign assessment included pulse, blood pressure, respiratory rate, and temperature. Clinically meaningful vital signs assessment was based on investigator interpretation. Number of participants with clinically meaningful abnormalities in vital signs were reported. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to Week 52

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End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	0			

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**Statistical analyses**

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No statistical analyses for this end point

### Secondary: Number of Participants With Clinically Meaningful Changes in Electrocardiogram (ECG) Parameters

End point title	Number of Participants With Clinically Meaningful Changes in Electrocardiogram (ECG) Parameters
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End point description:

ECG parameters included assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, and assessment of PR, QRS, QT, and corrected QT intervals. Clinically meaningful ECG assessment was based on investigator interpretation. Number of participants with clinically meaningful abnormalities in 12-lead ECG were reported. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to Week 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Renal Function as Assessed by Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 52

End point title	Renal Function as Assessed by Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 52
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End point description:

Renal function was assessed by eGFR using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for  $\geq 18$  years participants,  $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$  (if female)  $\times 1.159$  (if black) where: Scr is serum creatinine (milligram per deciliter [mg/dL]);  $\kappa$  is 0.7 for females and 0.9 for males;  $\alpha$  is -0.329 for females and -0.411 for males; min indicates the minimum of Scr/ $\kappa$  or 1; max indicates the maximum of Scr/ $\kappa$  or 1. For  $< 18$  years participants, Counahan-Barratt equation was used for calculation of eGFR.  $eGFR = (0.43 \times \text{height in centimeter [cm]}) / Scr$  where, Scr is serum creatinine (mg/dL). Renal function as assessed by eGFR was expressed using the unit: milliliters/minute/1.73 meter square (mL/min/1.73m<sup>2</sup>). Modified Intent-to-treat (mITT) Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard deviation)	4.1 (± 12.48)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Positive Neutralizing Antibodies (NAb) to REPLAGAL

End point title	Number of Participants With Positive Neutralizing Antibodies (NAb) to REPLAGAL
End point description: Number of participants with positive NAb to REPLAGAL were reported. Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.	
End point type	Secondary
End point timeframe: Baseline up to Week 52	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	5			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Left Ventricular Mass Index (LVMI) at Weeks 16 and 52

End point title	Change From Baseline in Left Ventricular Mass Index (LVMI) at Weeks 16 and 52
End point description: LVMI was measured by echocardiography at the clinical sites, and LVMI was derived using the following formula: $\text{LVM [grams]} = 0.8 \times [1.04 \times \{(\text{LVDd} + \text{IVSTd} + \text{PWTd})^3 - \text{LVDd}^3\}] + 0.6$ where: LVDd is left ventricular internal diameter (diastolic) (cm), IVSTd is intraventricular septum thickness (diastolic) (cm), and PWTd is posterior wall thickness (diastolic) (cm). LVM indexed to height (LVMI) = LVM/height <sup>2.7</sup> (g/m <sup>2.7</sup> ), where height was measured in meter. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. 'n' denotes the number of participants with data available for analysis at the specified timepoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 16 and 52	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: grams per meter (g/m)^2.7				
arithmetic mean (standard deviation)				
Week 16 (n=14)	-0.4696 (± 6.81928)			
Week 52 (n=12)	-1.7261 (± 9.87836)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Urine Protein/Creatinine Ratio

End point title	Change From Baseline in Urine Protein/Creatinine Ratio
End point description:	
The change from baseline in urine protein/creatinine ratio was derived from early morning spot urine samples collected at the specified time points. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. 'n' denotes the number of participants with data available for analysis at the specified timepoint.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 8, 16, 28, 40, and 52	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: gram per gram				
arithmetic mean (standard deviation)				
Week 8 (n=18)	0.0759 (± 0.17486)			
Week 16 (n=18)	0.1061 (± 0.21743)			
Week 28 (n=16)	0.0711 (± 0.16049)			
Week 40 (n=14)	0.0830 (± 0.16333)			
Week 52 (n=17)	0.0627 (± 0.16508)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Left Ventricular Ejection Fraction (LVEF) at Weeks 16 and 52

End point title	Change From Baseline in Left Ventricular Ejection Fraction (LVEF) at Weeks 16 and 52
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End point description:

LVEF is the central measure of left ventricular systolic function. LVEF is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume). This was measured by echocardiography at the clinical sites. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. 'n' denotes the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 16 and 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percent of LVEF				
arithmetic mean (standard deviation)				
Week 16 (n=14)	-1.1 (± 7.29)			
Week 52 (n=12)	0.8 (± 3.28)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Brief Pain Inventory (BPI) Short Form Pain Severity Total Score

End point title	Change From Baseline in Brief Pain Inventory (BPI) Short Form Pain Severity Total Score
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End point description:

The BPI short form is a numeric rating scale that assesses the severity of pain (severity scale), its impact on daily functioning (Pain Interference scale). BPI short form pain severity scale has been reported here. Pain severity scale has 4 questions that assess pain intensity (worst, least, average, right now) on 10-point rating scales (0=No pain to 10=Pain as bad as you can imagine). The pain severity score is calculated as the average of questions, with a total score ranging from 0 to 10 with higher scores indicating more pain. A negative change from baseline indicates better outcome. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. Subjects analyzed is the number of participants with pain at baseline. 'n' denotes the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 8, 16, 28, 40, and 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 8 (n=7)	-1.607 (± 2.8572)			
Week 16 (n=7)	-2.214 (± 2.4041)			
Week 28 (n=6)	-1.833 (± 2.6957)			
Week 40 (n=6)	-1.375 (± 2.8007)			
Week 52 (n=6)	-0.958 (± 3.3370)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in BPI Short Form Pain Interference Total Score

End point title	Change From Baseline in BPI Short Form Pain Interference Total Score
End point description:	
BPI short form is numeric rating scale that assesses severity of pain(severity scale), its impact on daily functioning(Pain Interference scale). BPI short form pain interference scale has been reported here. Pain interference scale has 7 questions that assess impact of pain on daily functions(general activity,mood,walking ability,normal work,relations with other people,sleep,enjoyment of life)on 10-point rating scales as(0=Does not interfere to 10=Completely interferes).Pain interference score=average of questions, with total score ranging from 0-10 with higher scores indicating more interference. Negative change from baseline indicates better outcome. mITT Set included all enrolled participants who had received at least 1 dose of investigational product & completed at least 1 post-baseline efficacy assessment of endpoints. Subjects analyzed is number of participants with pain at baseline. 'n' denotes number of participants with data available for analysis at the specified timepoint.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 8, 16, 28, 40, and 52	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 8 (n=7)	-2.286 (± 3.6636)			
Week 16 (n=7)	-3.571 (± 3.9812)			

Week 28 (n=6)	-4.738 ( $\pm$ 4.3221)			
Week 40 (n=6)	-3.810 ( $\pm$ 3.8222)			
Week 52 (n=6)	-3.643 ( $\pm$ 5.7020)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Hearing Loss as Assessed by Audiology Testing

End point title	Number of Participants With Hearing Loss as Assessed by Audiology Testing
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End point description:

Hearing loss was assessed in participants with the age <18 years old by audiology testing. Audiology testing included pure tone conduction and bone conduction for each ear using 4 different pure tone frequencies (500 hertz [Hz], 1000 Hz, 2000 Hz, and 4000 Hz). Any changes in threshold were to be categorized as conductive, sensorineural, or unknown. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. Subjects analyzed is the number of participants with age <18 years old.

End point type	Secondary
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End point timeframe:

Baseline up to Week 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Plasma Globotriaosylsphingosine (Lyso-Gb3) Level

End point title	Percent Change From Baseline in Plasma Globotriaosylsphingosine (Lyso-Gb3) Level
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End point description:

Plasma lyso-Gb3 determinations were performed at the central laboratory using a validated liquid chromatography-tandem mass spectrometry bioanalytical assay. mITT Set included all enrolled participants who had received at least 1 dose of investigational product and completed at least 1 post-baseline efficacy assessment of the endpoints. 'n' denotes the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 8, 16, 28, 40, and 52

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n=18)	-36.236 ( $\pm$ 24.7056)			
Week 16 (n=18)	-38.147 ( $\pm$ 24.7376)			
Week 28 (n=17)	-37.764 ( $\pm$ 25.8314)			
Week 40 (n=17)	-35.565 ( $\pm$ 27.7874)			
Week 52 (n=17)	-37.072 ( $\pm$ 27.5659)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under Serum Concentration-time Curve From Time Zero Extrapolated to Infinity (AUC<sub>0-inf</sub>) of REPLAGAL

End point title	Area Under Serum Concentration-time Curve From Time Zero Extrapolated to Infinity (AUC <sub>0-inf</sub> ) of REPLAGAL
End point description:	
Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe:	
Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: min*U/mL				
arithmetic mean (standard deviation)				
Week 0	233700 ( $\pm$ 49553)			
Week 28	309500 ( $\pm$ 157460)			

### Statistical analyses



No statistical analyses for this end point

### Secondary: Area Under Serum Concentration-time Curve From the Time of Dosing to the Last Measurable concentration (AUC<sub>0-last</sub>) of REPLAGAL

End point title	Area Under Serum Concentration-time Curve From the Time of Dosing to the Last Measurable concentration (AUC <sub>0-last</sub> ) of REPLAGAL
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End point description:

Intensive Pharmacokinetic (PK) Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
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End point timeframe:

Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: minutes*units per milliliter (min*U/mL)				
arithmetic mean (standard deviation)				
Week 0	229000 (± 48768)			
Week 28	297300 (± 139640)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Serum Clearance of Administered Dose (CL) of REPLAGAL

End point title	Serum Clearance of Administered Dose (CL) of REPLAGAL
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End point description:

Clearance is defined as a quantitative measure of the rate at which a drug substance is removed from the body. CL = dose/AUC. Intensive PK Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
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End point timeframe:

Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: milliliters per minute (mL/min)				
arithmetic mean (standard deviation)				
Week 0	187.4 (± 35.770)			
Week 28	195.5 (± 226.52)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Clearance of Administered Dose Normalized Based on Body Weight of REPLAGAL

End point title	Serum Clearance of Administered Dose Normalized Based on Body Weight of REPLAGAL
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End point description:

Clearance is defined as a quantitative measure of the rate at which a drug substance is removed from the body. CL normalized for body weight was reported.  $CL = (\text{dose}/AUC) / \text{body weight}$ . Clearance was expressed using the unit: milliliters/minute/kilogram (mL/min/kg). Intensive PK Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
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End point timeframe:

Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mL/min/kg				
arithmetic mean (standard deviation)				
Week 0	3.234 (± 0.78070)			
Week 28	3.183 (± 3.5632)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Serum Concentration (Cmax) of REPLAGAL

End point title	Maximum Observed Serum Concentration (Cmax) of REPLAGAL
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End point description:

Intensive PK Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
End point timeframe:	
Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: units per milliliter (U/mL)				
arithmetic mean (standard deviation)				
Week 0	4620.55 (± 1046.889)			
Week 28	4507.99 (± 1682.041)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Elimination Half-life (T1/2z) of REPLAGAL

End point title	Terminal Elimination Half-life (T1/2z) of REPLAGAL
End point description:	
T1/2 is defined as the natural log of 2 divided by the terminal rate constant (z). Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe:	
Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: minutes				
arithmetic mean (standard deviation)				
Week 0	45.36 (± 23.058)			
Week 28	66.34 (± 27.272)			

### Statistical analyses

No statistical analyses for this end point

**Secondary: Time to Reach Maximum Observed Serum Concentration (Tmax) of REPLAGAL**

End point title	Time to Reach Maximum Observed Serum Concentration (Tmax) of REPLAGAL
End point description: Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe: Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
median (full range (min-max))				
Week 0	40.000 (20.00 to 40.00)			
Week 28	40.000 (20.00 to 41.00)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Volume of Distribution at Steady State Normalized Based on Body Weight of REPLAGAL**

End point title	Volume of Distribution at Steady State Normalized Based on Body Weight of REPLAGAL
End point description: Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired serum concentration of a drug. Vss normalized for body weight was reported. $V(ss) = [(dose/AUC)*MRT]/ body\ weight$ , where MRT is mean residence time. Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe: Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: milliliters per kilogram (mL/kg)				
arithmetic mean (standard deviation)				
Week 0	135.9 (± 34.530)			

Week 28	202.1 (± 267.74)			
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of Distribution at Steady State (Vss) of REPLAGAL

End point title	Volume of Distribution at Steady State (Vss) of REPLAGAL
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End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired serum concentration of a drug.  $V(ss) = (dose/AUC) * MRT$ , where MRT is mean residence time. Intensive PK Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
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End point timeframe:

Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: milliliters (mL)				
arithmetic mean (standard deviation)				
Week 0	7834 (± 1625.9)			
Week 28	12310 (± 16988)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dose Normalized Maximum Observed Serum Concentration (Cmax/Dose) of REPLAGAL

End point title	Dose Normalized Maximum Observed Serum Concentration (Cmax/Dose) of REPLAGAL
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End point description:

Cmax/Dose was expressed using the unit: (units/milliliter)/(units/kilogram) [(U/mL)/(U/kg)]. Intensive PK Set included participants in the PK Set who provided intensive sampling.

End point type	Secondary
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End point timeframe:

Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: (U/mL)/(U/kg)				
arithmetic mean (standard deviation)				
Week 0	0.0001092 (± 0.000021579)			
Week 28	0.0001197 (± 0.000040471)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Dose Normalized Area Under the Serum Concentration-time Curve From Time Zero Extrapolated to Infinity (AUC<sub>0-inf</sub>/Dose) of REPLAGAL

End point title	Dose Normalized Area Under the Serum Concentration-time Curve From Time Zero Extrapolated to Infinity (AUC <sub>0-inf</sub> /Dose) of REPLAGAL
End point description:	
Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe:	
Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: (min*U/mL)/(U/kg)				
arithmetic mean (standard deviation)				
Week 0	0.005520 (± 0.0010993)			
Week 28	0.008489 (± 0.0051204)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Dose Normalized Area Under Serum Concentration-time Curve From Time Zero to the Last Sampling Time (AUC<sub>0-last</sub>/Dose) of REPLAGAL

End point title	Dose Normalized Area Under Serum Concentration-time Curve From Time Zero to the Last Sampling Time (AUC0-last/Dose) of REPLAGAL
End point description: AUC0-last/Dose was expressed using the unit: (minutes*units per milliliter)/(units per kilogram) [(min*U/mL)/(U/kg)]. Intensive PK Set included participants in the PK Set who provided intensive sampling.	
End point type	Secondary
End point timeframe: Pre-infusion (0 minutes), during infusion (20 minutes) and end of infusion (40 minutes), and post-infusion at 50, 60, 90, 120, 240, and 360 minutes at Weeks 0 and 28	

End point values	REPLAGAL			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: (min*U/mL)/(U/kg)				
arithmetic mean (standard deviation)				
Week 0	0.005411 (± 0.0010847)			
Week 28	0.008119 (± 0.0044732)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 14 days after EOT (up to Week 54)

Adverse event reporting additional description:

Safety Analysis Set included all participants in the ITT Set who received at least 1 dose of REPLAGAL.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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### Reporting groups

Reporting group title	REPLAGAL
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Reporting group description:

Participants received REPLAGAL 0.2 mg/kg body weight, IV infusion, EOW from Day 1 (Week 0) up to Week 52.

Serious adverse events	REPLAGAL		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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



<b>Non-serious adverse events</b>	REPLAGAL		
Total subjects affected by non-serious adverse events subjects affected / exposed	18 / 20 (90.00%)		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 4		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)  Oedema peripheral subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2  2 / 20 (10.00%) 2  5 / 20 (25.00%) 6		
Eye disorders Corneal opacity subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 6		
Renal and urinary disorders Albuminuria subjects affected / exposed occurrences (all)  Haematuria subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2  2 / 20 (10.00%) 2		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3		
Bone metabolism disorder subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	13 / 20 (65.00%) 13		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 14		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2022	The following changes were made as per Amendment 1: 1) Added cardiac LVMI and LVEF assessed by echocardiography test as one of the efficacy assessments. 2) Updated inclusion and exclusion criteria. 3) Added and clarified that the mITT analysis set will be used for efficacy analyses, instead of the ITT set. 4) Updated time points for height and weight measurement. 5) Removed the requirement that participants need to fast for at least 8 hours prior to the blood draw for plasma lyso-Gb3 assessment.
23 May 2023	The following changes were made as per Amendment 2: 1) Added EudraCT number. 2) Updated inclusion criteria. 3) Modified the ITT definition to include all participants enrolled in the study. 4) Added description of BMI calculation. 5) Added 'physical examination finding' to the list of clinical assessments.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported