Clinical trial results:
An Open-Label Extension Study of APD811-003 in Patients with Pulmonary Arterial Hypertension

Summary

EudraCT number	2014-003042-27
Trial protocol	CZ HU ES PL RO SK
Global end of trial date	29 March 2021

Results information

Result version number	v1 (current)
This version publication date	05 September 2024
First version publication date	05 September 2024

Trial information

Trial identification

Sponsor protocol code	APD811-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02279745
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corp.
Sponsor organisation address	55 TW Alexander Drive, Durham, United States, 27709
Public contact	Global Medical Information, United Therapeutics Corp., +1 9194858350, clinicaltrials@unither.com
Scientific contact	Global Medical Information, United Therapeutics Corp., +1 9194858350, clinicaltrials@unither.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	21 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2021
Global end of trial reached?	Yes
Global end of trial date	29 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
To evaluate the long-term safety and tolerability of ralinepag in patients with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who completed Study APD811-003.

Protection of trial subjects:

In accordance with federal/national regulations and ICH GCP guidelines, Clinical Monitors for UTC or its designee periodically contacted the sites and conducted on-site visits. During these visits, the Monitor, at a minimum, confirmed ethical treatment of subjects, assessed study progress, reviewed data collected, conducted source document verification, verified drug accountability periodically, and identified any issues requiring resolution. The Investigator was required to allow the Monitor direct access to all relevant documents and allocate his/her time and his/her staff to discuss any findings or any relevant issues. In addition, Auditors for UTC or its designee periodically contacted the sites and conducted on-site visits.

Background therapy:

Concomitant medications and concomitant nondrug treatments were recorded. Subjects were permitted PAH-specific oral therapy consisting of an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 inhibitor (PDE5-I) or a soluble guanylate cyclase (sGC) stimulator. If on a single therapy at Baseline, the on-study addition of an ERA or PDE5-I or a sGC stimulator was permitted. In addition to ralinepag, subjects could
be prescribed no more than 1 agent from the ERA class and 1 agent from the PDE5-I/sGC stimulator class at any given time. Substitution and dose adjustment within each of these classes was permitted. Subjects were evaluated for the presence of clinical worsening if additional therapy or dose adjustments/substitutions of current therapies was required.
In addition, the following therapies, which may have affected PAH, were permitted and adjusted in dose as needed:
• Vasodilators (including calcium channel blockers)
• Digoxin
• Spironolactone
• L-Arginine supplementation.
Diuretics were dosed as clinically indicated throughout the study. Subjects who required treatment with a prostacyclin/prostacyclin analogue (IV,
subcutaneous, oral, or inhaled), except for acute vasodilator testing during cardiac catheterization, were discontinued from the study.

Evidence for comparator: -

Actual start date of recruitment	08 July 2015
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	Poland: 2
Country: Number of subjects enrolled	Romania: 5

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Serbia: 9
Worldwide total number of subjects	45
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)	39
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted by 23 investigators at 23 study centers in the US, Europe, and Australia. No formal sample size calculation was conducted. All eligible subjects from Study APD811-003 could be enrolled into Study APD811-007.

Pre-assignment

Screening details:

Each subject must have met all of the inclusion criteria and none of the exclusion criteria to be eligible for enrollment in the study. Eligible subjects completed the Phase 2 study, APD811-003, or were assigned to receive placebo and were discontinued due to clinical worsening.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Received Placebo in APD811-003

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ralinepag
Investigational medicinal product code	
Other name	APD811
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Ralinepag was provided for oral administration as 10, 20, 30, 40, and 100 mcg immediate-release capsule dose strengths, and later was provided as 50, 250, and 400 mcg (0.05, 0.25, and 0.4 mg) extended-release tablet dose strengths.
Subjects who received ralinepag in Study APD811-003 remained on their current dose. Subjects in the placebo treatment group of Study APD811-003 underwent a ralinepag Dose Titration Period (up to 9 weeks) until a stable maximum tolerated dose (MTD) was reached. The maximum total daily dose (TDD) was 600 mcg which could be increased at the discretion of the Investigator. Incremental dose increases were allowed after the Dose Titration Period (ie, during the Treatment Period) at the discretion of the Investigator (as clinically indicated) and according to the stepwise titration scheme. If a dose was not tolerated by the subject, it could have been adjusted as directed by the Investigator.

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Period could have been maintained throughout the Treatment Period; however, incremental dose increases were allowed during the Treatment Period at the discretion of the Investigator (as clinically indicated) and according to the stepwise titration scheme. If a dose was not tolerated by the subject, it could have been adjusted as directed by the Investigator.

Number of subjects in period 1	Received Placebo in APD811-003	Received Ralinepag in APD811-003
Started	15	30
Completed	15	30

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Received Placebo in APD811-003

Arm description: -

Arm type	Experimental
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Arm description: -

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Number of subjects in period 2	Received Placebo in APD811-003	Received Ralinepag in APD811-003
Started	15	30
Completed	11	15
Not completed	4	15
Adverse event, serious fatal	2	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	5
Study Noncompliance	-	1
Clinical worsening as defined by protocol	-	2
Pregnancy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	39	39	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
median	51.0		
full range (min-max)	20 to 71	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	6	6	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	44	44	
Race Units: Subjects			
White	42	42	
Black or African American	1	1	
Asian	1	1	
Other	1	1	
Etiology of PAH Units: Subjects			
Idiopathic PAH	23	23	
Heritable PAH	4	4	
Drug or Toxin Induced PAH	2	2	
PAH Associated with Other Disease	16	16	
6MWD Category at Baseline Units: Subjects			
≤400 m	18	18	
>400 m	27	27	

WHO Functional Class at Baseline Units: Subjects			
FC I	3	3	
FC II	32	32	
FC III	10	10	
Background PAH Therapy at Randomization in APD811-003 - ERA Units: Subjects			
Yes	31	31	
No	14	14	
Background PAH Therapy at Randomization in APD811-003 - PDE5-I Units: Subjects			
Yes	38	38	
No	7	7	
Background PAH Therapy at Randomization in APD811-003 - sGC Stimulator Units: Subjects			
Yes	2	2	
No	43	43	
Background PAH Therapy at Randomization in APD811-003 - ERA + PDE5-I/sGC Stimulator Units: Subjects			
Yes	26	26	
No	19	19	
Time Since PAH Diagnosis Units: years			
median	2.3		
full range (min-max)	0.8 to 16.0	-	
6MWD at Baseline Units: meters			
median	425.0		
full range (min-max)	158 to 696	-	
NT-proBNP at Baseline Units: pg/mL			
median	357.60		
full range (min-max)	53.4 to 4309.3	-	
PVR at Baseline Units: dyn.sec/cm^5			
median	556.400		
full range (min-max)	126.30 to 1165.70	-	

End points

End points reporting groups

Reporting group title	Received Placebo in APD811-003
Reporting group description: -	
Reporting group title	Received Ralinepag in APD811-003
Reporting group description: -	
Reporting group title	Received Placebo in APD811-003
Reporting group description: -	
Reporting group title	Received Ralinepag in APD811-003
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included any subject who received ralinepag at any time during the course of Study APD811-007. All analyses were based on the Safety Population.

Primary: Change from Baseline in Pulmonary Vascular Resistance

End point title	Change from Baseline in Pulmonary Vascular Resistance[1]

End point description:

The hemodynamic parameters of pulmonary vascular resistance, cardiac output, cardiac index, and mean pulmonary artery pressure were collected by right heart catheterization (RHC).

End point type	Primary

End point timeframe:

At 1 or 2 years after the subject enrolled in the study, pending their last RHC prior to Protocol Amendment 2.

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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in pulmonary vascular resistance for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: dyn.sec/cm^5				
median (full range (min-max))	-52.2 (-573 to 846)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Cardiac Output

End point title	Change from Baseline in Cardiac Output[2]

End point description:

The hemodynamic parameters of pulmonary vascular resistance, cardiac output, cardiac index, and mean pulmonary artery pressure were collected by RHC.

End point type	Primary

End point timeframe:

At 1 or 2 years after the subject enrolled in the study, pending their last RHC prior to Protocol Amendment 2.

Notes:

[2] - 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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in cardiac output for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: L/min				
median (full range (min-max))	0.0 (-2 to 5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Cardiac Index

End point title	Change from Baseline in Cardiac Index[3]

End point description:

The hemodynamic parameters of pulmonary vascular resistance, cardiac output, cardiac index, and mean pulmonary artery pressure were collected by RHC.

End point type	Primary

End point timeframe:

At 1 or 2 years after the subject enrolled in the study, pending their last RHC prior to Protocol Amendment 2.

Notes:

[3] - 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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in cardiac index for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: L/min/m^2				
median (full range (min-max))	0.0 (-1 to 3)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Mean Pulmonary Artery Pressure

End point title	Change from Baseline in Mean Pulmonary Artery Pressure[4]

End point description:

The hemodynamic parameters of pulmonary vascular resistance, cardiac output, cardiac index, and mean pulmonary artery pressure were collected by RHC.

End point type	Primary

End point timeframe:

At 1 or 2 years after the subject enrolled in the study, pending their last RHC prior to Protocol Amendment 2.

Notes:

[4] - 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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in mean pulmonary artery pressure for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: mmHg				
median (full range (min-max))	-2.0 (-23 to 18)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in 6MWD

End point title	Change From Baseline in 6MWD[5]

End point description:

6-Minute Walk Distance (6MWD) was measured at Baseline (prior to starting study drug) and every 3 months thereafter including the End of Study Visit.

End point type	Primary

End point timeframe:

From Baseline to discontinuation of study drug, up to 235 weeks.

Notes:

[5] - 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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in 6MWD for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	45[6]			
Units: meters				
median (full range (min-max))				
Month 3	20.9 (-75 to 115)			
Month 6	17.6 (-118 to 90)			
Month 9	22.8 (-88 to 140)			
Month 12	28.5 (-126 to 138)			

Month 15	16.2 (-91 to 143)			
Month 18	16.0 (-100 to 179)			
Month 21	32.0 (-162 to 175)			
Month 24	41.0 (-111 to 237)			
Month 27	38.5 (-141 to 239)			
Month 30	21.0 (-159 to 267)			
Month 33	17.0 (-80 to 237)			
Month 36	47.0 (-60 to 123)			
Month 39	24.0 (-180 to 105)			
Month 42	53.0 (-162 to 112)			
Month 45	20.5 (-160 to 100)			
Month 48	1.0 (-160 to 57)			
Month 51	-120 (-120 to -120)			
End of Study (Time of Discontinuation of Study)	37.0 (-327 to 170)			

Notes:

[6] - The number of subjects varied from month to month based on total study population at each visit.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in WHO/NYHA FC

End point title	Change From Baseline in WHO/NYHA FC[7]

End point description:

WHO/New York Heart Association (NYHA) Functional Class (FC) was measured at Baseline (prior to starting study drug) and every 3 months thereafter including at the End of Study and 28-Day Follow-up Visits.

End point type	Primary

End point timeframe:

From Baseline to 28 days following discontinuation of study drug, up to 235 weeks.

Notes:

[7] - 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 was an open-label extension study, and all participants in the Safety Population received ralinepag. The presented results show the overall change from baseline in WHO/NYHA FC for the Safety Population.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	45[8]			
Units: Participants				
Month 3 Improved	1			
Month 3 No Change	43			

Month 3 Deteriorated	0			
Month 6 Improved	2			
Month 6 No Change	37			
Month 6 Deteriorated	3			
Month 9 Improved	1			
Month 9 No Change	36			
Month 9 Deteriorated	3			
Month 12 Improved	0			
Month 12 No Change	37			
Month 12 Deteriorated	2			
Month 15 Improved	0			
Month 15 No Change	33			
Month 15 Deteriorated	3			
Month 18 Improved	2			
Month 18 No Change	31			
Month 18 Deteriorated	1			
Month 21 Improved	0			
Month 21 No Change	30			
Month 21 Deteriorated	4			
Month 24 Improved	2			
Month 24 No Change	28			
Month 24 Deteriorated	3			
Month 27 Improved	2			
Month 27 No Change	28			
Month 27 Deteriorated	2			
Month 30 Improved	2			
Month 30 No Change	23			
Month 30 Deteriorated	4			
Month 33 Improved	1			
Month 33 No Change	21			
Month 33 Deteriorated	3			
Month 36 Improved	1			
Month 36 No Change	13			
Month 36 Deteriorated	2			
Month 39 Improved	1			
Month 39 No Change	11			
Month 39 Deteriorated	1			
Month 42 Improved	0			
Month 42 No Change	10			
Month 42 Deteriorated	1			
Month 45 Improved	1			
Month 45 No Change	6			
Month 45 Deteriorated	1			
Month 48 Improved	1			
Month 48 No Change	4			
Month 48 Deteriorated	0			
Month 51 Improved	0			
Month 51 No Change	2			
Month 51 Deteriorated	0			
End of Study (Discontinuation) Improved	2			

End of Study (Discontinuation) No Change	29			
End of Study (Discontinuation) Deteriorated	4			

Notes:

[8] - The number of subjects varied from month to month based on total study population at each visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Randomization to the First Protocol-defined Clinical Worsening Event

End point title	Time From Randomization to the First Protocol-defined Clinical Worsening Event

End point description:

Clinical worsening events were defined as death, or onset of a treatment-emergent AE with a fatal outcome occurring ≤14 days after treatment discontinuation; hospitalization for worsening PAH, heart-lung or lung transplant, or atrial septostomy; necessity of addition (or dose change) of any prostacyclin/prostacyclin analogue, PDE5-I or sGC stimulator, or ERA; and the combined occurrence of a decrease in 6MWD by at least 20% from Baseline, confirmed on two 6-Minute Walk Tests (6MWTs) on different days; worsening in WHO/NYHA FC from baseline; and appearance of or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy.

End point type	Secondary

End point timeframe:

From Baseline to 28 days following discontinuation of study drug, up to 235 weeks.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: weeks				
median (full range (min-max))	56.50 (16.9 to 136.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded for each subject throughout the course of the study from Baseline to 28 days following discontinuation of study drug (up to 235 weeks).

Adverse event reporting additional description:

Monitoring of AEs was continued up to 30 days after cessation of study drug administration. If an AE was not resolved or stabilized within 30 days, the Sponsor in consultation with the Investigator decided whether to continue to monitor the AE or close out the event in the database. SAEs were monitored until resolution or stabilization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 45 (46.67%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer in situ			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pleural effusion				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary infarction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Foot fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia supraventricular				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Atrial flutter			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Right ventricular failure			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 3		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	1 / 45 (2.22%)		
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 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myositis			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Brain abscess			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
COVID-19 pneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Clostridium difficile infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)		
Vascular disorders			
Flushing			
subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	16		
Hypotension			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	8		
Non-cardiac chest pain			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Dyspnoea exertional			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Pulmonary arterial hypertension			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	10		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Palpitations			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Right ventricular failure			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	29 / 45 (64.44%)		
occurrences (all)	60		
Presyncope			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 12		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 4 17 / 45 (37.78%) 27 14 / 45 (31.11%) 25 5 / 45 (11.11%) 7		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 4 / 45 (8.89%) 4		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Pain in jaw	 7 / 45 (15.56%) 8 3 / 45 (6.67%) 3 5 / 45 (11.11%) 6 12 / 45 (26.67%) 23 7 / 45 (15.56%) 13		

subjects affected / exposed occurrences (all)	15 / 45 (33.33%) 20		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 3 3 / 45 (6.67%) 3 4 / 45 (8.89%) 6 4 / 45 (8.89%) 5 3 / 45 (6.67%) 3 5 / 45 (11.11%) 6 4 / 45 (8.89%) 7		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Iron deficiency subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 3 3 / 45 (6.67%) 3 5 / 45 (11.11%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2014	The main changes implemented with this amendment were: • Added ECG assessments to all dose-titration visits (Weeks 1 to 9), to be completed pre-dose and 2 hours post-dose. • Moved clinical laboratory assessments from Weeks 4 and 8 to Weeks 5 and 9 and moved serum pregnancy test from Week 4 to Week 5. • Moved assessment of clinical worsening and WHO/NYHA FC to pre-dose procedures.
09 October 2017	The main changes implemented with this amendment were: • Secondary objectives: modified text explaining criteria for clinical worsening and added hemodynamics as an efficacy endpoint. • Changed treatment time from 6 months to indefinite. Information that incremental dose increases are allowed during the Treatment Period was added. • Added RHC to efficacy assessments.
04 June 2018	The main changes implemented with this amendment were: • Added plan to transition subjects from IR drug formulation to XR drug formulation. • Removed placebo capsule information and instruction, added XR tablet information and instruction. • Added dosing guidance to transition from IR to XR formulation.
15 May 2019	The main changes implemented with this amendment were: • Subjects who remain on ralinepag at study termination and meet all eligibility requirements are able to enroll in the Phase 3 open-label extension study (ROR-PH-303). • Removed stipulation that uptitration of ralinepag should not occur within 6 weeks of an efficacy assessment. • Removed treatment with inotropes for right ventricular failure as a prohibited medication. • Changed requirement for assessing subject mortality status from yearly contact following subject discontinuation from the study to contact of all subjects at the time of study termination. • Changed storage of XR tablet blister cards to 15ºC to 30ºC (59ºF to 86ºF). • Removed 250 and 400 mcg tablets for oral administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38198043