Clinical trial results:
A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Summary

EudraCT number	2018-004651-20
Trial protocol	GB DE FR CZ BE ES IT HU DK PL
Global end of trial date	08 August 2023

Results information

Result version number	v1 (current)
This version publication date	12 May 2024
First version publication date	12 May 2024

Trial information

Trial identification

Sponsor protocol code	402-C-1808

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03918447
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	08 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 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 assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108 and to assess safety and tolerability of bardoxolone methyl.

Protection of trial subjects:

Written informed consent was obtained from each participant or participant's legally authorised representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Participants or the participant'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	29 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 429
Country: Number of subjects enrolled	Japan: 64
Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Czechia: 7
Worldwide total number of subjects	667
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	631
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in the United States, Australia, Belgium, Czech Republic, France, Germany, Italy, Japan, Spain, and United Kingdom beginning on 29 May 2019. The study completion date was 8 August 2023.

Pre-assignment

Screening details:

A total of 667 participants were enrolled and randomized 1:1 to receive either bardoxolone methyl or placebo during the treatment period (up to Week 100) and continued to be assessed in the off-treatment period for 12 weeks (up to Week 112).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bardoxolone Methyl

Arm description:

During the treatment period, the 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, and to 20 mg at Week 4. If the eligibility urine albumin to creatinine ratio (UACR) was >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 until Week 100. Participants continued to be assessed during the off-treatment period up to Week 112.

Arm type	Experimental
Investigational medicinal product name	Bardoxolone methyl
Investigational medicinal product code	
Other name	RTA 402
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	Placebo

Arm description:

During the treatment period, participants received bardoxolone methyl matching-placebo capsules, orally, QD up to Week 100, with sham titration to maintain the blinding. Participants did not receive a bardoxolone methyl matching placebo capsule during the off-treatment period between Weeks 100 and 112.

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

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	Bardoxolone Methyl	Placebo
Started	334	333
Completed	106	112
Not completed	228	221
Adverse event, serious fatal	1	-
Consent withdrawn by subject	19	17
Study Terminated By Sponsor	195	197
Lost to follow-up	13	6
Reason not Specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bardoxolone Methyl
Reporting group description:	
During the treatment period, the 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, and to 20 mg at Week 4. If the eligibility urine albumin to creatinine ratio (UACR) was >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 until Week 100. Participants continued to be assessed during the off-treatment period up to Week 112.	
Reporting group title	Placebo
Reporting group description:	
During the treatment period, participants received bardoxolone methyl matching-placebo capsules, orally, QD up to Week 100, with sham titration to maintain the blinding. Participants did not receive a bardoxolone methyl matching placebo capsule during the off-treatment period between Weeks 100 and 112.	

Reporting group values	Bardoxolone Methyl	Placebo	Total
Number of subjects	334	333	667
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.6	48.3	
standard deviation	± 9.46	± 9.58	-
Gender categorical Units: Participants			
Male	146	160	306
Female	188	173	361
Race Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	34	45	79
Black or African American	23	18	41
Native Hawaiian or Other Pacific Islander	1	0	1
White	269	261	530
Other	6	8	14
Ethnicity Units: Subjects			
Hispanic/Latino	29	35	64
Non-Hispanic/Latino	305	298	603

End points

End points reporting groups

Reporting group title	Bardoxolone Methyl

Reporting group description:

During the treatment period, the 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, and to 20 mg at Week 4. If the eligibility urine albumin to creatinine ratio (UACR) was >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 until Week 100. Participants continued to be assessed during the off-treatment period up to Week 112.

Reporting group title	Placebo

Reporting group description:

During the treatment period, participants received bardoxolone methyl matching-placebo capsules, orally, QD up to Week 100, with sham titration to maintain the blinding. Participants did not receive a bardoxolone methyl matching placebo capsule during the off-treatment period between Weeks 100 and 112.

Subject analysis set title	Bardoxolone methyl
Subject analysis set type	Safety analysis

Subject analysis set description:

During the treatment period, the participants received bardoxolone methyl capsules, QD at a starting dose of 5 mg, followed by dose-escalation to 10 mg at Week 2, and to 20 mg at Week 4. If the eligibility UACR was >300 mg/g, the dose was increased to 30 mg starting from Week 6 until Week 100. Participants continued to be assessed during the off-treatment period up to Week 112. Safety population included all enrolled participants who had received at least 1 dose of study drug. Participants who received 1 dose of bardoxolone methyl were classified in the bardoxolone methyl group.

Primary: Off-treatment Period: Change From Baseline in eGFR at Week 108

End point title	Off-treatment Period: Change From Baseline in eGFR at Week 108

End point description:

Estimated Glomerular filtration rate (eGFR) is a measure of kidney function assessed through blood/serum. eGFR was measured in millilitres per minute per 1.73 meters square (mL/min/1.73 m^2). Higher eGFRs represent better/improved kidney function. Lower eGFRs represent poorer/decreased kidney function. A negative change from baseline in eGFR indicates worsened kidney function. Intent-to-Treat (ITT) included all enrolled participants categorised by their randomised treatment group (whether or not they received study drug). 'Subjects analyzed' indicates the number of participants with data available for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 108

End point values	Bardoxolone Methyl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	79		
Units: mL/min/1.73 m^2				
least squares mean (standard error)	-4.59 (± 0.817)	-5.56 (± 0.769)		

Statistical analyses

Statistical analysis title	Bardoxolone Methyl vs. Placebo
Statistical analysis description:	
ANCOVA model with baseline eGFR as a covariate, and treatment group as fixed effects.	
Comparison groups	Bardoxolone Methyl v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3886
Method	ANCOVA
Parameter estimate	Least Square Means Difference
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	3.19
Variability estimate	Standard error of the mean
Dispersion value	1.122

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

End point title	Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious TEAEs[1][2]

End point description:

AE:any untoward medical occurrence in a participant regardless of its causal relationship to study drug.AE can be any unfavorable & unintended sign,symptom/disease temporally associated with use of study drug,whether considered to be study-drug related/not.This includes clinically significant abnormal laboratory test result,any newly occurring events/previous conditions that have increased in severity/frequency since administration of study drug. SAE:any AE that at any dose results in death,life-threatening,requires hospitalization/prolongation of existing hospitalisation,substantial disruption of ability to conduct normal life functions,congenital anomaly or is an important medical event.AEs & SAEs that occurred within 30 days after last dose were considered TE. Safety population:Participants who received 1 dose of bardoxolone methyl were classified in bardoxolone methyl group; who received at least 1 dose of placebo & no dose of bardoxolone methyl were classified in placebo group.

End point type	Primary

End point timeframe:

From first dose of the study drug up to end of follow-up (up to Week 112)

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: As prespecified in the protocol, only descriptive statistics were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data has been reported in the safety analysis set- "Bardoxolone Methyl" arm for the subjects who received bardoxolone methyl.

End point values	Placebo	Bardoxolone methyl		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	331	335		
Units: participants				
TEAEs	296	314		
Serious TEAEs	26	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Period: Change From Baseline in eGFR at Week 100

End point title	Treatment Period: Change From Baseline in eGFR at Week 100

End point description:

eGFR is a measure of kidney function assessed through blood/serum. eGFR was measured in mL/min/1.73 m^2. Higher eGFRs represent better/improved kidney function. Lower eGFRs represent poorer/decreased kidney function. A negative change from baseline in eGFR indicates worsened kidney function. ITT included all enrolled participants categorised by their randomised treatment group (whether or not they received study drug). 'Subjects analyzed' indicates the number of participants with an eGFR assessment at Week 100.

End point type	Secondary

End point timeframe:

Baseline, Week 100

End point values	Bardoxolone Methyl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	167		
Units: mL/min/1.73 m^2				
least squares mean (standard error)	1.31 (± 0.550)	-6.64 (± 0.549)		

Statistical analyses

Statistical analysis title	Bardoxolone Methyl vs. Placebo

Statistical analysis description:

Mixed model repeated measure (MMRM) model used baseline eGFR as a covariate, and the following fixed factors: treatment group, time (Week 1 to 100, excluding Week 52), and the interaction between treatment and time. Within-participant errors are modeled using an unstructured covariance matrix.

Comparison groups	Bardoxolone Methyl v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models repeated measures analysis
Parameter estimate	Least square means difference
Point estimate	7.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.41
upper limit	9.47
Variability estimate	Standard error of the mean
Dispersion value	0.777

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of the study drug up to end of follow-up (up to Week 112)

Adverse event reporting additional description:

Safety population included all enrolled participants who had received at least 1 dose of study drug. Participants who received 1 dose of bardoxolone methyl were classified in the bardoxolone methyl group. Participants who received at least 1 dose of placebo and no dose of bardoxolone methyl were classified in the placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

During the treatment period, participants received bardoxolone methyl matching-placebo capsules, orally, QD up to Week 100, with sham titration to maintain the blinding. Participants did not receive a bardoxolone methyl matching placebo capsule during the off-treatment period between Weeks 100 and 112.

Reporting group title	Bardoxolone Methyl

Reporting group description:

During the treatment period, the 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, and to 20 mg at Week 4. If the eligibility urine albumin to creatinine ratio (UACR) was >300 milligrams per gram (mg/g), the dose was increased to 30 mg starting from Week 6 until Week 100. Participants continued to be assessed during the off-treatment period up to Week 112.

Serious adverse events	Placebo	Bardoxolone Methyl	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 331 (7.85%)	38 / 335 (11.34%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypotension			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Incarcerated hernia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst rupture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (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			
Pelvic haematoma			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
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			
Nasal septum deviation			

subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 331 (0.30%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 331 (0.00%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
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			
Post procedural haemorrhage			
subjects affected / exposed	1 / 331 (0.30%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Anastomotic ulcer			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic injury			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon injury			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic renal injury			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (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			

Transient global amnesia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 331 (0.30%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenic cyst			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Macular degeneration			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 331 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			

subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (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			
Calculus urinary			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	0 / 331 (0.00%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			

subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
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 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (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			
Cellulitis streptococcal			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyelonephritis			
subjects affected / exposed	2 / 331 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	2 / 331 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 331 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 331 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	1 / 331 (0.30%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (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	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 331 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	1 / 331 (0.30%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Bardoxolone Methyl	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	255 / 331 (77.04%)	299 / 335 (89.25%)	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 331 (0.30%)	46 / 335 (13.73%)	
occurrences (all)	1	56	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 331 (1.21%)	47 / 335 (14.03%)	
occurrences (all)	6	60	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 331 (0.91%)	76 / 335 (22.69%)	
occurrences (all)	3	92	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	23 / 331 (6.95%)	32 / 335 (9.55%)	
occurrences (all)	26	47	
Brain natriuretic peptide increased			
subjects affected / exposed	16 / 331 (4.83%)	31 / 335 (9.25%)	
occurrences (all)	18	41	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 331 (0.91%)	24 / 335 (7.16%)	
occurrences (all)	3	24	
Weight decreased			
subjects affected / exposed	4 / 331 (1.21%)	28 / 335 (8.36%)	
occurrences (all)	4	28	
Vascular disorders			
Hypertension			

subjects affected / exposed	34 / 331 (10.27%)	25 / 335 (7.46%)	
occurrences (all)	37	27	
Nervous system disorders			
Headache			
subjects affected / exposed	41 / 331 (12.39%)	55 / 335 (16.42%)	
occurrences (all)	70	74	
Dizziness			
subjects affected / exposed	13 / 331 (3.93%)	25 / 335 (7.46%)	
occurrences (all)	15	35	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 331 (5.74%)	22 / 335 (6.57%)	
occurrences (all)	23	25	
Oedema peripheral			
subjects affected / exposed	35 / 331 (10.57%)	27 / 335 (8.06%)	
occurrences (all)	38	39	
Fatigue			
subjects affected / exposed	29 / 331 (8.76%)	47 / 335 (14.03%)	
occurrences (all)	30	60	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	40 / 331 (12.08%)	49 / 335 (14.63%)	
occurrences (all)	52	79	
Vomiting			
subjects affected / exposed	9 / 331 (2.72%)	23 / 335 (6.87%)	
occurrences (all)	13	32	
Constipation			
subjects affected / exposed	16 / 331 (4.83%)	38 / 335 (11.34%)	
occurrences (all)	17	44	
Diarrhoea			
subjects affected / exposed	31 / 331 (9.37%)	35 / 335 (10.45%)	
occurrences (all)	40	45	
Abdominal pain			
subjects affected / exposed	21 / 331 (6.34%)	32 / 335 (9.55%)	
occurrences (all)	22	42	
Abdominal distension			

subjects affected / exposed	9 / 331 (2.72%)	22 / 335 (6.57%)	
occurrences (all)	11	31	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 331 (5.74%)	26 / 335 (7.76%)	
occurrences (all)	21	29	
Oropharyngeal pain			
subjects affected / exposed	9 / 331 (2.72%)	18 / 335 (5.37%)	
occurrences (all)	9	21	
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	18 / 331 (5.44%)	12 / 335 (3.58%)	
occurrences (all)	25	13	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	53 / 331 (16.01%)	164 / 335 (48.96%)	
occurrences (all)	73	334	
Flank pain			
subjects affected / exposed	21 / 331 (6.34%)	43 / 335 (12.84%)	
occurrences (all)	26	48	
Back pain			
subjects affected / exposed	36 / 331 (10.88%)	39 / 335 (11.64%)	
occurrences (all)	43	53	
Arthralgia			
subjects affected / exposed	15 / 331 (4.53%)	35 / 335 (10.45%)	
occurrences (all)	19	45	
Pain in extremity			
subjects affected / exposed	14 / 331 (4.23%)	23 / 335 (6.87%)	
occurrences (all)	16	36	
Myalgia			
subjects affected / exposed	12 / 331 (3.63%)	17 / 335 (5.07%)	
occurrences (all)	13	23	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 331 (3.93%)	26 / 335 (7.76%)	
occurrences (all)	15	32	

Nasopharyngitis			
subjects affected / exposed	31 / 331 (9.37%)	39 / 335 (11.64%)	
occurrences (all)	47	48	
Corona virus infection			
subjects affected / exposed	89 / 331 (26.89%)	76 / 335 (22.69%)	
occurrences (all)	95	87	
Urinary tract infection			
subjects affected / exposed	21 / 331 (6.34%)	24 / 335 (7.16%)	
occurrences (all)	28	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 331 (3.63%)	26 / 335 (7.76%)	
occurrences (all)	12	28	
Hypomagnesaemia			
subjects affected / exposed	5 / 331 (1.51%)	19 / 335 (5.67%)	
occurrences (all)	6	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2019	1. Limited total enrollment of participants with higher baseline eGFR. 2. Updated inclusion criteria to add requirement for evidence of ADPKD progression and inclusion requirements for participants currently receiving tolvaptan. 3. Updated participant exclusion criteria. 4. Updated protocol for participant unblinding. 5. Added eGFR ≤ 15 to the list of reasons for unscheduled visits. 6. Expanded AE reporting window to extend throughout study follow-up, irrespective of date of last dose. 7. Updated SAE reporting guidelines for specified events due to CKD disease progression.
16 July 2019	1. Updated the inclusion and exclusion criteria: participants receiving concomitant use of tolvaptan are excluded from the study. 2. Added tolvaptan (participants on tolvaptan who have already enrolled in FALCON under Version 2 of the protocol may remain in the trial) to the Excluded Medications section. 3. Primary analysis of efficacy and Sample size sections were updated to add Analysis of Covariance (ANCOVA) analysis for off-treatment efficacy endpoints (i.e., Week 52 and Week 104). 4. Added on-treatment efficacy endpoints of change from baseline in eGFR at Week 48 and Week 100 in the primary analysis of efficacy section.
25 June 2020	1. Updated data for the Cross-study comparison of increases in eGFR, inulin clearance, and creatinine clearance with bardoxolone methyl treatment. 2. Added 'off-treatment' change from baseline and specified the year of treatment in primary objective and endpoint. 3. Added 'off-treatment' change from baseline and specified the year of treatment in key secondary objective and endpoint. 4. Modifications made due to the COVID-19 pandemic.
24 February 2021	1. Increased sample size. 2. Updated efficacy endpoints analysis visit week from Week 52 to Week 104. 3. Updated inclusion criteria for screening eGFR. 4. Addition of exclusion criterion for COVID-19 diagnosis. 5. Shortened screening window to ensure stable clinical status from Screen A to randomisation. 6. Clarification of follow-up visit window and AE/SAE reporting.
03 February 2022	1. Updated schema for study of bardoxolone methyl in participants with autosomal dominant polycystic kidney disease (ADPKD) to reflect the removal of the off-treatment period between Weeks 48 to 52, the extended off-treatment period that follows Week 100, from a 4-week duration to a 12-week duration. 2. Changed primary objective and endpoint to evaluate efficacy at end of Year 2 (instead of at end of Year 1). 3. Removal of the key secondary objective and endpoint, and adjustment of the remaining secondary objective and endpoint. 4. Overall study design and assessment schedule updated to omit the off-treatment period between Week 48 and Week 52 based on updated endpoints. Increased sample size to reflect updated primary endpoint analysis.
25 May 2022	1. Updated inclusion criteria, to reflect that participants taking sodium-glucose co-transporter 2 (SGLT2) inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit. 2. Clarification added to specify both adults and adolescents will follow the same dose escalation plan. 3. Updated section to clarify that 5mg restarting dose must be used when interruption criteria are met. 4. Clarification on the duration of AE reporting. Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period.

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.

Due to discontinuation of all bardoxolone chronic kidney disease programs, study was terminated early.

Notes: