Clinical trial results:
A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects with Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy

Summary

EudraCT number	2012-000097-26
Trial protocol	GB DE AT NL IT SE BE DK GR PL
Global end of trial date	24 June 2018

Results information

Result version number	v1 (current)
This version publication date	19 December 2019
First version publication date	19 December 2019

Trial information

Trial identification

Sponsor protocol code	TDE-PH-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01560624
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corporation
Sponsor organisation address	55 TW Alexander Drive, Research Triangle Park, United States, 27709
Public contact	Rob Grover, United Therapeutics Corporation, 0044 01932573805, rgrover@unither.com
Scientific contact	Rob Grover, United Therapeutics Corporation, 0044 01932573805, rgrover@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	03 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2018
Global end of trial reached?	Yes
Global end of trial date	24 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the effect of oral UT-15C (oral treprostinil) with PAH-approved oral monotherapy compared to placebo with PAH-approved oral monotherapy on time to first adjudicated clinical worsening (morbidity/mortality) event, as defined by at least 1 of the following events: death (all causes), hospitalization due to worsening PAH, initiation of an inhaled or infused prostacyclin for the treatment of worsening PAH, disease progression, or unsatisfactory long-term clinical response.
2. To assess the effect of oral treprostinil with PAH-approved oral monotherapy compared to placebo combined with PAH-approved oral monotherapy on 6-Minute Walk Distance (6MWD), plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), combined 6MWD/Borg dyspnea score, exercise capacity as assessed by 6MWD, Borg dyspnea score, World Health Organization (WHO) Functional Class (FC), right heart catheterization (RHC) hemodynamics, and safety parameters.

Protection of trial subjects:

Subjects could have voluntarily withdrawn or been withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following: the subject wished to withdraw from further participation, a serious or life-threatening AE occurred or the Investigator considered that it was necessary to discontinue study drug to protect the safety of the subject, the subject violated the protocol, the subject’s behavior was likely to undermine the validity of his/her results, the subject experienced clinical worsening, or the subject became pregnant.

In addition, the dose and frequency of background PAH-approved oral monotherapy were not to be reduced during the study, unless changes were considered medically necessary to protect the safety of the subject.

Background therapy:

All subjects must have been treated with 1 PAH-approved oral monotherapy (eg, sildenafil, tadalafil, bosentan, ambrisentan, macitentan, riociguat, etc) for at least 30 days prior to randomization and stabilized on the same dose for at least 10 days prior to randomization.

Evidence for comparator: -

Actual start date of recruitment	26 July 2012
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	Netherlands: 4
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 41

Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	Brazil: 53
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Mexico: 95
Country: Number of subjects enrolled	India: 62
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	China: 166
Country: Number of subjects enrolled	Denmark: 4
Worldwide total number of subjects	690
EEA total number of subjects	89

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)	586
From 65 to 84 years	104
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study recruitment was between 26 June 2012 and 24 June 2018. 690 subjects were recruited from the following geographic regions: North America, Asia-Pacific, Europe, South America, and Latin America.

Pre-assignment

Screening details:

Key criteria for inclusion were: 18 to 75 years of age, diagnosis of symptomatic idiopathic or heritable PAH or PAH associated with connective tissue disease, human immunodeficiency virus infection, repaired congenital systemic-to-pulmonary shunt, or appetite suppressant or toxin use.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	UT-15C

Arm description:

Oral treprostinil

Arm type	Experimental
Investigational medicinal product name	UT-15C
Investigational medicinal product code	
Other name	oral treprostinil, treprostinil diolamine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects remained on their pre-randomization dose of background oral PAH monotherapy for the duration of the study and were administered oral treprostinil 3 times daily (TID) with food. Subjects received oral treprostinil as 0.125, 0.25, 0.5, 1, or 2.5 mg extended-release tablets (maximum dose 12 mg TID).

Arm title	Placebo

Arm description:

Placebo

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:

Subjects remained on their pre-randomization dose of background oral PAH monotherapy for the duration of the study and were administered placebo 3 times daily (TID) with food.

Number of subjects in period 1	UT-15C	Placebo
Started	346	344
Completed	346	344

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, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	UT-15C

Arm description:

Oral treprostinil

Arm type	Experimental
Investigational medicinal product name	UT-15C
Investigational medicinal product code	
Other name	oral treprostinil, treprostinil diolamine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects remained on their pre-randomization dose of background oral PAH monotherapy for the duration of the study and were administered oral treprostinil 3 times daily (TID) with food. Subjects received oral treprostinil as 0.125, 0.25, 0.5, 1, or 2.5 mg extended-release tablets (maximum dose 12 mg TID).

Arm title	Placebo

Arm description:

Placebo

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:

Subjects remained on their pre-randomization dose of background oral PAH monotherapy for the duration of the study and were administered placebo 3 times daily (TID) with food.

Number of subjects in period 2	UT-15C	Placebo
Started	346	344
Completed	0	0
Not completed	346	344
Clinical worsening event including death	91	133
Early Discontinuation	107	56
Completed without clinical worsening	148	155

Baseline characteristics

Reporting groups	
Reporting group title	UT-15C
Reporting group description: Oral treprostinil	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	UT-15C	Placebo	Total
Number of subjects	346	344	690
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	292	294	586
From 65-84 years	54	50	104
85 years and over	0	0	0
Age continuous Units: years			
median	44.0	42.0	
full range (min-max)	18 to 76	18 to 75	-
Gender categorical Units: Subjects			
Female	275	269	544
Male	71	75	146
Ethnicity Units: Subjects			
Hispanic or Latino	92	88	180
Not Hispanic or Latino	253	255	508
Missing	1	1	2
Race Units: Subjects			
White	187	173	360
Black or African American	8	13	21
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	150	156	306
Unknown	1	2	3
Etiology of PAH Units: Subjects			
Idiopathic or Heritable	219	216	435

Collagen Vascular Disease	94	84	178
HIV Infection	2	7	9
Other	11	10	21
Congenital Heart Defect	20	27	47
Background PAH Therapy at Baseline Units: Subjects			
ERA Alone	98	98	196
PDE5-I Alone or sGC Alone	248	246	494
6MWD at Baseline Category Units: Subjects			
<= 350 m	95	93	188
>350 m	251	251	502
WHO Functional Class at Baseline Category Units: Subjects			
Class I	9	13	22
Class II	205	228	433
Class III	131	103	234
Class IV	1	0	1
Time since PAH Diagnosis Units: years			
median	0.52	0.55	
full range (min-max)	0.0 to 17.9	0.0 to 22.3	-
6MWD at Baseline Units: meters			
median	400.5	410.0	
full range (min-max)	150 to 714	154 to 648	-

End points

End points reporting groups	
Reporting group title	UT-15C
Reporting group description: Oral treprostinil	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	UT-15C
Reporting group description: Oral treprostinil	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Time to Clinical Worsening	
End point title	Time to Clinical Worsening
End point description:	
End point type	Primary
End point timeframe: This is an event-based study; therefore, the duration of the study is dependent on the occurrence of the number of protocol-specified events. There was no prespecified timeframe.	

End point values	UT-15C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	344		
Units: weeks				
median (full range (min-max))	45.55 (4.4 to 195.4)	36.60 (0.3 to 205.7)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Estimates
Comparison groups	UT-15C v Placebo
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0391 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.97

Notes:

[1] - p-value is calculated with Logrank test stratified by background PAH therapy and baseline 6MWD category

Secondary: Change from Baseline in 6MWD at Week 24

End point title	Change from Baseline in 6MWD at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	UT-15C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	344		
Units: meters				
median (full range (min-max))	8.0 (-589 to 261)	7.0 (-597 to 538)		

Statistical analyses

Statistical analysis title	Mixed Model Repeated Measurement
Comparison groups	UT-15C v Placebo
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1169
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	7.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	17.92

Statistical analysis title	Nonparametric Analysis of Covariance

Statistical analysis description:

Nonparametric ANCOVA adjusted for PAH background therapy and baseline 6MWD measurement

Comparison groups	UT-15C v Placebo
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0913
Method	Nonparametric ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	16

Notes:

[2] - Hodges-Lehmann Estimation

Secondary: Change from Baseline in NT-proBNP at Week 24

End point title	Change from Baseline in NT-proBNP at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	UT-15C	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	344		
Units: pg/mL				
median (full range (min-max))	-49.10 (-5864.7 to 84055.0)	14.65 (-9822.6 to 31675.0)		

Statistical analyses

Statistical analysis title	Analysis of Covariance

Statistical analysis description:

The analysis of covariance with change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as fixed effect, and log-transformed baseline NT-proBNP as a covariate.

Comparison groups	UT-15C v Placebo
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference in Ratio
Point estimate	0.6998

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6037
upper limit	0.8112
Variability estimate	Standard error of the mean
Dispersion value	1.07809

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the informed consent form was signed to the end of the study.

Adverse event reporting additional description:

Pre-defined symptoms of PAH (disease-related events) were only recorded as AEs if the event was either serious; new; or unusual with respect to intensity, frequency, or duration as compared with symptoms in the subject's medical history; or there was a reasonable possibility that the event was caused by the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	UT-15C

Reporting group description:

Oral treprostinil

Reporting group title	Placebo

Reporting group description:

Matching placebo

Serious adverse events	UT-15C	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	116 / 346 (33.53%)	110 / 344 (31.98%)	
number of deaths (all causes)	17	18	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 346 (0.58%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	17 / 346 (4.91%)	12 / 344 (3.49%)	
occurrences causally related to treatment / all	3 / 18	2 / 12	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac failure			

subjects affected / exposed	5 / 346 (1.45%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 346 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 346 (1.16%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 346 (0.58%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 346 (0.58%)	5 / 344 (1.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	5 / 346 (1.45%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	26 / 346 (7.51%)	36 / 344 (10.47%)	
occurrences causally related to treatment / all	5 / 27	5 / 40	
deaths causally related to treatment / all	1 / 4	0 / 3	
Dyspnoea			

subjects affected / exposed	7 / 346 (2.02%)	8 / 344 (2.33%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Pneumonia			
subjects affected / exposed	10 / 346 (2.89%)	10 / 344 (2.91%)	
occurrences causally related to treatment / all	1 / 11	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 346 (1.45%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 346 (1.16%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 346 (1.16%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 346 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	1 / 346 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	UT-15C	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 346 (98.84%)	328 / 344 (95.35%)	
Vascular disorders			
Flushing			
subjects affected / exposed	154 / 346 (44.51%)	27 / 344 (7.85%)	
occurrences (all)	158	28	
Hypotension			
subjects affected / exposed	24 / 346 (6.94%)	14 / 344 (4.07%)	
occurrences (all)	24	17	
Cardiac disorders			
Palpitations			
subjects affected / exposed	47 / 346 (13.58%)	31 / 344 (9.01%)	
occurrences (all)	48	35	
Right ventricular failure			
subjects affected / exposed	22 / 346 (6.36%)	19 / 344 (5.52%)	
occurrences (all)	23	19	
Nervous system disorders			
Headache			
subjects affected / exposed	259 / 346 (74.86%)	120 / 344 (34.88%)	
occurrences (all)	283	134	
Dizziness			
subjects affected / exposed	81 / 346 (23.41%)	75 / 344 (21.80%)	
occurrences (all)	86	83	
Syncope			
subjects affected / exposed	20 / 346 (5.78%)	20 / 344 (5.81%)	
occurrences (all)	23	24	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	46 / 346 (13.29%)	81 / 344 (23.55%)	
occurrences (all)	50	89	
Fatigue			
subjects affected / exposed	37 / 346 (10.69%)	46 / 344 (13.37%)	
occurrences (all)	43	48	
Chest pain			
subjects affected / exposed	26 / 346 (7.51%)	45 / 344 (13.08%)	
occurrences (all)	34	48	

Chest discomfort			
subjects affected / exposed	29 / 346 (8.38%)	30 / 344 (8.72%)	
occurrences (all)	32	32	
Pyrexia			
subjects affected / exposed	25 / 346 (7.23%)	26 / 344 (7.56%)	
occurrences (all)	26	28	
Asthenia			
subjects affected / exposed	23 / 346 (6.65%)	17 / 344 (4.94%)	
occurrences (all)	23	18	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	240 / 346 (69.36%)	98 / 344 (28.49%)	
occurrences (all)	277	106	
Nausea			
subjects affected / exposed	139 / 346 (40.17%)	78 / 344 (22.67%)	
occurrences (all)	146	90	
Vomiting			
subjects affected / exposed	123 / 346 (35.55%)	35 / 344 (10.17%)	
occurrences (all)	135	37	
Abdominal pain upper			
subjects affected / exposed	40 / 346 (11.56%)	17 / 344 (4.94%)	
occurrences (all)	41	20	
Abdominal discomfort			
subjects affected / exposed	29 / 346 (8.38%)	12 / 344 (3.49%)	
occurrences (all)	30	14	
Abdominal pain			
subjects affected / exposed	28 / 346 (8.09%)	13 / 344 (3.78%)	
occurrences (all)	30	13	
Abdominal distension			
subjects affected / exposed	27 / 346 (7.80%)	16 / 344 (4.65%)	
occurrences (all)	28	16	
Gastrooesophageal reflux disease			
subjects affected / exposed	24 / 346 (6.94%)	12 / 344 (3.49%)	
occurrences (all)	25	12	
Dyspepsia			

subjects affected / exposed	18 / 346 (5.20%)	20 / 344 (5.81%)	
occurrences (all)	19	20	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	56 / 346 (16.18%)	77 / 344 (22.38%)	
occurrences (all)	61	88	
Cough			
subjects affected / exposed	46 / 346 (13.29%)	63 / 344 (18.31%)	
occurrences (all)	48	72	
Pulmonary hypertension			
subjects affected / exposed	38 / 346 (10.98%)	64 / 344 (18.60%)	
occurrences (all)	39	70	
Epistaxis			
subjects affected / exposed	21 / 346 (6.07%)	31 / 344 (9.01%)	
occurrences (all)	25	33	
Nasal congestion			
subjects affected / exposed	20 / 346 (5.78%)	17 / 344 (4.94%)	
occurrences (all)	21	19	
Oropharyngeal pain			
subjects affected / exposed	11 / 346 (3.18%)	18 / 344 (5.23%)	
occurrences (all)	11	19	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 346 (5.49%)	15 / 344 (4.36%)	
occurrences (all)	19	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 346 (6.36%)	16 / 344 (4.65%)	
occurrences (all)	22	17	
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	62 / 346 (17.92%)	10 / 344 (2.91%)	
occurrences (all)	64	11	
Pain in extremity			
subjects affected / exposed	61 / 346 (17.63%)	30 / 344 (8.72%)	
occurrences (all)	78	32	

Myalgia			
subjects affected / exposed	49 / 346 (14.16%)	37 / 344 (10.76%)	
occurrences (all)	53	42	
Arthralgia			
subjects affected / exposed	41 / 346 (11.85%)	31 / 344 (9.01%)	
occurrences (all)	51	39	
Back pain			
subjects affected / exposed	31 / 346 (8.96%)	27 / 344 (7.85%)	
occurrences (all)	32	27	
Muscle spasms			
subjects affected / exposed	10 / 346 (2.89%)	22 / 344 (6.40%)	
occurrences (all)	12	23	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	73 / 346 (21.10%)	82 / 344 (23.84%)	
occurrences (all)	105	109	
Viral upper respiratory tract infection			
subjects affected / exposed	56 / 346 (16.18%)	46 / 344 (13.37%)	
occurrences (all)	69	63	
Bronchitis			
subjects affected / exposed	24 / 346 (6.94%)	19 / 344 (5.52%)	
occurrences (all)	27	25	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 346 (9.25%)	16 / 344 (4.65%)	
occurrences (all)	33	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2012	The main changes implemented with this amendment were: • Changed Screening Period to 30 days. • Added/clarified study assessments for subjects who discontinued study drug before Week 24. • Clarification of collection and/or timing for clinical laboratory tests, height, NT-proBNP, and RHC. • Added that AEs extending beyond the final visit were followed for up to 30 days. • Inclusion criterion revised to require PCWP or LVEDP less than or equal to 15 mmHg. • Exclusion criterion clarified that discontinuation of PDE5-I or ERA could be within 30 days prior to Screening. • To continue to collect endpoint data (Week 24 6MWD) on subjects who added second PAH oral therapy, as well as collect safety data in subjects who were presumably declining during the study but did not meet the protocol definition of clinical worsening. • Removed allowance for subjects that have background PAH therapy removed during treatment to continue into the open-label extension study.
04 June 2012	The main changes implemented with this amendment were: • Definition of clinical worsening disease progression and unsatisfactory clinical response criteria revised. • Clarification of collection and/or timing for clinical laboratory test, contraceptive use, ECGs, NT-proBNP, RHC, visit windows, and telephone contact. • Minimum permitted dosage of tadalafil changed to 20 mg once daily if prescribed per the approved prescribing guidelines. • Updated guidelines and definitions for recording AEs to current practice. • The estimated study duration was revised to indicate an overall estimated study duration of 4 years. • Added language to indicate RHC, ECG, chest X-ray, ventilation perfusion scan, high resolution computerized tomography scan, multigated angiogram, pulmonary angiography, and pulmonary function tests may be performed during Screening if required to satisfy inclusion/exclusion criteria.
05 December 2012	The main changes implemented with this amendment were: • Dosing was changed from BID to TID and the maximum allowable dose was changed from 15 mg BID to 12 mg TID. • The term Events of Special Interest was removed and replaced by Clinical Worsening Events to ensure consistency in assessing and reporting. • Inclusion criteria revised so that subjects must have received an approved PDE5-I or ERA for at least 30 days, but no more than 1 year before randomization. • New exclusion criterion added for subjects that have chronic renal insufficiency as defined by either a Screening creatinine value >2.5 mg/dL (221 µmol/L) or the requirement for dialysis. • Clarification of collection and/or timing for exercise capacity testing (6MWT and Borg dyspnea score).

10 March 2014	The main changes implemented with this amendment were: • Changed PAH background therapy from ERA or PDE5-I to PAH-approved oral monotherapy. Also updated dosing requirements to indicate that dosing of the background therapy must comply with the approved prescribing information for the product. • Clarified the duration of background oral monotherapy for inclusion in the study: initial treatment with any approved PAH therapy occurring no more than 1 year prior to randomization and at a stable dose for a minimum of 10 days prior to randomization. • Dosing of study drug updated so first dose taken at the study site with food (0.125 mg). Dosing was then to continue at 0.125 mg TID with food. Dose escalations could occur no more frequently than every 24 hours. • Allowed temporary use of prostacyclins (28 days or less) for the treatment of clinical worsening and allowed those subjects to transition into the open-label study. • Clarified recording oxygen usage in the CRF when related to the 6MWT. In addition, limitations were placed on use of pulmonary rehabilitation during the study. • Inclusion criteria changed to require RHC within 3 years of Screening, to remove requirement for chest radiograph, and clarify total lung capacity assessments. • Included requirement for subject to complete dosing diary through Week 24. • Method for recording and reporting AEs associated with progression of PAH clarified.
06 January 2015	The main changes implemented with this amendment were: • Reduced sample size and number of clinical worsening events based on results from recently completed time to clinical worsening studies. • Removed 1-year time limit on approved PAH background monotherapy. • New exclusion criterion added to reduce the likelihood of enrolling subjects who had clinically relevant left ventricular diastolic dysfunction.
07 October 2015	The main changes implemented with this amendment were: • Added optional vital status data collection every 6 months for the duration of the study from subjects who discontinued early from the study.
29 September 2016	The main changes implemented with this amendment were: • Increased the sample size/corrected the sample size calculation. • Changed the previous co-primary endpoint of 6MWD at Week 24 to a secondary endpoint. • Added an interim efficacy analysis conducted after 75% of total adjudicated clinical worsening events occurred. • Revised the order of the 3 key secondary endpoints and included a hierarchical approach to analyzing the key secondary endpoints. • Added the secondary endpoint of exercise capacity as assessed by 6MWD measured at each visit up to Week 48 other than Week 24. • Clarified the definition of clinical worsening events and that clinical worsening events were adjudicated. • Addition of an approved pharmacotherapy for PAH. • Clarified RHC could be performed during Screening. • Clarified inclusion/exclusion criterion regarding PAH-approved oral therapies. • Revised when DMC meetings occurred.
09 August 2017	The main changes implemented with this amendment were: • Added exploratory objectives for optional evaluation of biomarkers and pharmacogenomics.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported