Clinical trial results:
A Phase 2/3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

Summary

EudraCT number	2016-004395-22
Trial protocol	DE GB ES FR
Global end of trial date	30 October 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	402-C-1603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03019185
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 131763

Notes:

Sponsors

Sponsor organisation name	Reata Pharmaceuticals, Inc
Sponsor organisation address	5320 Legacy Drive, Plano, United States, 75024
Public contact	Clinical Operations, Reata Pharmaceuticals, Inc, 001 4694424838,
Scientific contact	Clinical Operations, Reata Pharmaceuticals, Inc, 001 4694424838,

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	30 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2020
Global end of trial reached?	Yes
Global end of trial date	30 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 2:
- To assess the change from baseline in estimated glomerular filtration rate (eGFR) in bardoxolone methyl-treated patients after 12 weeks of treatment.
- To assess the safety of bardoxolone methyl after 12 weeks of treatment.
Phase 3:
- To assess the change from baseline in estimated glomerular filtration rate (eGFR) in bardoxolone methyl-treated patients relative to placebo after 48 weeks of treatment.
- To assess the safety of bardoxolone methyl relative to placebo after 48 weeks of treatment.

Protection of trial subjects:

The independent DMC, which operated under written charter, reviewed unblinded safety data throughout study conduct and made recommendations as appropriate. The DMC began data reviews approximately 3 months after the first patient was enrolled and continued quarterly reviews through the last dose of the last patient enrolled. The DMC evaluated available safety, tolerability, and efficacy data from the Study 1603 Phase 2 prior to opening enrollment in Study 1603 Phase 3. Additionally, the DMC reviewed the progress of Study 1603 Phase 3 and the accumulating unblinded data while the trial was ongoing. The DMC made written recommendations to Sponsor representatives following each meeting. The DMC provided advice to the Sponsor as to whether the trial should continue as is, be modified to protect patient safety, or be terminated. Intrapatient dose-modification decisions were made by investigators, not by the DMC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2017
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	Spain: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	United States: 135
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Puerto Rico: 6
Worldwide total number of subjects	187
EEA total number of subjects	20

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)	25
Adults (18-64 years)	159
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

CARDINAL Phase 2 and Phase 3 were conducted under the same protocol. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3.

Pre-assignment

Screening details:

Patients with a diagnosis of Alport syndrome by genetic testing (documented mutation in a gene associated with Alport syndrome) were screened per the Inclusion/Exclusion criteria defined in the protocol at approved clinical research sites.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 2 Bardoxolone Methyl

Arm description:

Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 2 Study

Arm type	Experimental
Investigational medicinal product name	Bardoxolone methyl capsules
Investigational medicinal product code	RTA-402
Other name	THYL, CDDO-Me, CDDO-Methyl Ester, NSC 713BARDOXOLONE ME200, Chemical Name: Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 2 Study

Arm title	Phase 3 Placebo

Arm description:

Participants who received placebo (with sham titration) in the Cardinal Phase 3 study

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

Dosage and administration details:

Placebo capsules administered orally once daily

Arm title	Phase 3 Bardoxolone Methyl

Arm description:

Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants

with UACR greater than 300 mg/g) daily in the Cardinal Phase 3 Study

Arm type	Active comparator
Investigational medicinal product name	Bardoxolone methyl capsules
Investigational medicinal product code	RTA-402
Other name	BARDOXOLONE METHYL, CDDO-Me, CDDO-Methyl Ester, NSC 713200, Chemical Name: Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 3 Study

Number of subjects in period 1	Phase 2 Bardoxolone Methyl	Phase 3 Placebo	Phase 3 Bardoxolone Methyl
Started	30	80	77
Completed	24	79	75
Not completed	6	1	2
Consent withdrawn by subject	1	-	-
ESKD Resulting in Kidney Transplant	1	-	-
Withdrawal by Subject	-	1	-
Lost to follow-up	3	-	2
Inability to continue due to increased serum creat	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase 2 Bardoxolone Methyl
Reporting group description:	
Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 2 Study	
Reporting group title	Phase 3 Placebo
Reporting group description:	
Participants who received placebo (with sham titration) in the Cardinal Phase 3 study	
Reporting group title	Phase 3 Bardoxolone Methyl
Reporting group description:	
Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 3 Study	

Reporting group values	Phase 2 Bardoxolone Methyl	Phase 3 Placebo	Phase 3 Bardoxolone Methyl
Number of subjects	30	80	77
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	43.63	39.6	38.8
standard deviation	± 12.557	± 16.03	± 14.55
Gender categorical Units: Subjects			
Female	18	48	43
Male	12	32	34
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	1	12	14
Native Hawaiian or Pacific Islander	0	0	1
Black or African American	3	2	3
White	26	63	55
Other	0	2	4
Ethnicity Units: Subjects			

Hispanic or Latino	3	10	9
Not Hispanic or Latino	27	70	68

Baseline Estimated Glomerular Filtration Rate (EGFR)			
Units: mL/min/1.73 m2			
arithmetic mean	54.17	62.63	62.74
standard deviation	± 24.075	± 18.234	± 17.719
Baseline Urine Albumin to Creatinine Ration (UACR)			
Units: mg/g			
geometric mean	147.83	134.45	148.09
full range (min-max)	2.4 to 1600.0	1.2 to 3031.0	2.1 to 3495.0

Reporting group values	Total		
Number of subjects	187		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	109		
Male	78		
Race			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	27		
Native Hawaiian or Pacific Islander	1		
Black or African American	8		
White	144		
Other	6		
Ethnicity			
Units: Subjects			
Hispanic or Latino	22		
Not Hispanic or Latino	165		
Baseline Estimated Glomerular Filtration Rate (EGFR)			
Units: mL/min/1.73 m2			
arithmetic mean			

standard deviation	-		
Baseline Urine Albumin to Creatinine Ration (UACR) Units: mg/g geometric mean full range (min-max)	 -	 	

Subject analysis sets	
Subject analysis set title	Phase 2 Comparator
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Phase 2 portion of this study was open-label. Patients in the Phase 2 cohort received bardoxolone methyl throughout the study. A formal test of mean change from baseline in eGFR ≠ 0 was conducted at Week 12, 48, and 100.

In order to report a statistical analysis related to a specific endpoint it is required to define at least two comparison groups. This analysis set has been created to provide a comparator for the outcome of the Phase 2 portion of the study.

Reporting group values	Phase 2 Comparator		
Number of subjects	30		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 46.63 ± 12.557	 	
Gender categorical Units: Subjects			
Female Male	18 12		
Race Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Pacific Islander Black or African American White Other	0 1 0 3 26 0		
Ethnicity Units: Subjects			
Hispanic or Latino	3		

Not Hispanic or Latino	27		

Baseline Estimated Glomerular Filtration Rate (EGFR) Units: mL/min/1.73 m2 arithmetic mean standard deviation	 54.17 ± 24.075		
Baseline Urine Albumin to Creatinine Ration (UACR) Units: mg/g geometric mean full range (min-max)	 147.83 2.4 to 1600.0		

End points

End points reporting groups

Reporting group title	Phase 2 Bardoxolone Methyl

Reporting group description:

Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 2 Study

Reporting group title	Phase 3 Placebo

Reporting group description:

Participants who received placebo (with sham titration) in the Cardinal Phase 3 study

Reporting group title	Phase 3 Bardoxolone Methyl

Reporting group description:

Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 3 Study

Subject analysis set title	Phase 2 Comparator
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Phase 2 portion of this study was open-label. Patients in the Phase 2 cohort received bardoxolone methyl throughout the study. A formal test of mean change from baseline in eGFR ≠ 0 was conducted at Week 12, 48, and 100.

In order to report a statistical analysis related to a specific endpoint it is required to define at least two comparison groups. This analysis set has been created to provide a comparator for the outcome of the Phase 2 portion of the study.

Primary: Change from baseline in estimated glomerular filtration rate (eGFR) after 12 weeks of treatment (Phase 2)

End point title	Change from baseline in estimated glomerular filtration rate (eGFR) after 12 weeks of treatment (Phase 2)[1]

End point description:

End point type	Primary

End point timeframe:

12 weeks after participant receives the first dose in the Phase 2 study

Notes:

[1] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 2 Bardoxolone Methyl	Phase 2 Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[2]	30		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at week 12	13.37 (± 1.4111)	0 (± 0)		

Notes:

[2] - Intent-to-treat population (all enrolled patients)

Statistical analyses

Statistical analysis title	Mean change from baseline eGFR at Week 12

Statistical analysis description:

A formal test of mean change from baseline in eGFR not equal to 0 was conducted at week 12

Comparison groups	Phase 2 Bardoxolone Methyl v Phase 2 Comparator
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean change from baseline
Point estimate	13.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.48
upper limit	16.27
Variability estimate	Standard error of the mean
Dispersion value	1.4111

Notes:

[3] - Available data from analysis visits Week 1 to Week 12 are included. Missing Data were not imputed

Primary: Change from baseline in eGFR after 48 weeks of treatment (Phase 3)

End point title	Change from baseline in eGFR after 48 weeks of treatment (Phase 3)[4]

End point description:

End point type	Primary

End point timeframe:

48 weeks after participant receives the first dose in the Phase 3 study

Notes:

[4] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 2 Bardoxolone Methyl	Phase 2 Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	30		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at week 48	7.4 (± 1.9451)	0 (± 0)		

Statistical analyses

Statistical analysis title	Mean change from baseline in eGFR after 48 weeks
Comparison groups	Phase 2 Bardoxolone Methyl v Phase 2 Comparator

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Net)
Point estimate	9.49
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	5.38
upper limit	13.6
Variability estimate	Standard error of the mean
Dispersion value	1.813

Notes:

[5] - Available data from analysis visits Week 1 to Week 48 were included. Missing data were not imputed.

Primary: Change from baseline in eGFR after 100 weeks of treatment (Phase 3)

End point title	Change from baseline in eGFR after 100 weeks of treatment (Phase 3)[6]

End point description:

End point type	Primary

End point timeframe:

100 weeks after participant receives the first dose in the Phase 3 study

Notes:

[6] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 2 Bardoxolone Methyl	Phase 2 Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	30		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at Week 100	4.28 (± 1.7484)	0 (± 0)		

Statistical analyses

Statistical analysis title	Mean change from baseline in eGFR after 100 weeks
Comparison groups	Phase 2 Bardoxolone Methyl v Phase 2 Comparator

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (Net)
Point estimate	7.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.41
upper limit	11.89
Variability estimate	Standard error of the mean
Dispersion value	2.144

Notes:

[7] - Available data from analysis visits Week 1 to Week 100 (excluding Week 52) were included. Missing data were not imputed.

Secondary: Change from baseline in eGFR after 48 weeks of treatment (Phase 2)

End point title	Change from baseline in eGFR after 48 weeks of treatment (Phase 2)[8]

End point description:

End point type	Secondary

End point timeframe:

48 weeks after participant receives the first dose in the Phase 2 study

Notes:

[8] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 2 Bardoxolone Methyl	Phase 2 Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[9]	30		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at Week 48	7.4 (± 1.9451)	0 (± 0)		

Notes:

[9] - Intent-to-treat population (all enrolled patients)

Statistical analyses

Statistical analysis title	Mean change from baseline in eGFR 48 weeks - Ph2

Statistical analysis description:

A formal test of mean change from baseline in eGFR ≠ 0 was conducted at Week 48.

Comparison groups	Phase 2 Bardoxolone Methyl v Phase 2 Comparator

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean change from baseline
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	11.39
Variability estimate	Standard error of the mean
Dispersion value	1.9451

Notes:

[10] - Available data from analysis visits Week 1 to Week 48 were included. Missing data were not imputed.

Secondary: Change from baseline in eGFR after 100 weeks of treatment (Phase 2)

End point title	Change from baseline in eGFR after 100 weeks of treatment (Phase 2)[11]

End point description:

End point type	Secondary

End point timeframe:

100 weeks after participant receives the first dose in the Phase 2 study

Notes:

[11] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 2 Bardoxolone Methyl	Phase 2 Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[12]	30		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at Week 100	4.28 (± 1.7484)	0 (± 0)		

Notes:

[12] - Intent-to-treat population (all enrolled patients)

Statistical analyses

Statistical analysis title	Mean change from baseline in eGFR 100 weeks - Ph2
Comparison groups	Phase 2 Bardoxolone Methyl v Phase 2 Comparator

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.015 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean change from baseline
Point estimate	4.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	7.72
Variability estimate	Standard error of the mean
Dispersion value	1.7484

Notes:

[13] - A formal test of mean change from baseline in eGFR ≠ 0 was conducted at Week 100.

[14] - Available data from analysis visits Week 1 to Week 100 (excluding Week 52) were included. Missing data were not imputed.

Secondary: Change from baseline at Week 52 following a 4-week drug treatment withdrawal period (Phase 3)

End point title	Change from baseline at Week 52 following a 4-week drug treatment withdrawal period (Phase 3)[15]

End point description:

End point type	Secondary

End point timeframe:

52 weeks after participant receives the first dose in the Phase 3 study (or 4 weeks after last dose for patients who discontinued early in the first year)

Notes:

[15] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 3 Placebo	Phase 3 Bardoxolone Methyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at Week 52	-6.08 (± 1.243)	-0.99 (± 1.253)		

Statistical analyses

Statistical analysis title	Mean change from baseline 52 weeks - Ph3
Comparison groups	Phase 3 Bardoxolone Methyl v Phase 3 Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [16]
Method	ANCOVA
Parameter estimate	LS Mean Difference (Net)
Point estimate	5.09
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.37
upper limit	8.8
Variability estimate	Standard error of the mean
Dispersion value	1.656

Notes:

[16] - Missing eGFR data were imputed using multiple imputation based on the treatment group to which the patient was assigned.

Secondary: Change from baseline in eGFR at Week 104 following a 4-week drug treatment withdrawal period (Phase 3)

End point title	Change from baseline in eGFR at Week 104 following a 4-week drug treatment withdrawal period (Phase 3)[17]

End point description:

End point type	Secondary

End point timeframe:

104 weeks after participant receives the first dose in the Phase 3 study (or 4 weeks after last dose for patients who discontinued early in the second year)

Notes:

[17] - 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: The protocol for this study covered both a Phase 2 study portion and a Phase 3 portion. Participants enrolled in Phase 2 were not allowed to enroll in Phase 3; therefore, the end results for each section only include the arms that had patients in that phase.

End point values	Phase 3 Placebo	Phase 3 Bardoxolone Methyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: mL/min/1.73 m^2				
least squares mean (standard error)				
Change from baseline at Week 104	-8.84 (± 1.353)	-4.52 (± 1.395)		

Statistical analyses

Statistical analysis title	Mean change from baseline 104 weeks - Ph3
Comparison groups	Phase 3 Placebo v Phase 3 Bardoxolone Methyl

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232 [18]
Method	ANCOVA
Parameter estimate	LS Mean Difference (Net)
Point estimate	4.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	7.94
Variability estimate	Standard error of the mean
Dispersion value	1.876

Notes:

[18] - Missing eGFR data were imputed using multiple imputation based on the treatment group to which the patient was assigned.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from study visit Day 1 to study visit Week 104/Follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Phase 2 Bardoxolone Methyl
Reporting group description:	
Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 2 Study	
Reporting group title	Phase 3 Bardoxolone Methyl
Reporting group description:	
Participants who received bardoxolone methyl capsules at a starting dose of 5 mg and titrated up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily in the Cardinal Phase 3 Study	
Reporting group title	Phase 3 Placebo
Reporting group description:	
Participants who received placebo (with sham titration) in the Cardinal Phase 3 study	

Serious adverse events	Phase 2 Bardoxolone Methyl	Phase 3 Bardoxolone Methyl	Phase 3 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	8 / 77 (10.39%)	15 / 80 (18.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoid tumour pulmonary			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			

subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian mass			

subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Scapula fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status migrainosus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	3 / 30 (10.00%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Empyema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Phase 2 Bardoxolone Methyl	Phase 3 Bardoxolone Methyl	Phase 3 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)	75 / 77 (97.40%)	76 / 80 (95.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basosquamous carcinoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Colon adenoma			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	2	1	0

Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	5 / 30 (16.67%)	7 / 77 (9.09%)	8 / 80 (10.00%)
occurrences (all)	5	7	8
Hypotension			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	2	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	0	1	3
Chills			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	6 / 30 (20.00%)	14 / 77 (18.18%)	12 / 80 (15.00%)
occurrences (all)	6	14	12
Malaise			
subjects affected / exposed	3 / 30 (10.00%)	4 / 77 (5.19%)	0 / 80 (0.00%)
occurrences (all)	3	4	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 30 (3.33%)	6 / 77 (7.79%)	2 / 80 (2.50%)
occurrences (all)	1	6	2
Oedema peripheral			
subjects affected / exposed	7 / 30 (23.33%)	12 / 77 (15.58%)	10 / 80 (12.50%)
occurrences (all)	7	12	10
Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	1	0	2
Peripheral swelling			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences (all)	0	2	2
Pyrexia			

subjects affected / exposed	1 / 30 (3.33%)	3 / 77 (3.90%)	4 / 80 (5.00%)
occurrences (all)	1	3	4
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Seasonal allergy			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Cervical discharge			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
Menorrhagia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	1	2	0
Oligomenorrhoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	4 / 80 (5.00%)
occurrences (all)	1	2	4
Cough			
subjects affected / exposed	3 / 30 (10.00%)	8 / 77 (10.39%)	3 / 80 (3.75%)
occurrences (all)	3	8	3
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Epistaxis			

subjects affected / exposed	3 / 30 (10.00%)	7 / 77 (9.09%)	0 / 80 (0.00%)
occurrences (all)	3	7	0
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Nasal dryness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	3 / 30 (10.00%)	4 / 77 (5.19%)	6 / 80 (7.50%)
occurrences (all)	3	4	6
Rhinitis allergic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Sinus congestion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Wheezing			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	2	0	1
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Confusional state			

subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	2	1	1
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 77 (2.60%)	3 / 80 (3.75%)
occurrences (all)	3	2	3
Sleep disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 30 (43.33%)	36 / 77 (46.75%)	2 / 80 (2.50%)
occurrences (all)	13	36	2
Albumin urine present			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 30 (20.00%)	19 / 77 (24.68%)	1 / 80 (1.25%)
occurrences (all)	6	19	1
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 30 (6.67%)	5 / 77 (6.49%)	9 / 80 (11.25%)
occurrences (all)	2	5	9
Blood creatinine increased			
subjects affected / exposed	1 / 30 (3.33%)	3 / 77 (3.90%)	8 / 80 (10.00%)
occurrences (all)	1	3	8
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Blood magnesium decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	0	1	3
Blood potassium increased			

subjects affected / exposed	0 / 30 (0.00%)	4 / 77 (5.19%)	2 / 80 (2.50%)
occurrences (all)	0	4	2
Brain natriuretic peptide abnormal			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Brain natriuretic peptide increased			
subjects affected / exposed	3 / 30 (10.00%)	11 / 77 (14.29%)	3 / 80 (3.75%)
occurrences (all)	3	11	3
Eosinophil count increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 30 (6.67%)	4 / 77 (5.19%)	1 / 80 (1.25%)
occurrences (all)	2	4	1
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	1	2	0
Low density lipoprotein increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 30 (0.00%)	5 / 77 (6.49%)	2 / 80 (2.50%)
occurrences (all)	0	5	2
Urine albumin/creatinine ratio increased			
subjects affected / exposed	2 / 30 (6.67%)	8 / 77 (10.39%)	7 / 80 (8.75%)
occurrences (all)	2	8	7
Vitamin D decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	3 / 30 (10.00%)	10 / 77 (12.99%)	1 / 80 (1.25%)
occurrences (all)	3	10	1
Weight increased			

subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	6 / 80 (7.50%)
occurrences (all)	0	2	6
White blood cell count decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	1 / 30 (3.33%)	4 / 77 (5.19%)	1 / 80 (1.25%)
occurrences (all)	1	4	1
Epicondylitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Laceration			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Ligament sprain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Limb injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Tendon injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Mitral valve incompetence			

subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	3 / 80 (3.75%)
occurrences (all)	0	2	3
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)	3 / 77 (3.90%)	12 / 80 (15.00%)
occurrences (all)	1	3	12
Dysgeusia			
subjects affected / exposed	4 / 30 (13.33%)	4 / 77 (5.19%)	1 / 80 (1.25%)
occurrences (all)	4	4	1
Headache			
subjects affected / exposed	6 / 30 (20.00%)	16 / 77 (20.78%)	16 / 80 (20.00%)
occurrences (all)	6	16	16
Migraine			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	2	1	2
Migraine without aura			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	1	0	2
Periodic limb movement disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	2	0	2
Sinus headache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0

Syncope			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 30 (6.67%)	4 / 77 (5.19%)	0 / 80 (0.00%)
occurrences (all)	2	4	0
Iron deficiency anaemia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	2	1	2
Eustachian tube dysfunction			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
Vertigo			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences (all)	1	2	2
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	3
Dry eye			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0

Abdominal distension			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)	8 / 77 (10.39%)	13 / 80 (16.25%)
occurrences (all)	2	8	13
Abdominal pain upper			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	4 / 80 (5.00%)
occurrences (all)	1	1	4
Aphthous ulcer			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	4 / 30 (13.33%)	7 / 77 (9.09%)	4 / 80 (5.00%)
occurrences (all)	4	7	4
Dental caries			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	2 / 80 (2.50%)
occurrences (all)	0	3	2
Diarrhoea			
subjects affected / exposed	4 / 30 (13.33%)	12 / 77 (15.58%)	6 / 80 (7.50%)
occurrences (all)	4	12	6
Dry mouth			
subjects affected / exposed	3 / 30 (10.00%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	3	3	1
Dyspepsia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	3	1	1
Flatulence			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	1	1	2
Food poisoning			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0

Gastritis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 30 (0.00%)	5 / 77 (6.49%)	3 / 80 (3.75%)
occurrences (all)	0	5	3
Lip dry			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	6 / 30 (20.00%)	13 / 77 (16.88%)	11 / 80 (13.75%)
occurrences (all)	6	13	11
Oral mucosal exfoliation			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Paraesthesia oral			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Tongue discolouration			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	3 / 30 (10.00%)	7 / 77 (9.09%)	3 / 80 (3.75%)
occurrences (all)	3	7	3
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
Hepatic steatosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 30 (20.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	6	2	0
Dry skin			

subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	2	1	0
Eczema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Petechiae			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Rash pruritic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Albuminuria			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Chronic kidney disease			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences (all)	1	2	2

Dysuria			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences (all)	0	2	2
Haematuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	0	1	3
Nephrolithiasis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	0	1	3
Proteinuria			
subjects affected / exposed	5 / 30 (16.67%)	7 / 77 (9.09%)	6 / 80 (7.50%)
occurrences (all)	5	7	6
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 77 (1.30%)	6 / 80 (7.50%)
occurrences (all)	2	1	6
Arthritis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	7 / 30 (23.33%)	9 / 77 (11.69%)	13 / 80 (16.25%)
occurrences (all)	7	9	13
Bursitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Coccydynia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Costochondritis			

subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Flank pain			
subjects affected / exposed	2 / 30 (6.67%)	2 / 77 (2.60%)	3 / 80 (3.75%)
occurrences (all)	2	2	3
Intervertebral disc protrusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	22 / 30 (73.33%)	38 / 77 (49.35%)	27 / 80 (33.75%)
occurrences (all)	22	38	27
Muscle twitching			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
Muscular weakness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Musculoskeletal pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)	4 / 77 (5.19%)	3 / 80 (3.75%)
occurrences (all)	2	4	3
Neck pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Osteoarthritis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	2 / 30 (6.67%)	7 / 77 (9.09%)	2 / 80 (2.50%)
occurrences (all)	2	7	2
Plantar fasciitis			

subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Rheumatoid arthritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Spondylitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Tendonitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	1	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 30 (13.33%)	3 / 77 (3.90%)	2 / 80 (2.50%)
occurrences (all)	4	3	2
Conjunctivitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
Cystitis			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	1	2	1
Fungal infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
Fungal skin infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0

Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	3 / 80 (3.75%)
occurrences (all)	1	2	3
Herpes zoster			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	1 / 80 (1.25%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	3 / 30 (10.00%)	6 / 77 (7.79%)	7 / 80 (8.75%)
occurrences (all)	3	6	7
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	3 / 30 (10.00%)	18 / 77 (23.38%)	24 / 80 (30.00%)
occurrences (all)	3	18	24
Oral herpes			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Otitis externa			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Peritonitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	1	1	3
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	2	2	1
Rhinitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 77 (1.30%)	3 / 80 (3.75%)
occurrences (all)	0	1	3

Sinusitis			
subjects affected / exposed	2 / 30 (6.67%)	6 / 77 (7.79%)	7 / 80 (8.75%)
occurrences (all)	2	6	7
Skin candida			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 30 (20.00%)	12 / 77 (15.58%)	8 / 80 (10.00%)
occurrences (all)	6	12	8
Urinary tract infection			
subjects affected / exposed	2 / 30 (6.67%)	3 / 77 (3.90%)	5 / 80 (6.25%)
occurrences (all)	2	3	5
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Acidosis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	2 / 80 (2.50%)
occurrences (all)	0	2	2
Decreased appetite			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Dehydration			
subjects affected / exposed	0 / 30 (0.00%)	3 / 77 (3.90%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
Dyslipidaemia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 77 (2.60%)	0 / 80 (0.00%)
occurrences (all)	0	2	0
Gout			

subjects affected / exposed	3 / 30 (10.00%)	2 / 77 (2.60%)	6 / 80 (7.50%)
occurrences (all)	3	2	6
Hyperkalaemia			
subjects affected / exposed	9 / 30 (30.00%)	11 / 77 (14.29%)	5 / 80 (6.25%)
occurrences (all)	9	11	5
Hyperlipidaemia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	1	2	1
Hyperphosphataemia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 77 (2.60%)	1 / 80 (1.25%)
occurrences (all)	2	2	1
Hyperuricaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 77 (0.00%)	4 / 80 (5.00%)
occurrences (all)	0	0	4
Hypoalbuminaemia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 77 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	4 / 30 (13.33%)	3 / 77 (3.90%)	0 / 80 (0.00%)
occurrences (all)	4	3	0
Metabolic acidosis			
subjects affected / exposed	4 / 30 (13.33%)	3 / 77 (3.90%)	1 / 80 (1.25%)
occurrences (all)	4	3	1
Vitamin D deficiency			
subjects affected / exposed	4 / 30 (13.33%)	1 / 77 (1.30%)	1 / 80 (1.25%)
occurrences (all)	4	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2018	Version 2.0
15 November 2018	Version 3.0
23 May 2019	Version 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported