ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 05/19/2014

Safety and Efficacy Study of Several Replagal Dosing Regimens on Cardiac Function in Adults With Fabry Disease

This study has been completed.

Sponsor:	Shire Human Genetic Therapies, Inc.
Collaborators:	
Information provided by (Responsible Party):	Shire Human Genetic Therapies, Inc.
ClinicalTrials.gov Identifier:	NCT00864851

Purpose

The purpose of this study is to compare the safety and effectiveness of various doses of Replagal in patients with cardiomyopathy due to Fabry disease.

Condition	Intervention	Phase
Fabry Disease	Biological/Vaccine: Replagal	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Multi-Center, Open-Label, Randomized Study Evaluating the Safety and Efficacy of Three Dosing Regimens of Replagal Enzyme Replacement Therapy in Adult Patients With Fabry Disease

Further study details as provided by Shire Human Genetic Therapies, Inc.:

Primary Outcome Measure:

- Change From Baseline to Month 12 in Left Ventricular Mass Indexed to Height (LVMI) [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]

  Left ventricular mass (LVM) was measured through echocardiography.

Secondary Outcome Measures:

- Change From Baseline to Month 12 in Maximal Oxygen Consumption (VO2 Max) at Peak Exercise [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
  Exercise tolerance as measured by VO2 max at peak exercise using the standard exponential exercise protocol (STEEP).
- Change From Baseline to Month 12 in Distance Walked in 6-Minute Walk Test (6MWT) [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
  Exercise tolerance using the 6MWT was measured as the total distance walked in 6 minutes.
- Change From Baseline to Month 12 in the Minnesota Living With Heart Failure Questionnaire (MLHF-Q) Summary Score [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
  Quality of life (QoL) was evaluated using the MLHF-Q, version 2. The questionnaire is designed to assess the degree to which heart failure symptoms affect a patient's daily life. The summary score ranges from 0 to 105, with a score of 105 representing the highest adverse impact on a patient's QoL.
- Change From Baseline to Month 12 in New York Heart Association (NYHA) Functional Class [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
  The NYHA functional classification system relates symptoms to everyday activities and the patient's quality of life. NYHA Classification - The Stages of Heart Failure: Class I (Mild): No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). Class II (Mild): Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III (Moderate): Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV (Severe): Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
- Change From Baseline to Month 12 in Plasma Globotriaosylceramide (GB3) [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
- Change From Baseline to Month 12 in Estimated Glomerular Filtration Rate (eGFR) [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
  Renal function was assessed by an evaluation of change from baseline to Month 12 in eGFR as calculated using the Modification of Diet for Renal Disease (MDRD) equation.
- Change From Baseline to Month 12 in Urinary Albumin/Creatinine (A/Cr) Ratio [Time Frame: Baseline, Month 12 (Week 53)] [Designated as safety issue: No]
- Safety Evaluation [Time Frame: 56 Weeks] [Designated as safety issue: Yes]
  Adverse events were collected throughout the study, from the time of informed consent to approximately 30 days post-final infusion.

Enrollment: 44
Study Start Date: December 2008
Primary Completion Date: June 2012
Study Completion Date: July 2012

Arms	Assigned Interventions
Active Comparator: Replagal 0.2 mg/kg, IV, every other week Patients randomized to receive Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.	Biological/Vaccine: Replagal Intravenous (IV) infusion for 12 months Other Names: algasidase alfa
Active Comparator: Replagal 0.2 mg/kg, IV, weekly	Biological/Vaccine: Replagal Intravenous (IV) infusion for 12 months Other Names: algasidase alfa

Arms	Assigned Interventions
Patients randomized to receive Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.	
Active Comparator: Replagal 0.4 mg/kg, IV, weekly Patients randomized to receive Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.	Biological/Vaccine: Replagal Intravenous (IV) infusion for 12 months Other Names: algasidase alfa

Detailed Description:

Fabry disease is an inherited, metabolic disease caused by mutations in the GALA gene. Patients with Fabry disease accumulate a complex glycosphingolipid named globotriaosylceramide (Gb3) in various tissues and organs. All organs are affected in Fabry disease but the majority of the morbidity and mortality are caused by cardiac, renal and neurological dysfunction. Accumulation of Gb3 in the heart causes hypertrophic cardiomyopathy, valvular abnormalities, arrhythmias and infarctions. Replagal has been shown to reduce Gb3 from key tissues and organs, and stabilize renal function in patients with Fabry disease. Evidence suggests that Replagal reduces left ventricular mass (LVM) and improves midwall fractional shortening (MFS) of the heart. Left ventricular hypertrophy is a major cause of morbidity and mortality in patients with Fabry disease.

This is a study of the safety and effectiveness of 3 dosing regimens of Replagal in adult patients with left ventricular hypertrophy due to Fabry disease.

The primary objective of the study is to compare the effects of 2 dosing regimens of Replagal (0.2 mg/kg IV every other week and 0.2 mg/kg IV weekly) on the reduction of left ventricular mass as measured by echocardiography.

The secondary objectives of this study are to compare the effects of 2 dosing regimens of Replagal (0.2 mg/kg IV every other week and 0.2 mg/kg IV weekly) on each of the following: exercise tolerance; improvement in disease-specific quality of life in heart failure patients; improvement of heart failure symptoms; magnitude of reduction in Gb3; rate of decline in renal function and improvement in the severity of proteinuria/albuminuria; and safety.

An alternative treatment regimen of 0.4 mg/kg Replagal IV weekly will also be explored but without formal comparison to the 0.2 mg/kg regimens. The investigation of the safety and efficacy of the 0.4 mg/kg IV weekly regimen is a secondary objective of this study.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- >18 years-old;
- Male:Fabry disease confirmed by deficiency of alfa galactosidase A activity OR Female:Fabry disease confirmed by a mutation of the alfa galactosidase A gene;
- ERT-naïve;
- LVM/h > 50g/m2.7 for males and >47 g/m2.7 for females;

- Negative pregnancy test at enrollment and contraception use required throughout study for female patients;
- Signed informed consent;

Exclusion Criteria:

- Class IV heart failure;
- Clinically significant hypertension;
- Hemodynamically significant valvular stenosis or regurgitation;
- Morbid obesity;
- Known autosomal dominant sarcoplasmic contractile protein gene mutation;
- Treatment with any investigational drug or device within the 30 days;
- Unable to comply with the protocol as determined by the Investigator;
- Positive for hepatitis B, hepatitis C or HIV

Contacts and Locations

Locations

United States, Arizona
AKDHC Tucson Access Center
Tucson, Arizona, United States, 85719
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Investigators

Principal Investigator:	Gregory M. Pastores, MD	New York University School of Medicine
Principal Investigator:	Ademola K. Abiose, MD	University of Iowa Hospitals and Clinics
Principal Investigator:	Bojan Vujkovac, MD	General Hospital Slovenj Gradec
Principal Investigator:	Myrl D. Holida, PA-C	University of Iowa Hospitals and Clinics
Principal Investigator:	Kathleen Nicholls, MB.BS, MD	The Royal Melbourne Hospital
Principal Investigator:	Jacek Musial, MD, PhD	Szpital Uniwersytecki w Krakowie
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Principal Investigator:	Derlis Emilio Gonzalez Rodriguez, MD	Gobernador Irala Y Coronel Lopez - Barrio Sajonia
Principal Investigator:	Lidia Chojnowska, MD, PhD	Instytut Kardiologii
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Principal Investigator:	Y. Howard Lien, MD, PhD	AKDHC Tucson Access Center
Principal Investigator:	Ozlem Goker-Alpan, MD	O & O Alpan, LLC
Principal Investigator:	Reena Sharma, MD	Salford Royal NHS Foundation Trust

More Information

Responsible Party:	Shire Human Genetic Therapies, Inc.
Study ID Numbers:	TKT028
Health Authority:	Poland: Ministry of Health Czech Republic: State Institute for Drug Control Australia: Department of Health and Ageing Therapeutic Goods Administration Paraguay: Ministerio de Salud Pública y Bienestar Social United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Results

Participant Flow

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients randomized to receive Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients randomized to receive Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients randomized to receive Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Overall Study

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Started	20	19	5
Completed	17	18	5
Not Completed	3	1	0
Withdrawal by Subject	0	1	0
Physician Decision	1	0	0
Death	1	0	0
Patient uncooperative	1	0	0

Baseline Characteristics

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.

	Description
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Baseline Measures

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly	Total
Number of Participants	20	19	5	44
Age, Continuous [units: years] Mean (Standard Deviation)	50.3 (7.23)	51.8 (11.42)	49.4 (9.75)	50.8 (9.34)
Age, Customized [units: participants]				
18 to <45 years	5	6	1	12
>=45 years	15	13	4	32
Gender, Male/Female [units: participants]				
Female	6	9	3	18
Male	14	10	2	26
Ethnicity (NIH/OMB) [units: participants]				
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	19	18	5	42
Unknown or Not Reported	0	0	0	0
Race (NIH/OMB) [units: participants]				
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	20	19	5	44
More than one race	0	0	0	0

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly	Total
Unknown or Not Reported	0	0	0	0
Baseline Left Ventricular Mass Indexed to Height (LVMI) [units: g/m^2.7] Mean (Standard Deviation)	76.1 (22.8)	82.6 (28.3)	99.3 (46.2)	81.5 (28.5)
Baseline Maximal Oxygen Consumption (VO2 max) at Peak Exercise [1] [units: mL/min/kg] Mean (Standard Deviation)	20.2 (6.20)	22.6 (6.89)	24.0 (11.69)	21.6 (7.05)
Baseline Distance Walked in 6-Minute Walk Test (6MWT) [2] [units: m] Mean (Standard Deviation)	459.6 (103.0)	514.3 (87.3)	530.7 (90.2)	492.8 (97.0)
Baseline Minnesota Living with Heart Failure Questionnaire (MLHF-Q) Summary Score [3] [units: scores on a scale] Mean (Standard Deviation)	37.0 (23.8)	21.1 (21.0)	19.6 (26.5)	28.1 (23.8)
Baseline New York Heart Association (NYHA) Functional Class [4] [units: participants]				
Class I	6	10	2	18
Class II	11	9	2	22
Class III	3	0	1	4
Class IV	0	0	0	0
Baseline Plasma Globotriaosylceramide (GB3) [units: nmol/ml] Mean (Standard Deviation)	6.067 (3.388)	5.652 (5.212)	5.292 (1.865)	5.800 (4.104)
Baseline Estimated Glomerular Filtration Rate (eGFR) [units: mL/min/1.73 m^2] Mean (Standard Deviation)	82.0 (34.1)	78.1 (33.8)	72.1 (31.2)	79.2 (33.1)

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly	Total
Baseline Urinary Albumin/ Creatinine (A/Cr) Ratio [units: mg/g] Mean (Standard Deviation)	313.4 (614.07)	293.4 (521.23)	298.2 (175.85)	303.0 (532.27)

[1] 0.2 mg/kg Every Other Week: n=19 0.2 mg/kg Weekly: n=16 0.4 mg/kg Weekly: n=4 Total: n=39

[2] 0.2 mg/kg Every Other Week: n=18 0.2 mg/kg Weekly: n=19 0.4 mg/kg Weekly: n=5 Total: n=42

[3] Quality of life (QoL) was evaluated using the MLHF-Q, version 2. The questionnaire is designed to assess the degree to which heart failure symptoms affect a patient's daily life. The summary score ranges from 0 to 105, with a score of 105 representing the highest adverse impact on a patient's QoL.

[4] Class I: Cardiac disease without limitation of physical activity. Ordinary physical activity does not cause undue symptoms.

Class II: Cardiac disease with slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes symptoms.

Class III: Cardiac disease with marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms.

Class IV: Cardiac disease and unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest.

Note: Symptoms include fatigue, palpitation or dyspnea

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Left Ventricular Mass Indexed to Height (LVMI)
Measure Description	Left ventricular mass (LVM) was measured through echocardiography.
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	15	18	5
Change From Baseline to Month 12 in Left Ventricular Mass Indexed to Height (LVMI) [units: g/m^2.7] Mean (Standard Deviation)	3.2 (12.5)	0.5 (15.8)	-10.3 (11.8)

2. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Maximal Oxygen Consumption (VO2 Max) at Peak Exercise
Measure Description	Exercise tolerance as measured by VO2 max at peak exercise using the standard exponential exercise protocol (STEEP).
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	14	15	4
Change From Baseline to Month 12 in Maximal Oxygen Consumption (VO2 Max) at Peak Exercise [units: mL/min/kg] Mean (Standard Deviation)	-2.0 (3.24)	-0.3 (4.76)	2.2 (5.85)

3. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Distance Walked in 6-Minute Walk Test (6MWT)
Measure Description	Exercise tolerance using the 6MWT was measured as the total distance walked in 6 minutes.
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly
Number of Participants Analyzed	15	18	5
Change From Baseline to Month 12 in Distance Walked in 6-Minute Walk Test (6MWT) [units: m] Mean (Standard Deviation)	-10.4 (87.7)	37.9 (70.5)	24.7 (45.7)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in the Minnesota Living With Heart Failure Questionnaire (MLHF-Q) Summary Score
Measure Description	Quality of life (QoL) was evaluated using the MLHF-Q, version 2. The questionnaire is designed to assess the degree to which heart failure symptoms affect a patient's daily life. The summary score ranges from 0 to 105, with a score of 105 representing the highest adverse impact on a patient's QoL.
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	17	17	5
Change From Baseline to Month 12 in the Minnesota Living With Heart Failure Questionnaire (MLHF-Q) Summary Score [units: scores on a scale] Mean (Standard Deviation)	-3.1 (16.7)	2.1 (11.5)	-8.6 (12.3)

5. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in New York Heart Association (NYHA) Functional Class
Measure Description	The NYHA functional classification system relates symptoms to everyday activities and the patient's quality of life. NYHA Classification - The Stages of Heart Failure: Class I (Mild): No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). Class II (Mild): Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III (Moderate): Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV (Severe): Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	17	18	5
Change From Baseline to Month 12 in New York Heart Association (NYHA) Functional Class [units: participants]			
Improved ≥ 1 NYHA Functional Class	2	2	2
Maintained NYHA Functional Class	15	16	3

6. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Plasma Globotriaosylceramide (GB3)
Measure Description	
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	17	18	5
Change From Baseline to Month 12 in Plasma Globotriaosylceramide (GB3) [units: nmol/ml] Mean (Standard Deviation)	-1.046 (2.256)	-2.132 (4.363)	-2.076 (1.248)

7. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Estimated Glomerular Filtration Rate (eGFR)
Measure Description	Renal function was assessed by an evaluation of change from baseline to Month 12 in eGFR as calculated using the Modification of Diet for Renal Disease (MDRD) equation.
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/ kg, IV, Weekly	Replagal 0.4 mg/ kg, IV, Weekly
Number of Participants Analyzed	17	18	5
Change From Baseline to Month 12 in Estimated Glomerular Filtration Rate (eGFR) [units: mL/min/1.73m^2] Mean (Standard Deviation)	-1.2 (12.2)	-3.3 (12.7)	-1.7 (9.9)

8. Secondary Outcome Measure:

Measure Title	Change From Baseline to Month 12 in Urinary Albumin/Creatinine (A/Cr) Ratio
Measure Description	
Time Frame	Baseline, Month 12 (Week 53)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly
Number of Participants Analyzed	17	17	5
Change From Baseline to Month 12 in Urinary Albumin/Creatinine (A/Cr) Ratio [units: mg/g] Mean (Standard Deviation)	83.9 (624.82)	-54.1 (322.51)	-54.2 (294.86)

9. Secondary Outcome Measure:

Measure Title	Safety Evaluation
Measure Description	Adverse events were collected throughout the study, from the time of informed consent to approximately 30 days post-final infusion.
Time Frame	56 Weeks
Safety Issue?	Yes

Analysis Population Description

Intent to Treat (ITT) Population: All randomized patients who received at least 1 complete or partial dose of Replagal. Analyses were performed on the ITT population because it was identical to the safety population.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.
Overall	Total of all reporting groups.

Measured Values

	Replagal 0.2 mg/kg, IV, Every Other Week	Replagal 0.2 mg/kg, IV, Weekly	Replagal 0.4 mg/kg, IV, Weekly	Overall
Number of Participants Analyzed	20	19	5	44
Safety Evaluation [units: participants]				
No adverse event (AE)	1	2	0	3
At least one AE	19	17	5	41
At least one study drug-related AE	6	6	2	14
At least one infusion-related AE	5	4	2	11
At least one severe or life-threatening AE	8	4	0	12
At least one serious AE (SAE)	8	5	2	15
At least one study drug-related SAE	1	0	0	1
Discontinued due to an AE	0	0	0	0
Deaths	1	0	0	1

Reported Adverse Events

Time Frame	56 Weeks
Additional Description	Adverse events were collected throughout the study, from the time of informed consent to approximately 30 days post-final infusion.

Reporting Groups

	Description
Replagal 0.2 mg/kg, IV, Every Other Week	Patients who received Replagal 0.2 mg/kg via intravenous infusion every other week for 52 weeks.
Replagal 0.2 mg/kg, IV, Weekly	Patients who received Replagal 0.2 mg/kg via intravenous infusion every week for 52 weeks.
Replagal 0.4 mg/kg, IV, Weekly	Patients who received Replagal 0.4 mg/kg via intravenous infusion every week for 52 weeks.
Overall	Total of all reporting groups.

Serious Adverse Events

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	8/20 (40%)		5/19 (26.32%)		2/5 (40%)		15/44 (34.09%)	
Cardiac disorders								
Angina pectoris [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Atrial fibrillation [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Atrioventricular block complete [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Cardiac arrest [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Coronary artery stenosis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Palpitations [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Sinus bradycardia [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Supraventricular tachycardia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Gastrointestinal disorders								

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Nausea [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Vomiting [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
General disorders								
Inflammation [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Infections and infestations								
Meningitis aseptic [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Injury, poisoning and procedural complications								
Traumatic haematoma [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Musculoskeletal and connective tissue disorders								
Gouty arthritis [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Musculoskeletal chest pain [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Nervous system disorders								
Facial paresis [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Spastic paralysis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Psychiatric disorders								
Depression [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Renal and urinary disorders								

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Renal failure chronic [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Vascular disorders								
Hypotension [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (12.0)

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	19/20 (95%)		17/19 (89.47%)		5/5 (100%)		41/44 (93.18%)	
Blood and lymphatic system disorders								
Anaemia [A] †	0/20 (0%)	0	2/19 (10.53%)	2	0/5 (0%)	0	2/44 (4.55%)	2
Neutropenia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Cardiac disorders								
Angina pectoris [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Atrial fibrillation [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Atrioventricular block complete [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Atrioventricular block first degree [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Bradycardia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Bundle branch block right [A] †	0/20 (0%)	0	2/19 (10.53%)	2	1/5 (20%)	1	3/44 (6.82%)	3
Cardiac arrest [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Cardiac failure [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Coronary artery stenosis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Dilatation atrial [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Extrasystoles [A] †	0/20 (0%)	0	1/19 (5.26%)	2	1/5 (20%)	2	2/44 (4.55%)	4
Hypertrophic cardiomyopathy [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Left ventricular hypertrophy [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Palpitations [A] †	2/20 (10%)	2	1/19 (5.26%)	1	1/5 (20%)	1	4/44 (9.09%)	4
Sinus bradycardia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	1/5 (20%)	1	2/44 (4.55%)	2
Sinus tachycardia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Supraventricular extrasystoles [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Supraventricular tachycardia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Tachycardia [A] †	0/20 (0%)	0	2/19 (10.53%)	2	1/5 (20%)	1	3/44 (6.82%)	3
Ventricular tachycardia [A] †	1/20 (5%)	4	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	5
Congenital, familial and genetic disorders								
Myocardial bridging [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Ear and labyrinth disorders								
Ear pain [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Hypoacusis [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Tinnitus [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Vertigo [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Eye disorders								
Blindness [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Eye pain [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Photophobia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Vision blurred [A] †	1/20 (5%)	1	0/19 (0%)	0	1/5 (20%)	1	2/44 (4.55%)	2
Gastrointestinal disorders								

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Abdominal pain [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Constipation [A] †	0/20 (0%)	0	1/19 (5.26%)	2	0/5 (0%)	0	1/44 (2.27%)	2
Dental caries [A] †	3/20 (15%)	3	1/19 (5.26%)	1	0/5 (0%)	0	4/44 (9.09%)	4
Diarrhoea [A] †	2/20 (10%)	2	2/19 (10.53%)	3	0/5 (0%)	0	4/44 (9.09%)	5
Dyspepsia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Dysphagia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Flatulence [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Gastrointestinal disorder [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Haemorrhoids [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Hiatus hernia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Hypoaesthesia oral [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Inguinal hernia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Nausea [A] †	2/20 (10%)	4	3/19 (15.79%)	9	0/5 (0%)	0	5/44 (11.36%)	13
Pyrexia [A] †	3/20 (15%)	4	2/19 (10.53%)	2	1/5 (20%)	1	6/44 (13.64%)	7

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Tooth impacted [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Toothache [A] †	2/20 (10%)	3	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	3
Vomiting [A] †	1/20 (5%)	1	2/19 (10.53%)	2	0/5 (0%)	0	3/44 (6.82%)	3
General disorders								
Catheter site haematoma [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Catheter site swelling [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Chest discomfort [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Chest pain [A] †	2/20 (10%)	2	2/19 (10.53%)	2	1/5 (20%)	1	5/44 (11.36%)	5
Chills [A] †	2/20 (10%)	2	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	2
Fatigue [A] †	5/20 (25%)	13	7/19 (36.84%)	13	1/5 (20%)	13	13/44 (29.55%)	39
Feeling cold [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Feeling hot [A] †	1/20 (5%)	3	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	3
Implant site paraesthesia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Implant site reaction [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Inflammation [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Influenza like illness [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Infusion site haematoma [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Malaise [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Non-cardiac chest pain [A] †	1/20 (5%)	1	2/19 (10.53%)	3	0/5 (0%)	0	3/44 (6.82%)	4
Oedema peripheral [A] †	1/20 (5%)	1	4/19 (21.05%)	5	1/5 (20%)	3	6/44 (13.64%)	9
Pain [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Thirst [A] †	1/20 (5%)	8	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	8
Hepatobiliary disorders								
Biliary dilataton [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Liver injury [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Infections and infestations								
Bronchitis [A] †	2/20 (10%)	2	3/19 (15.79%)	3	1/5 (20%)	1	6/44 (13.64%)	6
Ear infection [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Gastroenteritis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Influenza [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

	Replagal 0.2 mg/kg, IV, Every Other Week		Replagal 0.2 mg/kg, IV, Weekly		Replagal 0.4 mg/kg, IV, Weekly		Overall	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Localised infection [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Lower respiratory tract infection [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Meningitis aseptic [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Nasopharyngitis [A] †	2/20 (10%)	2	6/19 (31.58%)	11	0/5 (0%)	0	8/44 (18.18%)	13
Oral herpes [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Pharyngitis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Post procedural infection [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Respiratory tract infection [A] †	0/20 (0%)	0	4/19 (21.05%)	4	0/5 (0%)	0	4/44 (9.09%)	4
Rhinitis [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Sinusitis [A] †	1/20 (5%)	1	0/19 (0%)	0	1/5 (20%)	1	2/44 (4.55%)	2
Skin infection [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Upper respiratory tract infection [A] †	1/20 (5%)	1	3/19 (15.79%)	3	0/5 (0%)	0	4/44 (9.09%)	4
Urinary tract infection [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Urinary tract infection bacterial [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Vaginal infection [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Viral infection [A] †	1/20 (5%)	1	2/19 (10.53%)	2	0/5 (0%)	0	3/44 (6.82%)	3
Injury, poisoning and procedural complications								
Contusion [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Fall [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Mouth injury [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Muscle injury [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Procedural pain [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Rib fracture [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Skin laceration [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Tendon rupture [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Tooth injury [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Traumatic haematoma [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Investigations								
Alanine aminotransferase increased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Aspartate aminotransferase increased [A] †	2/20 (10%)	2	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	2
Blood alkaline phosphatase increased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Blood creatinine increased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Blood creatinine phosphokinase increased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Blood glucose increased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Blood iron decreased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Blood lactate dehydrogenase increased [A] †	2/20 (10%)	2	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	2
Blood pressure decreased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Blood urea increased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Body temperature decreased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Body temperature increased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
C-reactive protein increased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Cardiac murmur [A] †	2/20 (10%)	2	2/19 (10.53%)	2	0/5 (0%)	0	4/44 (9.09%)	4
Electrocardiogram QRS complex prolonged [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Electrocardiogram QT prolonged [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Gamma-glutamyltransferase increased [A] †	2/20 (10%)	2	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	2
Haematocrit decreased [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Haemoglobin increased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Heart rate decreased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Heart rate irregular [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Mean haemoglobin decreased [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
QRS axis abnormal [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Red blood cell count decreased [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Serum ferritin decreased [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Urinary lipids present [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Metabolism and nutrition disorders								
Gout [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Hyperuricaemia [A] †	0/20 (0%)	0	1/19 (5.26%)	2	0/5 (0%)	0	1/44 (2.27%)	2
Hypoalbuminaemia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hyponatraemia [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Hypoproteinaemia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Impaired fasting glucose [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Type 2 diabetes mellitus [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Musculoskeletal and connective tissue disorders								
Arthralgia [A] †	0/20 (0%)	0	5/19 (26.32%)	5	0/5 (0%)	0	5/44 (11.36%)	5
Back pain [A] †	1/20 (5%)	1	2/19 (10.53%)	2	1/5 (20%)	1	4/44 (9.09%)	4
Gouty arthritis [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Intervertebral disc degeneration [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Joint stiffness [A] †	1/20 (5%)	3	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	3
Joint swelling [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Muscle spasms [A] †	2/20 (10%)	2	3/19 (15.79%)	4	0/5 (0%)	0	5/44 (11.36%)	6
Muscle tightness [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Muscular weakness [A] †	1/20 (5%)	2	0/19 (0%)	0	1/5 (20%)	2	2/44 (4.55%)	4
Musculoskeletal chest pain [A] †	2/20 (10%)	2	3/19 (15.79%)	4	1/5 (20%)	1	6/44 (13.64%)	7

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Musculoskeletal pain [A] †	1/20 (5%)	1	1/19 (5.26%)	1	1/5 (20%)	1	3/44 (6.82%)	3
Musculoskeletal stiffness [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Myalgia [A] †	2/20 (10%)	2	1/19 (5.26%)	10	0/5 (0%)	0	3/44 (6.82%)	12
Osteoarthritis [A] †	0/20 (0%)	0	1/19 (5.26%)	2	0/5 (0%)	0	1/44 (2.27%)	2
Osteopenia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Pain in extremity [A] †	3/20 (15%)	3	4/19 (21.05%)	6	0/5 (0%)	0	7/44 (15.91%)	9
Spinal osteoarthritis [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Basal cell carcinoma [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Nervous system disorders								
Amnesia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Aphasia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Aphonia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Balance disorder [A] †	1/20 (5%)	3	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	3
Disturbance in attention [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Dizziness [A] †	2/20 (10%)	6	3/19 (15.79%)	4	0/5 (0%)	0	5/44 (11.36%)	10
Dizziness postural [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Dysgeusia [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Facial paresis [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Headache [A] †	2/20 (10%)	3	4/19 (21.05%)	6	1/5 (20%)	2	7/44 (15.91%)	11
Hyperreflexia [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Hypoaethesia [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Lethargy [A] †	1/20 (5%)	5	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	5
Loss of consciousness [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Paraesthesia [A] †	1/20 (5%)	1	2/19 (10.53%)	2	2/5 (40%)	3	5/44 (11.36%)	6
Poor quality sleep [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Sensory loss [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Spastic paralysis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Syncope [A] †	1/20 (5%)	1	2/19 (10.53%)	2	0/5 (0%)	0	3/44 (6.82%)	3

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Tremor [A] †	1/20 (5%)	2	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	3
Psychiatric disorders								
Alcohol abuse [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Anxiety [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Depression [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Disorientation [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Renal and urinary disorders								
Dysuria [A] †	0/20 (0%)	0	3/19 (15.79%)	3	0/5 (0%)	0	3/44 (6.82%)	3
Haematuria [A] †	1/20 (5%)	2	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	3
Proteinuria [A] †	2/20 (10%)	2	0/19 (0%)	0	0/5 (0%)	0	2/44 (4.55%)	2
Renal cyst [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Renal failure chronic [A] †	1/20 (5%)	1	1/19 (5.26%)	2	0/5 (0%)	0	2/44 (4.55%)	3
Renal impairment [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Urinary tract obstruction [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Reproductive system and breast disorders								
Benign prostatic hyperplasia [A] †	2/20 (10%)	2	1/19 (5.26%)	1	0/5 (0%)	0	3/44 (6.82%)	3

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Breast pain [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Cervical polyp [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Menopausal symptoms [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Prostatitis [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Uterine polyp [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Respiratory, thoracic and mediastinal disorders								
Asthma [A] †	0/20 (0%)	0	2/19 (10.53%)	2	0/5 (0%)	0	2/44 (4.55%)	2
Cough [A] †	4/20 (20%)	5	3/19 (15.79%)	5	1/5 (20%)	1	8/44 (18.18%)	11
Dyspnoea [A] †	1/20 (5%)	1	2/19 (10.53%)	2	1/5 (20%)	1	4/44 (9.09%)	4
Dyspnoea exertional [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Epistaxis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Hyperventilation [A] †	1/20 (5%)	1	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	2
Laryngeal oedema [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Oropharyngeal pain [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2
Rhinorrhoea [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Skin and subcutaneous tissue disorders								
Dermatitis [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	2	1/44 (2.27%)	2
Eczema [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Exfoliative rash [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Haematoma [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Hyperhidrosis [A] †	1/20 (5%)	2	1/19 (5.26%)	1	0/5 (0%)	0	2/44 (4.55%)	3
Rosacea [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Seborrhoea [A] †	0/20 (0%)	0	0/19 (0%)	0	1/5 (20%)	1	1/44 (2.27%)	1
Skin tightness [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Swelling face [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Urticaria [A] †	1/20 (5%)	1	2/19 (10.53%)	2	0/5 (0%)	0	3/44 (6.82%)	3
Vascular disorders								
Aortic stenosis [A] †	1/20 (5%)	1	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	1
Hot flush [A] †	0/20 (0%)	0	1/19 (5.26%)	2	0/5 (0%)	0	1/44 (2.27%)	2
Hypertension [A] †	0/20 (0%)	0	1/19 (5.26%)	1	1/5 (20%)	1	2/44 (4.55%)	2

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	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hypotension [A] †	1/20 (5%)	1	1/19 (5.26%)	1	1/5 (20%)	2	3/44 (6.82%)	4
Pallor [A] †	0/20 (0%)	0	1/19 (5.26%)	1	0/5 (0%)	0	1/44 (2.27%)	1
Peripheral coldness [A] †	1/20 (5%)	2	0/19 (0%)	0	0/5 (0%)	0	1/44 (2.27%)	2

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (12.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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