Clinical trial results:
A Study of the Efficacy and Safety of Bardoxolone Methyl in Patients With Connective Tissue Disease-associated Pulmonary Arterial Hypertension

Summary

EudraCT number	2016-000196-24
Trial protocol	ES DE BE NL CZ GB
Global end of trial date	07 May 2020

Results information

Result version number	v2 (current)
This version publication date	18 November 2021
First version publication date	10 July 2021
Version creation reason	• Changes to summary attachments Updates on Trial information

Trial information

Trial identification

Sponsor protocol code	402-C-1504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02657356
WHO universal trial number (UTN)	-
Other trial identifiers	RTA 402-C-1504: Catalyst

Notes:

Sponsors

Sponsor organisation name	Reata Pharmaceuticals, Inc.
Sponsor organisation address	5320 Legacy Drive, Plano, United States, 75024
Public contact	Kris Loerwald, Reata Pharmaceuticals, Inc., 1 972 865-2219, MedicalAffairs-Team@reatapharma.com
Scientific contact	Kris Loerwald, Reata Pharmaceuticals, Inc., 1 972 865-2219, MedicalAffairs-Team@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	07 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2020
Global end of trial reached?	Yes
Global end of trial date	07 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of bardoxolone methyl relative to placebo.

Protection of trial subjects:

IDMC reviewed unblinded safety data throughout the study and made recommendations regarding study continuation, modification or termination as appropriate to protect patient safety.

Background therapy:

Bardoxolone methyl or placebo was administered orally once a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

Evidence for comparator:

N/A

Actual start date of recruitment	04 October 2016
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	Brazil: 9
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Argentina: 26
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Philippines: 5
Country: Number of subjects enrolled	United States: 80
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	202
EEA total number of subjects	37

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)	134
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruited patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH).

Pre-assignment

Screening details:

Qualified patients with WHO Group I CTD-PAH were screened and enrolled per protocol inclusion/exclusion criteria.

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	Assessor, Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

All patients, investigators, site personnel, laboratories, and central readers with direct involvement in the conduct of the study or their designees were blinded to treatment assignments throughout the trial. To maintain the blind, An IWRS system managed treatment assignments and distributed blinded study drug treatment kits. Investigators and patients were not blinded to dose level, but were be blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo capsules

Arm description:

Placebo capsules administered orally once a day for 24 weeks.

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

Dosage and administration details:

Placebo administered orally once a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

Arm title	Bardoxolone methyl capsules

Arm description:

Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4

Arm type	Experimental
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 administered orally once a day at 2.5, 5, or 10 mg, using 2.5 and 5.0 mg capsules up to 24 weeks.

Number of subjects in period 1	Placebo capsules	Bardoxolone methyl capsules
Started	102	100
Completed	90	93
Not completed	12	7
Adverse event, not serious	5	6
Consent withdrawn by subject	1	1
Study terminated by Sponsor	5	-
Protocol-specified withdrawal criterion met	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo capsules
Reporting group description:	
Placebo capsules administered orally once a day for 24 weeks.	
Reporting group title	Bardoxolone methyl capsules
Reporting group description:	
Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4	

Reporting group values	Placebo capsules	Bardoxolone methyl capsules	Total
Number of subjects	102	100	202
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 56.5 ± 13.17	 55 ± 13.57	 -
Gender categorical Units: Subjects			
Female	91	88	179
Male	11	12	23

Subject analysis sets	
Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients categorized by their assigned treatment group regardless of treatment exposure. Analyses of both the primary and secondary efficacy outcomes will use the ITT population.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of randomized study drug.	

Reporting group values	Intent-to-treat population	Safety Population	
Number of subjects	202	202	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 55.7 ± 13.36	 ±	

Gender categorical Units: Subjects			
Female	179		
Male	23		

End points

End points reporting groups

Reporting group title	Placebo capsules
Reporting group description:	
Placebo capsules administered orally once a day for 24 weeks.	
Reporting group title	Bardoxolone methyl capsules
Reporting group description:	
Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4	
Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients categorized by their assigned treatment group regardless of treatment exposure. Analyses of both the primary and secondary efficacy outcomes will use the ITT population.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of randomized study drug.	

Primary: Change from baseline in six-minute-walk distance (6MWD)

End point title	Change from baseline in six-minute-walk distance (6MWD)
End point description:	
The 6MWT is a core clinical measure in the management of PAH and has been used as the primary endpoint in most previous registrational studies for PAH therapy. This unencouraged hallway walking test evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	Placebo capsules	Bardoxolone methyl capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[1]	100[2]		
Units: Meters				
least squares mean (standard error)	9.25 (± 4.954)	-3.61 (± 4.952)		

Notes:

[1] - Placebo capsules administered orally once a day for 24 weeks.

[2] - Bardoxolone methyl capsules administered orally once a day for 24 weeks.

Statistical analyses

Statistical analysis title	Change from baseline in 6MWT at Week 24

Statistical analysis description:

A mixed model was fit with this outcome using Screening 6MWT, number of background PAH medications, and Day 1 hemoglobin as covariates, treatment group and visit as fixed factors, as well as the interaction of treatment group and visit, and Screening 6MWT and visit. Missing values were not

imputed.

Comparison groups	Placebo capsules v Bardoxolone methyl capsules
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-12.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.69
upper limit	0.98
Variability estimate	Standard error of the mean
Dispersion value	7.012

Notes:

[3] - Primary efficacy analysis compares changes from baseline (6WMT) between patients on μ BARD to patients on μ placebo at the wk 24 visit according to: Null hypothesis,H0:(μ BARD)–(μ placebo)=0m; Alternative hypothesis H1: (μ BARD) – (μ placebo) ≠ 0 m

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the time administration of the first dose at the Day 1 visit until the final visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo capsules administered orally once a day for 24 weeks	
Reporting group title	Bardoxolone methyl capsules
Reporting group description:	
Bardoxolone methyl capsules administered orally once a day for 24 weeks. Starting dosage is 5 mg with dose-escalation to 10 mg at week 4	

Serious adverse events	Placebo	Bardoxolone methyl capsules	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 102 (17.65%)	16 / 100 (16.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 102 (1.96%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			

subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematochezia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis ulcerative			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Upper respiratory tract infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 102 (0.98%)	4 / 100 (4.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			

subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 102 (2.94%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Bardoxolone methyl capsules	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 102 (83.33%)	91 / 100 (91.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Headache			
subjects affected / exposed	21 / 102 (20.59%)	14 / 100 (14.00%)	
occurrences (all)	28	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 102 (12.75%)	9 / 100 (9.00%)	
occurrences (all)	13	9	
Oedema peripheral			
subjects affected / exposed	12 / 102 (11.76%)	9 / 100 (9.00%)	
occurrences (all)	14	9	
Non-cardiac chest pain			

subjects affected / exposed	6 / 102 (5.88%)	3 / 100 (3.00%)	
occurrences (all)	7	3	
Pyrexia			
subjects affected / exposed	3 / 102 (2.94%)	3 / 100 (3.00%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 102 (11.76%)	9 / 100 (9.00%)	
occurrences (all)	12	9	
Cough			
subjects affected / exposed	10 / 102 (9.80%)	6 / 100 (6.00%)	
occurrences (all)	12	6	
Dyspnoea exertional			
subjects affected / exposed	3 / 102 (2.94%)	4 / 100 (4.00%)	
occurrences (all)	3	4	
Epistaxis			
subjects affected / exposed	1 / 102 (0.98%)	4 / 100 (4.00%)	
occurrences (all)	1	4	
Rales			
subjects affected / exposed	3 / 102 (2.94%)	3 / 100 (3.00%)	
occurrences (all)	4	3	
Nasal congestion			
subjects affected / exposed	3 / 102 (2.94%)	2 / 100 (2.00%)	
occurrences (all)	3	2	
Oropharyngeal pain			
subjects affected / exposed	6 / 102 (5.88%)	1 / 100 (1.00%)	
occurrences (all)	6	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 102 (5.88%)	3 / 100 (3.00%)	
occurrences (all)	6	3	
Depression			
subjects affected / exposed	3 / 102 (2.94%)	1 / 100 (1.00%)	
occurrences (all)	3	1	
Investigations			

Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 102 (1.96%)	8 / 100 (8.00%)	
occurrences (all)	2	8	
Weight decreased			
subjects affected / exposed	2 / 102 (1.96%)	7 / 100 (7.00%)	
occurrences (all)	2	7	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 102 (0.98%)	6 / 100 (6.00%)	
occurrences (all)	1	6	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 102 (0.00%)	6 / 100 (6.00%)	
occurrences (all)	0	6	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 102 (0.98%)	5 / 100 (5.00%)	
occurrences (all)	1	5	
Brain natriuretic peptide increased			
subjects affected / exposed	2 / 102 (1.96%)	3 / 100 (3.00%)	
occurrences (all)	2	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	
occurrences (all)	1	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 102 (1.96%)	3 / 100 (3.00%)	
occurrences (all)	2	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 102 (11.76%)	8 / 100 (8.00%)	
occurrences (all)	12	10	
Presyncope			
subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	
occurrences (all)	1	4	
Dizziness postural			

subjects affected / exposed	3 / 102 (2.94%)	0 / 100 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 102 (1.96%)	6 / 100 (6.00%)	
occurrences (all)	2	6	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 102 (2.94%)	1 / 100 (1.00%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 102 (20.59%)	13 / 100 (13.00%)	
occurrences (all)	25	15	
Nausea			
subjects affected / exposed	11 / 102 (10.78%)	12 / 100 (12.00%)	
occurrences (all)	13	12	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 102 (3.92%)	9 / 100 (9.00%)	
occurrences (all)	4	10	
Vomiting			
subjects affected / exposed	7 / 102 (6.86%)	8 / 100 (8.00%)	
occurrences (all)	8	8	
Constipation			
subjects affected / exposed	6 / 102 (5.88%)	5 / 100 (5.00%)	
occurrences (all)	6	5	
Abdominal pain			
subjects affected / exposed	3 / 102 (2.94%)	3 / 100 (3.00%)	
occurrences (all)	3	3	
Abdominal distension			
subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	
occurrences (all)	1	3	
Dyspepsia			

subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	
occurrences (all)	1	3	
Abdominal tenderness			
subjects affected / exposed	0 / 102 (0.00%)	3 / 100 (3.00%)	
occurrences (all)	0	3	
Gastritis			
subjects affected / exposed	0 / 102 (0.00%)	3 / 100 (3.00%)	
occurrences (all)	0	3	
Dry mouth			
subjects affected / exposed	3 / 102 (2.94%)	0 / 100 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	2 / 102 (1.96%)	3 / 100 (3.00%)	
occurrences (all)	2	3	
Rash			
subjects affected / exposed	3 / 102 (2.94%)	1 / 100 (1.00%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	6 / 102 (5.88%)	17 / 100 (17.00%)	
occurrences (all)	7	19	
Back pain			
subjects affected / exposed	7 / 102 (6.86%)	9 / 100 (9.00%)	
occurrences (all)	7	10	
Pain in extremity			
subjects affected / exposed	2 / 102 (1.96%)	8 / 100 (8.00%)	
occurrences (all)	2	9	
Myalgia			
subjects affected / exposed	5 / 102 (4.90%)	6 / 100 (6.00%)	
occurrences (all)	5	6	
Arthralgia			
subjects affected / exposed	12 / 102 (11.76%)	3 / 100 (3.00%)	
occurrences (all)	13	5	
Rheumatoid arthritis			

subjects affected / exposed	3 / 102 (2.94%)	1 / 100 (1.00%)	
occurrences (all)	5	1	
Joint swelling			
subjects affected / exposed	3 / 102 (2.94%)	0 / 100 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 102 (10.78%)	19 / 100 (19.00%)	
occurrences (all)	15	27	
Nasopharyngitis			
subjects affected / exposed	5 / 102 (4.90%)	11 / 100 (11.00%)	
occurrences (all)	5	13	
Urinary tract infection			
subjects affected / exposed	6 / 102 (5.88%)	8 / 100 (8.00%)	
occurrences (all)	11	11	
Bronchitis			
subjects affected / exposed	5 / 102 (4.90%)	7 / 100 (7.00%)	
occurrences (all)	5	7	
Sinusitis			
subjects affected / exposed	4 / 102 (3.92%)	4 / 100 (4.00%)	
occurrences (all)	4	4	
Gastroenteritis			
subjects affected / exposed	2 / 102 (1.96%)	4 / 100 (4.00%)	
occurrences (all)	2	4	
Pneumonia			
subjects affected / exposed	3 / 102 (2.94%)	3 / 100 (3.00%)	
occurrences (all)	3	3	
Influenza			
subjects affected / exposed	7 / 102 (6.86%)	2 / 100 (2.00%)	
occurrences (all)	7	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 102 (0.98%)	5 / 100 (5.00%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	3 / 102 (2.94%)	9 / 100 (9.00%)	
occurrences (all)	3	9	
Gout			
subjects affected / exposed	0 / 102 (0.00%)	5 / 100 (5.00%)	
occurrences (all)	0	7	
Fluid retention			
subjects affected / exposed	1 / 102 (0.98%)	4 / 100 (4.00%)	
occurrences (all)	1	6	
Hypokalaemia			
subjects affected / exposed	1 / 102 (0.98%)	4 / 100 (4.00%)	
occurrences (all)	1	4	
Hypomagnesaemia			
subjects affected / exposed	0 / 102 (0.00%)	3 / 100 (3.00%)	
occurrences (all)	0	3	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 102 (1.96%)	4 / 100 (4.00%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2016	Version 2.0: Updated estimated study start and end dates, Clarified dose escalation and de-escalation rules, Updated Patient Inclusion Critera (Criteron 7, 9, 10, 16, 21, and 30); Clarified Patient discontinuation criteria and management of fluid status; Added guidelines on Anemia treatment; Removed unnecessary excluded medication; Added guidelines for additional medications that may affect PAH walking distance and clarified the requirements for use of background medications for the treatment of CTD; Removed use of home health vendor; Clarification to consider potential comorbidities; Procedural clarification regarding the Assessment of Digital Ulcers; Clarification for patients not participating in PK sub-study; Clarification AE documentation to continue 28 days after last dose and made procedural reporting clarifications; Added Borg Dyspnea Scale appendix

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 May 2020	Exposure of these high-risk patients to clinic or in-person visits during the Covid-19 pandemic presented an unacceptable risk to their health, as such the trial was terminated.	-

Notes:

Limitations and caveats

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

Due to the risk of severe adverse outcomes associated with COVID-19 among patients with respiratory and autoimmune diseases, and on recommendation from the study's DSMB, the Sponsor terminated the trial due to unacceptable health risks to patients.

Notes: