Clinical trial results:
An Extended Access Program to Assess Long-Term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension

Summary

EudraCT number	2016-004365-16
Trial protocol	ES BE CZ GB DE
Global end of trial date	30 September 2020

Results information

Result version number	v1 (current)
This version publication date	17 October 2021
First version publication date	17 October 2021

Trial information

Trial identification

Sponsor protocol code	402-C-1602

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03068130
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Reata Pharmaceuticals
Sponsor organisation address	5320 Legacy Drive, Plano, United States, 75024
Public contact	Clinical Study Manager, Reata Pharmaceuticals, Inc., 972 8652219, 408C1602DNK@reatapharma.com
Scientific contact	Clinical Study Manager, Reata Pharmaceuticals, Inc., 972 8652219, 408C1602DNK@reatapharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	Yes
Global end of trial date	30 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This extended access (open label) study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl. Qualified patients will receive 10 mg of bardoxolone methyl once daily until the drug is available through commercial channels or until patient withdrawal, whichever is sooner. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Protection of trial subjects:

The study sites will be monitored remotely by the CRO periodically during the study to ensure that all aspects of the protocol will be followed and will include an electronic data collection which has a set of automatic data checks with data queries for programmed data collection. There will be monitoring of study site by telephone to ensure that the drug supplies have been provided and protocol instructions are well understood and applied. The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Council for Harmonisation (ICH) guideline E6(R1): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Argentina: 23
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Philippines: 5

Country: Number of subjects enrolled	United States: 161
Worldwide total number of subjects	261
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)	0
Adults (18-64 years)	171
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Treatment-compliant patients who are participating in qualifying ongoing studies and have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl.

Pre-assignment

Screening details:

This is an extended access (Open label) study assessing the long-term safety and tolerability of bardoxolone methyl in patients with PH who previously participated in qualifying clinical studies 402-C-1504 and 402-C-1302 (also referred to as previous qualifying studies of Study 1602) with bardoxolone methyl. All patients received bardoxolone methyl

Period 1

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

Arms

Arm title	Experimental: Bardoxolone Methyl 10 mg

Arm description:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Arm type	Experimental
Investigational medicinal product name	Bardoxolone methyl capsules 10mg
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 administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Number of subjects in period 1	Experimental: Bardoxolone Methyl 10 mg
Started	261
Completed	0
Not completed	261
Adverse event, serious fatal	14
Administrative Reasons	3
Consent withdrawn by subject	26
Adverse event, non-fatal	19
Protocol Specified Withdrawal Criterion	1
Study Terminated by Sponsor	194

Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	261	261	
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			
Experimental: Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.			
Units: years			
arithmetic mean	56.7		
standard deviation	± 12.79	-	
Gender categorical			
Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.			
Units: Subjects			
Female	221	221	
Male	40	40	
Ethnic Group			
Experimental: Bardoxolone methyl will be administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	22	22	
Native Hawaiian or Pacific Islander	0	0	
Black or African American	30	30	
More than one race	204	204	
Unknown or Not Reported	5	5	

End points

End points reporting groups

Reporting group title	Experimental: Bardoxolone Methyl 10 mg

Reporting group description:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Primary: Long term safety as measured by incidence and severity of adverse events during the duration of the study

End point title	Long term safety as measured by incidence and severity of adverse events during the duration of the study[1]

End point description:

Severity was defined using the following definitions: Mild: Symptoms causing no or minimal interference with usual social and functional activities; Moderate: Symptoms causing greater than minimual interference with usual social and functional activities; Severe: Symptoms causing inability to perform usual social and functional activities.

End point type	Primary

End point timeframe:

From time of first dose until the final visit, up to 172 weeks

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: This extended access (open label) study assessed the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl. The Primary endpoint was long term safety as measured by incidence and severity of adverse events during the duration of the study. As such, no additional statistical analysis was performed.

End point values	Experimental: Bardoxolone Methyl 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	261			
Units: Count of Participants				
number (not applicable)				
Number of subjects with at least one AE	232			
Number of subjects with a related AE	89			
Number of subjects with a serious AE	106			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time from the date of a participant's first dose to his or her last participation or event date, a maximum of 172 weeks

Adverse event reporting additional description:

All AEs/SAEs from the time of admin of the first dose until final visit were to be reported. AEs/SAEs occurring within 30 days after last dose were considered treatment emergent. For SAEs, the PI was to follow the patient until the SAE subsided or until the condition became chronic in nature, stabilized (persistent impairment) or the patient died.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Experimental: Bardoxolone Methyl 10 mg

Reporting group description:

Bardoxolone methyl administered orally once daily at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Serious adverse events	Experimental: Bardoxolone Methyl 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 261 (40.61%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salivary gland cancer			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Squamous cell carcinoma			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Complication associated with device			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related thrombosis			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Menometrorrhagia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst ruptured				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute respiratory failure				
subjects affected / exposed	4 / 261 (1.53%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Asthma				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	3 / 261 (1.15%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	13 / 261 (4.98%)			
occurrences causally related to treatment / all	2 / 16			
deaths causally related to treatment / all	1 / 2			
Pulmonary embolism				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				

subjects affected / exposed	5 / 261 (1.92%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	3 / 261 (1.15%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Investigations				
Norovirus test positive				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Drug administration error				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Environmental exposure				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eschar				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint injury				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina unstable				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	4 / 261 (1.53%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Cardiac failure acute				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiogenic shock				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dilatation ventricular				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	3 / 261 (1.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular dysfunction				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	7 / 261 (2.68%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 1			
Systolic dysfunction				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebellar artery thrombosis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolic stroke				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lateral medullary syndrome				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lumbar radiculopathy				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal epidural haematoma				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vasculitis cerebral				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Agranulocytosis				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ascites				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dental cyst				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 261 (1.15%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids thrombosed				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mallory-Weiss syndrome				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal motility disorder				

subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	2 / 261 (0.77%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders				
Bursitis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Costochondritis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Scleroderma				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal deformity				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic lupus erythematosus				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Appendicitis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bursitis infective				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	4 / 261 (1.53%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cellulitis staphylococcal				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ecthyma				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	4 / 261 (1.53%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	13 / 261 (4.98%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				

subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 261 (1.15%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Upper respiratory tract infection				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 261 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 261 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 261 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental: Bardoxolone Methyl 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 261 (75.86%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 261 (4.60%)		
occurrences (all)	12		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 261 (2.30%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	19 / 261 (7.28%)		
occurrences (all)	19		
Non-cardiac chest pain			

subjects affected / exposed	10 / 261 (3.83%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	16 / 261 (6.13%)		
occurrences (all)	169		
Pyrexia			
subjects affected / exposed	8 / 261 (3.07%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 261 (9.58%)		
occurrences (all)	25		
Dyspnoea			
subjects affected / exposed	25 / 261 (9.58%)		
occurrences (all)	25		
Dyspnoea exertional			
subjects affected / exposed	7 / 261 (2.68%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	9 / 261 (3.45%)		
occurrences (all)	9		
Nasal congestion			
subjects affected / exposed	6 / 261 (2.30%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	8 / 261 (3.07%)		
occurrences (all)	8		
Pulmonary arterial hypertension			
subjects affected / exposed	9 / 261 (3.45%)		
occurrences (all)	9		
Pulmonary hypertension			
subjects affected / exposed	7 / 261 (2.68%)		
occurrences (all)	7		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	8 / 261 (3.07%) 8		
Investigations Brain natriuretic peptide increased subjects affected / exposed occurrences (all) N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 6 / 261 (2.30%) 6 21 / 261 (8.05%) 21 16 / 261 (6.13%) 16		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	 6 / 261 (2.30%) 6		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	 12 / 261 (4.60%) 12		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	 22 / 261 (8.43%) 22 26 / 261 (9.96%) 26 9 / 261 (3.45%) 9		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	 14 / 261 (5.36%) 14		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	10 / 261 (3.83%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	11 / 261 (4.21%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	41 / 261 (15.71%)		
occurrences (all)	41		
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 261 (4.98%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	31 / 261 (11.88%)		
occurrences (all)	31		
Vomiting			
subjects affected / exposed	12 / 261 (4.60%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 261 (2.68%)		
occurrences (all)	7		
Skin ulcer			
subjects affected / exposed	7 / 261 (2.68%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 261 (4.98%)		
occurrences (all)	13		
Back pain			
subjects affected / exposed	13 / 261 (4.98%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	33 / 261 (12.64%)		
occurrences (all)	33		
Musculoskeletal pain			

subjects affected / exposed occurrences (all)	9 / 261 (3.45%) 9		
Myalgia subjects affected / exposed occurrences (all)	13 / 261 (4.98%) 13		
Neck pain subjects affected / exposed occurrences (all)	9 / 261 (3.45%) 9		
Pain in extremity subjects affected / exposed occurrences (all)	17 / 261 (6.51%) 17		
Pain in jaw subjects affected / exposed occurrences (all)	7 / 261 (2.68%) 7		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	21 / 261 (8.05%) 21		
Cellulitis subjects affected / exposed occurrences (all)	8 / 261 (3.07%) 8		
Conjunctivitis subjects affected / exposed occurrences (all)	10 / 261 (3.83%) 10		
Herpes zoster subjects affected / exposed occurrences (all)	9 / 261 (3.45%) 9		
Influenza subjects affected / exposed occurrences (all)	14 / 261 (5.36%) 14		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	8 / 261 (3.07%) 8		
Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 261 (4.98%) 13		

Pneumonia subjects affected / exposed occurrences (all)	11 / 261 (4.21%) 11		
Respiratory tract infection subjects affected / exposed occurrences (all)	9 / 261 (3.45%) 9		
Sinusitis subjects affected / exposed occurrences (all)	22 / 261 (8.43%) 22		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	51 / 261 (19.54%) 51		
Urinary tract infection subjects affected / exposed occurrences (all)	30 / 261 (11.49%) 30		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	15 / 261 (5.75%) 15		
Hypokalaemia subjects affected / exposed occurrences (all)	13 / 261 (4.98%) 13		
Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 261 (2.68%) 7		
Vitamin D deficiency subjects affected / exposed occurrences (all)	6 / 261 (2.30%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2016	Protocol Version 1.0
05 January 2017	Protocol Version 2.0
05 January 2017	Protocol Version 2.1 (Japan)
01 March 2017	Protocol Version 2.2 (Japan)
09 May 2017	Protocol Version 2.1 (UK)
23 June 2017	Protocol Version 2.2 (Germany)
16 July 2018	Protocol Version 3.0
16 July 2018	Protocol Version 3.1 (UK)
16 July 2018	Protocol Version 3.1 (Germany)
25 July 2018	Protocol Version 3.1 (Japan)
11 July 2019	Protocol Version 3.2 (Germany)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

30 September 2020	Due to the COVID-19 pandemic and consideration of the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases, and on recommendation from the parent study's DSMB (402-C-1504), the Sponsor decided to stop the Phase 3 Study (1504) in patients with CTD-PAH. Patients with CTD-PAH have compromised cardiopulmonary function, are often receiving immunosuppressants, and are at an inherently high risk of adverse outcomes in the event of infection. The Sponsor concluded that continued exposure of these high-risk patients to clinic or in-person visits presented an unacceptable risk. The 1504 parent study was not stopped as a result of any bardoxolone methyl-related safety concern, and the DSMB did not reported any treatment-related safety concerns. There were no deaths in the bardoxolone methyl arm of study 1504, and fewer patients reported serious adverse events (SAE) in the bardoxolone methyl arm compared to the placebo arm within the 1504 study. While no futility analyses were performed, an initial review of available efficacy data provided by the DSMB suggested that Study 1504 was unlikely to meet the primary endpoint of improvement in 6MWD compared to placebo at Week 24. Concomitant with the decision to close Study 1504, the Sponsor also closed Study this study 402-C-1602.	-

Notes:

Limitations and caveats

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

Early termination of this study due to COVID-19 Pandemic and in consideration of the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases.

Notes: