Clinical trial results:
A Randomized, Double-blind, Parallel-group, Placebo-controlled Phase 2 Trial of Ralinepag, an Oral IP Receptor Agonist, in Patients with Pulmonary Arterial Hypertension

Summary

EudraCT number	2014-000667-40
Trial protocol	CZ HU ES PL RO SK
Global end of trial date	22 June 2017

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	APD811-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02279160
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	04 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2017
Global end of trial reached?	Yes
Global end of trial date	22 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of ralinepag on hemodynamics and on 6-Minute Walk Distance (6MWD) in subjects with pulmonary arterial hypertension (PAH) after 22 weeks of treatment, including an initial dose titration period of up to 9 weeks.

Protection of trial subjects:

A Safety Monitoring Committee (SMC) oversaw the safe conduct of the study, and in particular, the SMC monitored dose titration to achieve the optimal dose within the 9-week titration period while maintaining subject safety. Based on review of safety and tolerability information, the SMC was allowed to recommend a higher starting dose, different dose increments and/or time at each dose before escalation (escalation scheme), different dosage strengths, and even a higher final dose level than 0.3 mg twice daily (BID). The roles and responsibilities of the SMC were outlined in a separate charter. The SMC included at least 2 physicians, representing expertise in clinical care of subjects with PAH and expertise in drug development, and a biostatistician.

Background therapy:

Subjects enrolled in the study were on stable oral disease-specific PAH therapy with either an endothelin receptor antagonist (ERA) and/or an agent acting on the nitric oxide (NO) pathway, phosphodiesterase type 5 inhibitor (PDE5-I), or as a soluble guanylate cyclase (sGC) stimulator. Stable was defined as no change in dose within 3 months of the start of screening and for the duration of the study. If the subject's disease-specific PAH therapy did not include a PDE5-I, the use of a PDE5-I as needed for erectile dysfunction (ED) was permitted as long as the subject had not taken a dose within 48 hours of any baseline or study-related efficacy assessment. In addition, the subject must not have taken more than 8 sildenafil tablets, 6 vardenafil tablets, or 4 tadalafil tablets per month for ED. Subjects could have been on one agent active in the NO pathway, either a PDE5-I or a sGC stimulator at a stable dose (but not both).

Evidence for comparator: -

Actual start date of recruitment	08 January 2015
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	Australia: 10
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Czechia: 4

Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	61
EEA total number of subjects	28

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)	57
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 28 study sites in the US, Australia, Poland, Romania, Bulgaria, Serbia, Spain, Hungary, and Czech Republic. Approximately 60 subjects with PAH were planned to be enrolled.

Pre-assignment

Screening details:

The Screening Visit(s) began no more than 28 days prior to randomization. Each subject must have met all of the inclusion criteria and none of the exclusion criteria to have been eligible for enrollment in the study.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The Sponsor, subjects, and personnel involved with the conduct of the study were blinded to the identity of study drug, with the exception of the independent statistician (Novella Clinical LLC) responsible for generating the randomization code and interacting with the SMC. The appearance of the ralinepag and matching placebo capsules was identical. Although the identity of study drug (ralinepag or placebo) was blinded, the dose level was not.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo tablets

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

Dosage and administration details:

Study drug (ie, ralinepag or matching placebo) was supplied as 0.01, 0.02, 0.03, 0.04, and 0.10 mg capsules. Study drug was supplied as liquid-filled, size 4, hard-gelatin capsules. The starting dose was 0.01 mg BID. Dosage was then uptitrated, as tolerated, over the course of a 9-week dose-titration period. The dose was potentially escalated to a maximum total daily dose of 0.6 mg (0.3 mg BID). If the initial ralinepag dose of 0.01 mg BID was not tolerated, the dose was decreased to 0.01 mg once daily (QD). At any time point during the titration phase, if subsequent doses were not tolerated, the ralinepag dose was decreased to the previous dose level.

Arm title	Ralinepag

Arm description:

Ralinepag capsules (oral) 0.01, 0.02, 0.03, 0.04, and 0.10 mg titrated to the individual maximum tolerated dose (maximum dose of 0.6 mg).

Arm type	Experimental

Investigational medicinal product name	Ralinepag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Study drug (ie, ralinepag or matching placebo) was supplied as 0.01, 0.02, 0.03, 0.04, and 0.10 mg capsules. Study drug was supplied as liquid-filled, size 4, hard-gelatin capsules. The starting dose was 0.01 mg BID. Dosage was then uptitrated, as tolerated, over the course of a 9-week dose-titration period. The dose was potentially escalated to a maximum total daily dose of 0.6 mg (0.3 mg BID). If the initial ralinepag dose of 0.01 mg BID was not tolerated, the dose was decreased to 0.01 mg QD. At any time point during the titration phase, if subsequent doses were not tolerated, the ralinepag dose was decreased to the previous dose level.

Number of subjects in period 1	Placebo	Ralinepag
Started	21	40
Completed	21	40

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The Sponsor, subjects, and personnel involved with the conduct of the study were blinded to the identity of study drug, with the exception of the independent statistician (Novella Clinical LLC) responsible for generating the randomization code and interacting with the SMC. The appearance of the ralinepag and matching placebo capsules was identical. Although the identity of study drug (ralinepag or placebo) was blinded, the dose level was not.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo tablets

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

Dosage and administration details:

Study drug (ie, ralinepag or matching placebo) was supplied as 0.01, 0.02, 0.03, 0.04, and 0.10 mg capsules. Study drug was supplied as liquid-filled, size 4, hard-gelatin capsules. The starting dose was

0.01 mg BID. Dosage was then uptitrated, as tolerated, over the course of a 9-week dose-titration period. The dose was potentially escalated to a maximum total daily dose of 0.6 mg (0.3 mg BID). If the initial ralinepag dose of 0.01 mg BID was not tolerated, the dose was decreased to 0.01 mg QD. At any time point during the titration phase, if subsequent doses were not tolerated, the ralinepag dose was decreased to the previous dose level.

Arm title	Ralinepag

Arm description:

Ralinepag capsules (oral) 0.01, 0.02, 0.03, 0.04, and 0.10 mg titrated to the individual maximum tolerated dose (maximum dose of 0.6 mg).

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

Dosage and administration details:

Study drug (ie, ralinepag or matching placebo) was supplied as 0.01, 0.02, 0.03, 0.04, and 0.10 mg capsules. Study drug was supplied as liquid-filled, size 4, hard-gelatin capsules. The starting dose was 0.01 mg BID. Dosage was then uptitrated, as tolerated, over the course of a 9-week dose-titration period. The dose was potentially escalated to a maximum total daily dose of 0.6 mg (0.3 mg BID). If the initial ralinepag dose of 0.01 mg BID was not tolerated, the dose was decreased to 0.01 mg QD. At any time point during the titration phase, if subsequent doses were not tolerated, the ralinepag dose was decreased to the previous dose level.

Number of subjects in period 2	Placebo	Ralinepag
Started	21	40
Completed	19	34
Not completed	2	6
Adverse event, serious fatal	2	-
Physician decision	-	1
Adverse event, non-fatal	-	5

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	61	61	
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)	57	57	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
median	51.0		
full range (min-max)	19 to 73	-	
Gender categorical Units: Subjects			
Female	53	53	
Male	8	8	
Race Units: Subjects			
White	57	57	
Black or African American	1	1	
Asian	1	1	
Other	2	2	
PAH Classification Units: Subjects			
Idiopathic PAH	32	32	
Heritable PAH	5	5	
Drugs or Toxin Induced	4	4	
Associated PAH	20	20	
PAH Disease Specific Concomitant Medication - ERA Units: Subjects			
Yes	42	42	
No	19	19	
PAH Monotherapy or Combination Therapy Units: Subjects			
ERA	6	6	

PDE5-I	19	19	
sGC Stimulator	0	0	
ERA + PDE5-I	34	34	
ERA + sGC Stimulator	2	2	
Baseline WHO/NYHA Functional Classification Units: Subjects			
Class I	0	0	
Class II	34	34	
Class III	26	26	
Class IV	1	1	
PAH Disease Specific Concomitant Medication - PDE5-I Units: Subjects			
Yes	53	53	
No	8	8	
PAH Disease Specific Concomitant Medication - sGC stimulator Units: Subjects			
Yes	2	2	
No	59	59	
Weight Units: kilogram(s)			
median	72.5		
full range (min-max)	43 to 122	-	
Height Units: centimetre			
median	161.0		
full range (min-max)	145 to 182	-	
Body Mass Index Units: kilogram(s)/square metre			
median	27.13		
full range (min-max)	18.1 to 43.8	-	
Duration of PAH Units: year			
median	2.00		
full range (min-max)	0.3 to 27.0	-	
Baseline Pulmonary Vascular Resistance Units: dyn.sec/cm^5			
median	575.70		
full range (min-max)	282.4 to 2119.4	-	
Baseline 6MWT Units: metre			
median	400.0		
full range (min-max)	105 to 686	-	
Baseline BNP Units: pg/mL			
median	58.0		
full range (min-max)	10 to 1359	-	
Baseline NT-proBNP Units: pg/mL			
median	343.0		

full range (min-max)	50 to 8924	-	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All 61 subjects randomized into the study received at least 1 dose of study drug and were included in the Safety Population as part of this report.

Reporting group values	Safety Population		
Number of subjects	61		
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)	57		
From 65-84 years	4		
85 years and over	0		
Age continuous Units: years			
median	51.0		
full range (min-max)	19 to 73		
Gender categorical Units: Subjects			
Female	53		
Male	8		
Race Units: Subjects			
White	57		
Black or African American	1		
Asian	1		
Other	2		
PAH Classification Units: Subjects			
Idiopathic PAH	32		
Heritable PAH	5		
Drugs or Toxin Induced	4		
Associated PAH	20		
PAH Disease Specific Concomitant Medication - ERA Units: Subjects			
Yes	42		
No	19		

PAH Monotherapy or Combination Therapy Units: Subjects			
ERA	6		
PDE5-I	19		
sGC Stimulator	0		
ERA + PDE5-I	34		
ERA + sGC Stimulator	2		
Baseline WHO/NYHA Functional Classification Units: Subjects			
Class I	0		
Class II	34		
Class III	26		
Class IV	1		
PAH Disease Specific Concomitant Medication - PDE5-I Units: Subjects			
Yes	53		
No	8		
PAH Disease Specific Concomitant Medication - sGC stimulator Units: Subjects			
Yes	2		
No	59		
Weight Units: kilogram(s)			
median	72.5		
full range (min-max)	43 to 122		
Height Units: centimetre			
median	161.0		
full range (min-max)	145 to 182		
Body Mass Index Units: kilogram(s)/square metre			
median	27.13		
full range (min-max)	18.1 to 43.8		
Duration of PAH Units: year			
median	2.00		
full range (min-max)	0.3 to 27.0		
Baseline Pulmonary Vascular Resistance Units: dyn.sec/cm^5			
median	575.70		
full range (min-max)	282.4 to 2119.4		
Baseline 6MWT Units: metre			
median	400.0		
full range (min-max)	105 to 686		
Baseline BNP Units: pg/mL			
median	58.0		
full range (min-max)	10 to 1359		

Baseline NT-proBNP Units: pg/mL median full range (min-max)	 343.0 50 to 8924		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets	
Reporting group title	Ralinepag
Reporting group description:	
Ralinepag capsules (oral) 0.01, 0.02, 0.03, 0.04, and 0.10 mg titrated to the individual maximum tolerated dose (maximum dose of 0.6 mg).	

Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets	
Reporting group title	Ralinepag
Reporting group description:	
Ralinepag capsules (oral) 0.01, 0.02, 0.03, 0.04, and 0.10 mg titrated to the individual maximum tolerated dose (maximum dose of 0.6 mg).	

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All 61 subjects randomized into the study received at least 1 dose of study drug and were included in the Safety Population as part of this report.	

Primary: Change from baseline in PVR after 22 weeks of treatment

End point title	Change from baseline in PVR after 22 weeks of treatment
End point description:	

End point type	Primary
End point timeframe:	
Baseline and 22 weeks	

End point values	Placebo	Ralinepag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	34		
Units: dyn.sec/cm^5				
geometric mean (standard deviation)	512.0 (± 1.62)	514.6 (± 1.85)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis of PVR by Point Estimate
Comparison groups	Ralinepag v Placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Multiple imputation
Point estimate	0.742
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.575
upper limit	0.958

Notes:

[1] - GMR of PVR at Week 22 over Baseline comparing Ralinepag arm over Placebo arm.

Primary: Change from baseline in 6MWD after 22 weeks of treatment

End point title	Change from baseline in 6MWD after 22 weeks of treatment

End point description:

End point type	Primary

End point timeframe:

Baseline and 22 weeks

End point values	Placebo	Ralinepag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	38		
Units: meters				
least squares mean (standard error)	29.4 (± 16.16)	36.2 (± 11.79)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis of 6MWD
Comparison groups	Placebo v Ralinepag
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9002
Method	Stratified Wilcoxon
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	30

Secondary: Percent change from baseline in PVR after 22 weeks of treatment

End point title	Percent change from baseline in PVR after 22 weeks of treatment

End point description:

End point type	Secondary

End point timeframe:

Baseline to 22 weeks

End point values	Placebo	Ralinepag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: percent				
arithmetic mean (standard deviation)	12.1 (± 50.98)	-19.7 (± 29.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who progress to clinical worsening

End point title	Proportion of subjects who progress to clinical worsening

End point description:

End point type	Secondary

End point timeframe:

Baseline to 22 weeks

End point values	Placebo	Ralinepag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	40		
Units: percent				
number (confidence interval 95%)	2 (1.2 to 30.4)	1 (0.1 to 13.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed from the time the subject provided informed consent through the duration of the study (22 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo tablets

Reporting group title	Ralinepag

Reporting group description:

Ralinepag capsules (oral) 0.01, 0.02, 0.03, 0.04, and 0.10 mg titrated to the individual maximum tolerated dose (maximum dose of 0.6 mg).

Serious adverse events	Placebo	Ralinepag	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	4 / 40 (10.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypovolaemic shock			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 21 (4.76%)	0 / 40 (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: 5 %

Non-serious adverse events	Placebo	Ralinepag	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)	40 / 40 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 21 (4.76%)	13 / 40 (32.50%)	
occurrences (all)	5	18	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 21 (28.57%)	31 / 40 (77.50%)	
occurrences (all)	7	67	
Dizziness			
subjects affected / exposed	3 / 21 (14.29%)	7 / 40 (17.50%)	
occurrences (all)	3	11	
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 21 (4.76%)	6 / 40 (15.00%)	
occurrences (all)	2	8	
Asthenia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	5	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	5 / 21 (23.81%)	20 / 40 (50.00%)	
occurrences (all)	9	35	
Diarrhoea			
subjects affected / exposed	3 / 21 (14.29%)	19 / 40 (47.50%)	
occurrences (all)	5	32	
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	10 / 40 (25.00%)	
occurrences (all)	5	14	
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	7 / 40 (17.50%)	
occurrences (all)	0	10	
Abdominal pain upper			
subjects affected / exposed	1 / 21 (4.76%)	4 / 40 (10.00%)	
occurrences (all)	1	9	
Abdominal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	3 / 40 (7.50%)	
occurrences (all)	1	4	
Cough			
subjects affected / exposed	0 / 21 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	3 / 21 (14.29%)	14 / 40 (35.00%)	
occurrences (all)	4	18	
Myalgia			
subjects affected / exposed	1 / 21 (4.76%)	11 / 40 (27.50%)	
occurrences (all)	1	20	
Pain in extremity			

subjects affected / exposed	1 / 21 (4.76%)	7 / 40 (17.50%)	
occurrences (all)	1	13	
Neck pain			
subjects affected / exposed	0 / 21 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Muscle spasms			
subjects affected / exposed	2 / 21 (9.52%)	3 / 40 (7.50%)	
occurrences (all)	4	5	
Musculoskeletal pain			
subjects affected / exposed	0 / 21 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 21 (14.29%)	3 / 40 (7.50%)	
occurrences (all)	3	5	
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Arthralgia			
subjects affected / exposed	1 / 21 (4.76%)	5 / 40 (12.50%)	
occurrences (all)	4	14	
Decreased appetite			
subjects affected / exposed	0 / 21 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2014	The main changes to the protocol were as follows: • Removed Part A, open-label pilot study. • Revised study objectives, endpoints and analyses to reflect changes after Part A removal and to include a 22-week randomized, double-blind, treatment period. • Revised primary endpoint to include co-primary endpoint (6MWD). • Revised secondary and exploratory endpoints to include, but not be limited to, the effect on clinical worsening and assessment of WHO/NYHA functional class. • Reduced subject enrollment size from approximately 80 subjects total (Part A and Part B) to approximately 60 total enrolled. • Revised duration of study to include 3±1 week follow-up transition period to OLE Study APD811-007. • Revised end-of-study and exit visits to accommodate transition to OLE study while still allowing the Week 25 Follow-up Visit to serve as the Baseline Visit for the OLE study. • Removed 3x weekly visits with 6-hour postdose safety assessments and observation at 6 weeks of dose titration to 1x weekly visits with 4-hour postdose safety assessments and observation at 9 weeks, in-clinic titration. • Added the following assessments: VQ scan, echocardiogram, and optional DNA sample. • Revised storage and handling conditions for study material "bottles should be stored at room temperature (approximately 15ºC - 30ºC)" to "under refrigeration at 2ºC (36ºF) to 8ºC (46ºF)".
15 August 2014	The main changes to the protocol were as follows: • Added ECG assessments to all dose-titration period visits (Weeks 1 through 9), to be completed predose and 2 hours postdose. • Corrected requirement for 6MWD distance at screening. – Previously: "Has a 6MWT distance of ≥50 meters and ≤500 meters, and within 15% of each other on 2 consecutive tests on different days during screening". – Corrected: "Has a 6MWT distance of ≥100 meters and ≤500 meters, and within 15% of each other on 2 consecutive tests on different days during screening". • Removed exclusion criteria of positive drug test at screening and added collection of history of alcohol or substance (drug/solvent) abuse per exclusion #21.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported