Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Ralinepag to Evaluate Safety and Effects on Exercise Capacity Assessed by Cardiopulmonary Exercise Testing in Subjects with World Health Organization Group 1 Pulmonary Hypertension Who Recently Initiated Therapy

Summary

EudraCT number	2019-003309-88
Trial protocol	GB AT DE ES PL BE IT PT
Global end of trial date	12 April 2023

Results information

Result version number	v1 (current)
This version publication date	28 June 2024
First version publication date	28 June 2024

Trial information

Trial identification

Sponsor protocol code	ROR-PH-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04084678
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 109021

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	12 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2023
Global end of trial reached?	Yes
Global end of trial date	12 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of ralinepag therapy on exercise capacity as assessed by change in peak oxygen consumption (VO2) derived from cardiopulmonary exercise testing (CPET) after 28 weeks of treatment

Protection of trial subjects:

The study was conducted per the Declaration of Helsinki and sites were well-trained on the CPET procedures. The study protocol was approved by each site's IRB/IEC. Additionally, subjects were monitored continuously by ECG throughout the CPET testing and could request to terminate the exercise testing at any time.

Background therapy:

Subjects could be treated with either 1 or 2 approved background PAH-specific therapies

Evidence for comparator: -

Actual start date of recruitment	20 January 2021
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: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	10
EEA total number of subjects	4

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)	7
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was discontinued by the Sponsor on 27 February 2023 due to slow enrollment. This decision was not related to reasons of safety or efficacy. The study was planned for 50 centers; however, only 9 study centers randomized a total of 10 subjects in Australia, Brazil, Germany, Spain, Italy, and the United States.

Pre-assignment

Screening details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo tablets (oral)

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

Dosage and administration details:

The study drug (ie, ralinepag or matching placebo) was supplied as 50, 250, and 400 mcg tablets for oral administration. The starting dose of study drug was 50 mcg once daily for 1 week. Up titration of study drug occurred in 50-mcg increments each week up to a dose of 1400 mcg once daily or until the individual maximum tolerated dose was achieved. The dose of study drug was not titrated in the 7 days prior to Week 28.

Arm title	Ralinepag

Arm description:

Ralinepag once daily extended-release tablets (oral) 50, 250, and 400 mcg titrated to the individual maximum tolerated dose (maximum dose of 1400 mcg)

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

Dosage and administration details:

The study drug (ie, ralinepag or matching placebo) was supplied as 50, 250, and 400 mcg tablets for oral administration. The starting dose of study drug was 50 mcg once daily for 1 week. Up titration of study drug occurred in 50-mcg increments each week up to a dose of 1400 mcg once daily or until the individual maximum tolerated dose was achieved. The dose of study drug was not titrated in the 7 days prior to Week 28.

Number of subjects in period 1	Placebo	Ralinepag
Started	2	8
Completed	2	8

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo tablets (oral)

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

Dosage and administration details:

The study drug (ie, ralinepag or matching placebo) was supplied as 50, 250, and 400 mcg tablets for oral administration. The starting dose of study drug was 50 mcg once daily for 1 week. Up titration of study drug occurred in 50-mcg increments each week up to a dose of 1400 mcg once daily or until the individual maximum tolerated dose was achieved. The dose of study drug was not titrated in the 7 days prior to Week 28.

Arm title	Ralinepag

Arm description:

Ralinepag once daily extended-release tablets (oral) 50, 250, and 400 mcg titrated to the individual maximum tolerated dose (maximum dose of 1400 mcg)

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

Dosage and administration details:

The study drug (ie, ralinepag or matching placebo) was supplied as 50, 250, and 400 mcg tablets for oral administration. The starting dose of study drug was 50 mcg once daily for 1 week. Up titration of study drug occurred in 50-mcg increments each week up to a dose of 1400 mcg once daily or until the

individual maximum tolerated dose was achieved. The dose of study drug was not titrated in the 7 days prior to Week 28.

Number of subjects in period 2	Placebo	Ralinepag
Started	2	8
Completed	2	2
Not completed	0	6
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
Study Terminated by Sponsor	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets (oral)	
Reporting group title	Ralinepag
Reporting group description:	
Ralinepag once daily extended-release tablets (oral) 50, 250, and 400 mcg titrated to the individual maximum tolerated dose (maximum dose of 1400 mcg)	

Reporting group values	Placebo	Ralinepag	Total
Number of subjects	2	8	10
Age categorical			
Units: Subjects			
Adults (18-64 years)	2	5	7
From 65-84 years	0	3	3
Age continuous			
Units: years			
median	45.0	59.0	
full range (min-max)	39 to 51	25 to 75	-
Gender categorical			
Units: Subjects			
Female	2	7	9
Male	0	1	1
Race			
Units: Subjects			
White	2	6	8
Black or African American	0	1	1
Multiple	0	1	1
Weight at Baseline			
Units: kilograms			
median	68.75	72.0	
full range (min-max)	57.1 to 80.4	56.8 to 88.0	-
Height at Baseline			
Units: centimeters			
median	157	165.5	
full range (min-max)	156 to 158	151 to 174	-
BMI at Baseline			
Units: kilograms/meters squared			
median	27.4	26.95	
full range (min-max)	22.7 to 32.1	20.3 to 37.0	-

Subject analysis sets	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All 10 subjects randomized into the study received at least 1 dose of study drug and were included in	

Reporting group values	Safety Population		
Number of subjects	10		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	3		
Age continuous Units: years			
median	53.0		
full range (min-max)	25 to 75		
Gender categorical Units: Subjects			
Female	9		
Male	1		
Race Units: Subjects			
White	8		
Black or African American	1		
Multiple	1		
Weight at Baseline Units: kilograms			
median	72.80		
full range (min-max)	56.8 to 88.0		
Height at Baseline Units: centimeters			
median	161.5		
full range (min-max)	151 to 174		
BMI at Baseline Units: kilograms/meters squared			
median	26.95		
full range (min-max)	20.3 to 37.0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo tablets (oral)	
Reporting group title	Ralinepag
Reporting group description: Ralinepag once daily extended-release tablets (oral) 50, 250, and 400 mcg titrated to the individual maximum tolerated dose (maximum dose of 1400 mcg)	
Reporting group title	Placebo
Reporting group description: Matching placebo tablets (oral)	
Reporting group title	Ralinepag
Reporting group description: Ralinepag once daily extended-release tablets (oral) 50, 250, and 400 mcg titrated to the individual maximum tolerated dose (maximum dose of 1400 mcg)	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All 10 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: Comparison of reported AEs

End point title	Comparison of reported AEs[1]
End point description: Due to the early termination of the study, efficacy results were not summarized or discussed in the final abbreviated clinical study report. Safety event results were reported as the primary study result.	
End point type	Primary
End point timeframe: Baseline to 28 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety events were not analyzed statistically. Event totals in each treatment group were used for comparison.

End point values	Placebo	Ralinepag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	8		
Units: Events				
AEs	3	77		
Treatment-related AEs	1	70		
AEs leading to discontinuation of study drug	0	2		
SAEs	0	1		
Treatment-related SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were instructed that they may report AEs at any time. AEs should be reported beyond this period if per the Investigator, they are considered possibly or probably related to the study drug.

Adverse event reporting additional description:

Monitoring of nonserious AEs will be continued to 28 days after the last dose of study drug or until the 28-day Follow-up Visit, whichever is later. In the event that a nonserious AE is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Ralinepag
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Ralinepag	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Submandibular abscess			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (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: 0 %

Non-serious adverse events	Ralinepag	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	2 / 2 (100.00%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

Heart rate decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 8 (87.50%)	0 / 2 (0.00%)	
occurrences (all)	14	0	
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo positional			

subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 8 (75.00%)	0 / 2 (0.00%)	
occurrences (all)	9	0	
Nausea			
subjects affected / exposed	4 / 8 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	7	0	
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	
occurrences (all)	11	0	
Pain in jaw			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	
occurrences (all)	7	0	
Arthralgia			

subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
Muscle spasms			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Submandibular abscess			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2021	• Clarified that when a Study Drug Termination Visit occurred close in time to the next regular visit, the Study Drug Termination Visit could take the place of the next regularly scheduled visit. • Clarified CPET procedures and variables and the scope of the CPET core laboratory. • Added details around the full physical examination. • Removed echocardiogram as a required assessment. • Added CD4+ test to list of laboratory tests. • Added language to ensure subjects were not excluded due to a positive drug screen caused by prescription medication. • Changed timeframe of diagnostic right heart catheterization from 1 to 3 years before Screening. • Removed time restriction of ventilation-perfusion lung scan. • Updated number of centers to "50 to 60". • Updated inclusion criterion for stable dose(s) of PAH-specific oral therapy to be defined as no change in dose or regimen for at least 120 days prior to Randomization. • Added that eligible male subjects must agree not to participate in sperm donation for 90 days after the last dose of study drug, and changed the timeframe for the prohibition on conception from 28 to 30 days. • Removed current unstable angina as an exclusion criterion. • Updated chronic renal insufficiency to be defined using estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study equation instead of creatinine. • Updated exclusion criterion timeframe for diagnosed and/or treated malignancy from within 5 to 3 years of Screening. • Added clarification around how to deal with contact between scheduled clinic visits (timing of calls, what to do after Week 16, etc). • Added description that the Investigator would attempt to discuss unblinding with the Sponsor prior to unblinding. • Removed electrocardiogram response to exercise and duration of exercise from additional endpoints.

29 November 2022	• Aligned definition of PAH and risk categories with current European Society of Cardiology/European Respiratory Society guidelines. • Changed pulmonary vascular resistance requirement from ≥3 (240 dynes/sec/cm5) to >2 (160 dynes/sec/cm5) Wood units. • Clarified that the study would end when all subjects completed their final study visit. • Clarified that subjects did not need to have newly initiated therapy to be eligible. • Added that subjects must have completed ROR-PH-302 on study drug to be eligible for the OLE study. • Removed limitation of only 1 re-test for re-screened subjects. • Clarified that subjects who discontinued study drug after Week 24 would attend the Follow-up Visit. • Removed specifics for biological quality control test timing from protocol. • Clarified that only 1 CPET was required prior to randomization. • Clarified that electrocardiograms were recorded in triplicate using a device provided by the Sponsor unless not allowed by local regulations. • Clarified AE collection procedures. Updated nonserious AE monitoring procedures. • Revised urine human chorionic gonadotropin analysis for females of childbearing potential instead of only postmenopausal females. • Revised the requirement for stable doses of PAH-specific oral therapy prior to randomization from 120 days to 90 days. • Removed VE/VCO2 slope requirement for study entry. • Amended required peak VO2 from ≥10 to ≥9 mL/min/kg (upper limit remained <18 mL/min/kg). • Removed requirement for dosage of concomitant medications to remain unchanged throughout the study. • Updated exclusion criteria to allow prostacyclin pathway agents for PAH within 90 days of randomization. • Clarified that PAH-specific medications are not to be added or changed during the study. • Added that if study was terminated early for safety reasons, the Sponsor would inform regulatory authorities without delay in accordance with local reporting requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported