Clinical trial results:
An open-label extension of BPS-MR-PAH-203 in pulmonary arterial hypertension (PAH) patients

Summary

EudraCT number	2009-014453-32
Trial protocol	BE IE DE CZ
Global end of trial date	26 November 2013

Results information

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

Trial information

Trial identification

Sponsor protocol code	BPS-MR-PAH-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00990314
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lung Biotechnology PBC
Sponsor organisation address	1040 Spring Street, Silver Spring, United States, 20910
Public contact	Lung Biotechnology PBC Study Director, Lung Biotechnology PBC, +1 3016089292,
Scientific contact	Lung Biotechnology PBC Study Director, Lung Biotechnology PBC, +1 3016089292,

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	27 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is an open-label study for patients who participated in the BPS-MR-PAH-203 study and have volunteered to continue treatment for PAH with Beraprost Sodium Modified Release (BPS-MR) tablets.

Protection of trial subjects:

The study was conducted in accordance with U.S. 21 CFR Parts 50, 56, and 312 and in accordance with the Declaration of Helsinki.

Background therapy:

Patients on background therapy (ERA alone, PDE-5 inhibitor alone, and ERA and PDE-5 inhibitor) were combined for the analysis.

Evidence for comparator: -

Actual start date of recruitment	05 May 2010
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	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	31
EEA total number of subjects	16

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)	27

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label study for subjects who participated in the BPS-MR-PAH-203 study and volunteered to continue treatment for PAH with BPS-MR tablets.

Pre-assignment

Screening details:

A Protocol Amendment was to include an optional arm investigating Beraprost Sodium Modified Release Tablets administered four times daily (QID), however, no subjects were enrolled into this arm.

Period 1

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

Arms

Arm title	Beraprost Sodium

Arm description:

Beraprost Sodium Modified Release Tablet, 60 micrograms(mcg), twice a day dosing

Arm type	Experimental
Investigational medicinal product name	Beraprost Sodium Modified Release Tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

60 mcg twice a day

Number of subjects in period 1	Beraprost Sodium
Started	31
Completed	19
Not completed	12
Adverse event, serious fatal	2
Consent withdrawn by subject	3
Non-Compliance	1
Physician decision	3
Adverse event, non-fatal	2
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Beraprost Sodium
Reporting group description:	
Beraprost Sodium Modified Release Tablet, 60 micrograms(mcg), twice a day dosing	

Reporting group values	Beraprost Sodium	Total	
Number of subjects	31	31	
Age categorical			
Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
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)	27	27	
From 65-84 years	4	4	
85 years and over	0	0	
Age Continuous			
Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: years			
arithmetic mean	46.5		
standard deviation	± 14.16	-	
Sex: Female, Male			
Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: Subjects			
Female	26	26	
Male	5	5	
Race (NIH/OMB)			
Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	30	30	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	27	27	
Unknown or Not Reported	0	0	

Six-Minute Walk Distance			
Area used for the Six Minute Walk Test (6MWT) was 30 meters in length. Rest periods were allowed if patient could no longer continue. If patient needed to rest, he could stand or sit and then begin again when rested but the clock continued to run. For purposes of the 6MWT, if patient was assessed at Baseline w/ oxygen therapy, all 6MWT were conducted in the same manner. All efficacy results are descriptive; no statistical analysis was conducted. Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: meters			
arithmetic mean	360.7		
standard deviation	± 78.0	-	
Borg Dyspnea Score			
Modified 0–10 Borg scale consists of 11-point rating level of dyspnea during the 6MWT. Scores range from 0 (best) and 10 (worst) with spacing of verbal descriptors of severity corresponding to specific numbers. Number or verbal descriptor to reflect presumed ratio properties of sensation/intensity. Only subjects w/ both a measurement at baseline and given visit are presented. Efficacy results are descriptive; no statistical analysis conducted. Baseline characteristics were defined at the baseline visit of the lead-in study, BPS-MR-PAH-203.			
Units: score			
arithmetic mean	3.2		
standard deviation	± 1.97	-	

End points

End points reporting groups

Reporting group title	Beraprost Sodium

Reporting group description:

Beraprost Sodium Modified Release Tablet, 60 micrograms(mcg), twice a day dosing

Primary: Number of Subjects Reporting at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Subjects Reporting at Least One Treatment-Emergent Adverse Event (TEAE)[1]

End point description:

A treatment-emergent adverse event (TEAE) is defined as an event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment. AEs occurring more than 3 days after the last day study drug was taken in the study was not included in the statistical analyses or summaries (except for subjects with adverse events leading to study drug withdrawn). Only TEAEs that occurred during the treatment period of the BPS-MR-PAH-204 study were summarized. Any adverse event starting prior to the first dose of study drug was excluded from the summary analyses and only presented in the data listings. All efficacy results are descriptive; no statistical analysis was conducted

End point type	Primary

End point timeframe:

Up to 42 months

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: subjects	27			

Statistical analyses

No statistical analyses for this end point

Primary: Number of reported Treatment-Emergent Adverse Events

End point title	Number of reported Treatment-Emergent Adverse Events[2]

End point description:

A treatment-emergent adverse event (TEAE) is defined as an event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment. AEs occurring more than 3 days after the last day study drug was taken in the study was not included in the statistical analyses or summaries (except for subjects with adverse events leading to study drug withdrawn). Only TEAEs that occurred during the treatment period of the BPS-MR-PAH-204 study were summarized. Any adverse event starting prior to the first dose of study drug was excluded from the summary analyses and only presented in the data listings. All efficacy results are descriptive; no statistical analysis was conducted.

End point type	Primary

End point timeframe:

Up to 42 months

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: TEAEs	230			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Six-Minute-Walk Distance (6MWD)

End point title	Change in Six-Minute-Walk Distance (6MWD)

End point description:

Area used for the Six Minute Walk Test (6MWT) was pre-measured at 30 meters in length. Rest periods were allowed if patient could no longer continue. If patient needed to rest, he/she could stand or sit and then begin again when rested but the clock continued to run. At the end of 6 minutes, the tester called "stop" while stopping the watch and then measured the distance walked. For purposes of the 6MWT, if patient was assessed at Baseline using oxygen therapy, all future 6MWT were conducted in the same manner. All efficacy results are descriptive; no statistical analysis was conducted.

End point type	Secondary

End point timeframe:

Baseline and 42 months

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: meters				
arithmetic mean (standard deviation)	24.09 (± 81.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Borg Dyspnea Score

End point title	Change in Borg Dyspnea Score

End point description:

The modified 0–10 category-ratio Borg scale consists of an 11-point scale rating the maximum level of

dyspnea experienced during the 6MWT. Scores range from 0 (for the best condition) and 10 (for the worst condition) with nonlinear spacing of verbal descriptors of severity corresponding to specific numbers. The participant chose the number or the verbal descriptor to reflect presumed ratio properties of sensation or symptom intensity. Baseline was defined as the last non-missing evaluation preceding the first dose of study drug in study BPS-MR-PAH-203. Only subjects with both a measurement at baseline and at the given visit are presented. All efficacy results are descriptive; no statistical analysis was conducted.

End point type	Secondary

End point timeframe:

Baseline and 42 months

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: scores on a scale				
arithmetic mean (standard deviation)	0.86 (± 1.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects that experienced Clinical Worsening

End point title	Number of subjects that experienced Clinical Worsening

End point description:

Number of subjects that experienced Clinical Worsening in the opinion of the Investigator. Clinical Worsening was defined as any of these events following the Baseline visit: Death, Transplantation or atrial septostomy, Clinical deterioration as defined by: Hospitalization as a result of PAH symptoms or Initiation of any new PAH specific therapy (e.g. ERA, PDE-5 inhibitor, prostanoid). All efficacy results are descriptive; no statistical analysis was conducted.

End point type	Secondary

End point timeframe:

Up to 42 months

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: subjects				
Death	1			
Hospitalization As A Result of PAH Symptoms	2			
New PAH Therapies	4			
Transplantation or atrial septostomy	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects With a Change in WHO Functional Class

End point title	Number of subjects With a Change in WHO Functional Class

End point description:

Change from Baseline in participant clinical status was recorded according to the World Health Organization (WHO) Functional Class. A change from lower to higher functional class (i.e. 'III to IV' or 'II to III') was considered as a deterioration. A change from higher to lower functional class (i.e. 'III to II' or 'II to I') was considered as an improvement. All efficacy results are descriptive; no statistical analysis was conducted.

End point type	Secondary

End point timeframe:

Baseline and 42 months

End point values	Beraprost Sodium			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: subjects				
Improved: Change from Class II to Class I	2			
Improved: Change from Class III to Class II	7			
Deteriorated: Change from Class II to Class III	5			
Deteriorated: Change from Class III to Class IV	1			
No Change in Class	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to 30 days after study treatment discontinuation, up to 42 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Beraprost Sodium

Reporting group description:

Beraprost Sodium Modified Release Tablet, 60 micrograms(mcg), twice a day dosing

Serious adverse events	Beraprost Sodium		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 31 (35.48%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 2		
Right ventricular failure			

subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial flutter				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 2			
General disorders and administration site conditions				
Edema peripheral				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Inguinal hernia				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Worsening pulmonary arterial hypertension				

subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Varicella			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Beraprost Sodium		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 31 (83.87%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Carbon dioxide decreased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Neutrophil count increased			

subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Urine analysis abnormal subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
White blood cell count increased subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Brain natriuretic peptide increased subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 6		
Hypotension subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Hot flush subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 5		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	10 / 31 (32.26%) 22		
Dizziness subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 8		
Somnolence subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Syncope			

subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Chest Pain subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all)	 5 / 31 (16.13%) 5 2 / 31 (6.45%) 2 2 / 31 (6.45%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 9 / 31 (29.03%) 9 7 / 31 (22.58%) 13 2 / 31 (6.45%) 2		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 3 / 31 (9.68%) 3 2 / 31 (6.45%) 3 2 / 31 (6.45%) 2		

Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Tooth abscess subjects affected / exposed occurrences (all)	 4 / 31 (12.90%) 5 2 / 31 (6.45%) 3 3 / 31 (9.68%) 3 2 / 31 (6.45%) 2		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 3 / 31 (9.68%) 3 2 / 31 (6.45%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2011	Amendment 1 dated 13 October 2011 (USA, Belgium, Romania): Revised to extend the calendar end date to allow ongoing subjects to continue to receive BPS-MR until 31 December 2013 or Lung LLC discontinues the project. A further administrative revision was applied to reflect the change of the Sponsor name from Lung Rx to Lung LLC.
25 June 2012	Amendment 2 dated 25 June 2012 (USA, Belgium, Romania): Revised to include an optional substudy investigating the safety, tolerability, and pharmacokinetics of BPS-MR tablets administered four times daily (QID). An additional revision was applied to extend the calendar end date to allow ongoing subjects to receive BPS-MR until 31 December 2014 or Lung LLC discontinues the project. Revisions were made to update the status of recently completed studies

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported