Clinical trial results:
An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients With Chronic Kidney Disease

Summary

EudraCT number	2018-003253-24
Trial protocol	ES FR BE DE CZ
Global end of trial date	23 August 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	402-C-1803

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03749447
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Reata, a wholly owned subsidiary of Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Study Medical Director, Reata, a wholly owned subsidiary of Biogen, clinicaltrials@biogen.com
Scientific contact	Study Medical Director, Reata, a wholly owned subsidiary of Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorised representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorised representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2019
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	United States: 215
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Puerto Rico: 4
Worldwide total number of subjects	270
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	9
Adults (18-64 years)	239
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in the United States, Australia, Japan, Spain, Puerto Rico and France from 08 March 2019 to 23 August 2023.

Pre-assignment

Screening details:

A total of 270 eligible participants who participated in the previous qualifying studies i.e., 402-C-1603 (NCT03019185) and 402-C-1808 (NCT03918447) of bardoxolone methyl were enrolled in this study. Data was summarized as per the treatment received in the previous qualifying studies.

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

Are arms mutually exclusive?	Yes
Arm title	Prior Placebo to Bardoxolone Methyl

Arm description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility urine albumin to creatinine ratio (UACR) >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

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

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Prior Bardoxolone Methyl to Bardoxolone Methyl

Arm description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

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Arm type	Experimental

Investigational medicinal product name	Bardoxolone methyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	Prior Placebo to Bardoxolone Methyl	Prior Bardoxolone Methyl to Bardoxolone Methyl
Started	143	127
Completed	0	0
Not completed	143	127
Adverse event, serious fatal	1	1
Protocol-Specified Withdrawal Criteria Met	1	3
Physician decision	4	3
Consent withdrawn by subject	12	6
Adverse event, non-fatal	11	3
Reason Not Specified	-	3
Non-Compliance With Study Drug	-	1
Study Terminated by Sponsor	112	105
Lost to follow-up	2	2

Baseline characteristics

Reporting groups

Reporting group title	Prior Placebo to Bardoxolone Methyl

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility urine albumin to creatinine ratio (UACR) >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

Reporting group title	Prior Bardoxolone Methyl to Bardoxolone Methyl

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

Reporting group values	Prior Placebo to Bardoxolone Methyl	Prior Bardoxolone Methyl to Bardoxolone Methyl	Total
Number of subjects	143	127	270
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.8	48.3	
standard deviation	± 13.26	± 13.82	-
Gender categorical Units: Participants			
Male	55	49	104
Female	88	78	166
Race Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	17	16	33
Black or African American	9	9	18
Native Hawaiian or Other Pacific Islander	0	1	1
White	112	96	208

Other	3	5	8
Ethnicity Units: Subjects			
Hispanic/Latino	15	12	27
Non-Hispanic/Latino	128	115	243

End points

End points reporting groups

Reporting group title	Prior Placebo to Bardoxolone Methyl

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, once daily (QD) at a starting dose of 5 milligrams (mg), followed by dose-escalation to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility urine albumin to creatinine ratio (UACR) >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

Reporting group title	Prior Bardoxolone Methyl to Bardoxolone Methyl

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

Primary: Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An SAE is any untoward medical occurrence that at any dose results in death, places the participant at immediate risk of death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or is a medically important event. AEs and SAEs that occurred within 30 days after the last dose were considered treatment-emergent. The study follow-up assessment was collected within 14 to 35 days after the last dose. The safety population included all participants who had received at least 1 dose of bardoxolone methyl in the 402-C-1803 study.

End point type	Primary

End point timeframe:

From the first dose of the study drug (baseline) up to the end of the study follow-up (up to 4.2 years)

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 to be analyzed.

End point values	Prior Placebo to Bardoxolone Methyl	Prior Bardoxolone Methyl to Bardoxolone Methyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	127		
Units: participants				
AEs	128	105		
SAEs	12	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of the study drug (baseline) up to the end of the study follow-up (up to 4.2 years)

Adverse event reporting additional description:

The safety population included all participants who had received at least 1 dose of bardoxolone methyl in the 402-C-1803 study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Prior Placebo to Bardoxolone Methyl

Reporting group description:

Participants who received placebo in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose- escalation to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

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Reporting group title	Prior Bardoxolone Methyl to Bardoxolone Methyl

Reporting group description:

Participants who received bardoxolone methyl in the previous qualifying studies, 402-C-1603 (NCT03019185) or 402-C-1808 (NCT03918447), and received bardoxolone methyl in this study.

Adult participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalated to 10 mg at Week 2 (Day 14 ± 3), and to 20 mg at Week 4 (Day 28 ± 3). Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 (Day 42 ± 3) until the end of the study.

Participants under 18 years of age received bardoxolone methyl capsules at a starting dose of 5 mg every other day during the first week and QD during the second week of the study, followed by dose-escalation to 10 mg at Week 2 and to 20 mg at Week 4. Based on the eligibility UACR >300 mg/g, the dose was increased to 30 mg starting from Week 6 until the end of the study.

Serious adverse events	Prior Placebo to Bardoxolone Methyl	Prior Bardoxolone Methyl to Bardoxolone Methyl	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 143 (8.39%)	20 / 127 (15.75%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			

subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			

subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy kidney			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	1 / 143 (0.70%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar stroke			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid hemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
End stage renal disease			
subjects affected / exposed	0 / 143 (0.00%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 143 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			

subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gangrene			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	0 / 143 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 143 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prior Placebo to Bardoxolone Methyl	Prior Bardoxolone Methyl to Bardoxolone Methyl	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 143 (88.81%)	104 / 127 (81.89%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 143 (16.78%)	7 / 127 (5.51%)	
occurrences (all)	26	7	
Alanine aminotransferase increased			
subjects affected / exposed	37 / 143 (25.87%)	8 / 127 (6.30%)	
occurrences (all)	38	9	
Blood creatinine increased			
subjects affected / exposed	3 / 143 (2.10%)	7 / 127 (5.51%)	
occurrences (all)	3	7	
Brain natriuretic peptide increased			
subjects affected / exposed	11 / 143 (7.69%)	5 / 127 (3.94%)	
occurrences (all)	18	12	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 143 (7.69%)	0 / 127 (0.00%)	
occurrences (all)	14	0	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	13 / 143 (9.09%)	11 / 127 (8.66%)	
occurrences (all)	18	13	
Vascular disorders			

Hypertension			
subjects affected / exposed	8 / 143 (5.59%)	9 / 127 (7.09%)	
occurrences (all)	8	9	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 143 (11.19%)	9 / 127 (7.09%)	
occurrences (all)	29	10	
Dizziness			
subjects affected / exposed	5 / 143 (3.50%)	7 / 127 (5.51%)	
occurrences (all)	6	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 143 (6.29%)	6 / 127 (4.72%)	
occurrences (all)	9	6	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	10 / 143 (6.99%)	11 / 127 (8.66%)	
occurrences (all)	11	15	
Pyrexia			
subjects affected / exposed	7 / 143 (4.90%)	7 / 127 (5.51%)	
occurrences (all)	9	8	
Fatigue			
subjects affected / exposed	14 / 143 (9.79%)	8 / 127 (6.30%)	
occurrences (all)	15	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 143 (11.19%)	8 / 127 (6.30%)	
occurrences (all)	20	8	
Abdominal pain			
subjects affected / exposed	9 / 143 (6.29%)	5 / 127 (3.94%)	
occurrences (all)	11	6	
Nausea			
subjects affected / exposed	12 / 143 (8.39%)	13 / 127 (10.24%)	
occurrences (all)	12	16	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 143 (2.80%)	11 / 127 (8.66%)	
occurrences (all)	4	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 143 (8.39%)	12 / 127 (9.45%)	
occurrences (all)	15	13	
Muscle spasms			
subjects affected / exposed	57 / 143 (39.86%)	45 / 127 (35.43%)	
occurrences (all)	96	75	
Pain in extremity			
subjects affected / exposed	4 / 143 (2.80%)	7 / 127 (5.51%)	
occurrences (all)	6	10	
Infections and infestations			
Sinusitis			
subjects affected / exposed	5 / 143 (3.50%)	8 / 127 (6.30%)	
occurrences (all)	5	9	
Corona virus infection			
subjects affected / exposed	22 / 143 (15.38%)	27 / 127 (21.26%)	
occurrences (all)	23	27	
Nasopharyngitis			
subjects affected / exposed	5 / 143 (3.50%)	8 / 127 (6.30%)	
occurrences (all)	8	11	
Upper respiratory tract infection			
subjects affected / exposed	12 / 143 (8.39%)	12 / 127 (9.45%)	
occurrences (all)	13	15	
Urinary tract infection			
subjects affected / exposed	8 / 143 (5.59%)	12 / 127 (9.45%)	
occurrences (all)	9	22	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	10 / 143 (6.99%)	11 / 127 (8.66%)	
occurrences (all)	10	14	
Hypomagnesaemia			
subjects affected / exposed	10 / 143 (6.99%)	4 / 127 (3.15%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2019	1. Defined qualifying clinical study, as CARDINAL (2016-004395-22). 2. Clarified intent to measure B-type natriuretic peptide (BNP) and N-Terminal prohormone B-type natriuretic peptide (NT-Pro BNP) levels.
30 June 2020	1. Added FALCON (2018-004651-20) as another qualifying study to enroll in EAGLE. 2. Updated for clarification regarding recording of AEs between prior qualifying study and Day 1 of EAGLE. 3. Updated text to include results of physical examinations as a safety parameter. 4. Updated section to manage transaminases (ALT/AST) elevations. 5. Updated information for resuming drug therapy after temporary discontinuation due to elevated liver enzymes. 6. Updated inclusion and exclusion criteria. 7. COVID-19 Mitigation Appendix was added to describe protocol modifications due to the pandemic. 8. Added section for participants reaching end stage kidney disease.
08 November 2022	1. Lipid panel and Tanner Staging added to study visits. 2. Defined the qualifying study lab assessments which may be used for eligibility due to the variability of the-off treatment follow-up schedule for studies 402-C-1603 (2016-004395-22)/402-C-1808 (2018-004651-20) protocol v5 and older vs. 402-C-1808 (2018-004651-20) protocol v6 and newer. 3. Differentiated between dose-titration period for adolescent participants enrolling from study 402-C-1603 (2016-004395-22) versus adolescent and adult participants enrolling from study 402-C-1808 (2018-004651-20). 4. Aligned with specific criteria and communication requirements added to study 402-C-1808 (2018-004651-20) protocol v6 related to the weight loss of adolescent and adult patients in the study to monitor for safety. 5. Simplified the instructions provided to investigators in the event of an increase in urinary albumin to creatinine ratios and to clarify that proteinuria is not required to be associated with other concurrent signs to consult with the medical monitor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of trial due to discontinuation of all bardoxolone chronic kidney disease programs.

Notes: