Clinical trial results:
An Open-Label Extension Trial of UT-15C SR in Subjects with Pulmonary Arterial Hypertension

Summary

EudraCT number	2006-000804-18
Trial protocol	IE GB NL AT FR BE IT DE SE PT ES
Global end of trial date	12 February 2020

Results information

Result version number	v1 (current)
This version publication date	24 February 2021
First version publication date	24 February 2021

Trial information

Trial identification

Sponsor protocol code	TDE-PH-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01027949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corporation
Sponsor organisation address	55 TW Alexander Drive, Durham, United States, 27709
Public contact	Louis Holdstock, PhD , United Therapeutics Corporation, 1 919-485-8350, lholdstock@unither.com
Scientific contact	Louis Holdstock, PhD , United Therapeutics Corporation, 1 919-485-8350, lholdstock@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	01 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2020
Global end of trial reached?	Yes
Global end of trial date	12 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to provide oral treprostinil for eligible subjects who participated in Studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308.

Protection of trial subjects:

Subjects could voluntarily withdraw or be withdrawn from the study by the Investigator at any time for reasons including, but not limited to, the following: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 adverse event (AE) occurred, or the Investigator considered that it was necessary to discontinue study drug to protect the safety of the subject.
- The subject deviated from the protocol.
- The subject's behavior was likely to undermine the validity of his/her results.
- The subject became pregnant.

Throughout the conduct of the study, monitoring personnel from United Therapeutics Corporation (UTC) or designated contract research organizations (CROs) (as appropriate) contacted the centers by telephone and conducted on-site visits. At these visits, subject data were quality reviewed, general study conduct assessed, and if needed, continuing education was provided on study procedures in an effort to confirm the ethical treatment of subjects and assess compliance with International Council for Harmonisation Good Clinical Practice guidelines and all applicable regulations.

Background therapy:

Subjects were allowed to continue any approved pulmonary arterial hypertension (PAH) background medication in use during the parent studies.

Evidence for comparator: -

Actual start date of recruitment	16 January 2007
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	Australia: 44
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	United States: 436
Country: Number of subjects enrolled	China: 124
Country: Number of subjects enrolled	India: 79
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Poland: 16

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	894
EEA total number of subjects	131

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)	11
Adults (18-64 years)	760
From 65 to 84 years	123
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in this study had remained on study drug/completed all assessments of previous studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308 OR permanently discontinued study drug on the previous study due to clinical worsening OR was in Group 1 or 2 in TDE-PH-202 and discontinued due to clinical worsening.

Pre-assignment

Screening details:

Subjects who met recruitment criteria were enrolled as follows: 541 subjects from TDE-PH-301 and TDE-PH-308, 279 subjects from TDE-PH-302, and 74 subjects from TDE-PH-202, TDE-PH-203, TDE-PH-205 and de novo.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label extension study.

Arms

Arm title	Oral Treprostinil

Arm description:

Subjects from previous studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308.

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

Dosage and administration details:

Subjects randomly allocated to placebo in TDE-PH-301, TDE-PH-302, or TDE-PH-308 were initiated/optimized on oral treprostinil therapy as specified in the previous study protocol; the first dose of study drug in the open-label study was taken by the subject at the study site immediately following a meal. The subject remained close to the study site for approximately 3 to 6 hours for periodic observation and monitoring of possible AEs. Subjects were instructed to take the appropriate amount of 0.125, 0.25, 0.5, 1, and/or 2.5 mg tablets twice daily (BID) or 3 times daily (TID) based upon their prescribed dose. Investigators increased the dose of oral treprostinil in the absence of dose-limiting drug-related AEs to ensure each subject received the optimal clinical dose. Subjects who were randomized to oral treprostinil or were receiving active therapy in the previous study began open-label therapy at the same dose and regimen they were receiving at the final visit in the previous study.

Number of subjects in period 1	Oral Treprostinil
Started	894
Early Discontinuation from Treatment	686
Completed	208
Not completed	686
Consent withdrawn by subject	113

Adverse event, non-fatal	172
Death	174
Various other	34
Lost to follow-up	17
Progressive disease	163
Protocol deviation	13

Baseline characteristics

Reporting groups	
Reporting group title	Oral Treprostinil
Reporting group description:	
Subjects from previous studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308.	

Reporting group values	Oral Treprostinil	Total	
Number of subjects	894	894	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	47.7		
full range (min-max)	12 to 80	-	
Gender categorical Units: Subjects			
Female	696	696	
Male	198	198	
Etiology of PAH Units: Subjects			
Idiopathic or Familial	608	608	
Collagen Vascular Disease	224	224	
Other	60	60	
Missing	2	2	
Background PAH Therapy Units: Subjects			
Endothelin Receptor Antagonist (ERA)	136	136	
Phosphodiesterase Type 5 Inhibitor (PDE5-I)	214	214	
ERA + PDE5-I	251	251	
None	293	293	
World Health Organization Functional Class Units: Subjects			
II	298	298	
III	527	527	
IV	11	11	

Missing	40	40	
_I	18	18	

Years Since PAH Diagnosis			
Units: Years			
median	1.569		
full range (min-max)	-1.64 to 34.47	-	
6-Minute Walk Distance (6MWD)			
Units: Meters			
median	366.0		
full range (min-max)	30 to 705	-	
Borg Score			
Units: Numerical Score			
median	3.00		
full range (min-max)	0 to 10	-	

End points

End points reporting groups

Reporting group title	Oral Treprostinil
Reporting group description:	
Subjects from previous studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308.	
Subject analysis set title	Overall analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects	

Primary: Change in 6MWD at Month 12

End point title	Change in 6MWD at Month 12[1]
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Month 12	

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: There were no statistics run on the end point - only summary statistics for this open-label extension study. There were no statistics run on the end point - only summary statistics for this open-label extension study. There were no statistics run on the end point - only summary statistics for this open-label extension study.

End point values	Oral Treprostinil			
Subject group type	Reporting group			
Number of subjects analysed	569			
Units: Meters				
median (full range (min-max))	22.00 (-345.0 to 282.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Borg Score at Month 12

End point title	Change in Borg Score at Month 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Month 12	

End point values	Oral Treprostinil			
Subject group type	Reporting group			
Number of subjects analysed	565			
Units: Numerical Score				
median (full range (min-max))	0.00 (-10.0 to 7.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Full Study Period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Oral Treprostinil

Reporting group description:

Subjects eligible for TDE-PH-304 previously participated in Studies TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308.

Serious adverse events	Oral Treprostinil		
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 894 (14.43%)		
number of deaths (all causes)	174		
number of deaths resulting from adverse events	89		
Vascular disorders			
Hypotension			
subjects affected / exposed	23 / 894 (2.57%)		
occurrences causally related to treatment / all	10 / 26		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	36 / 894 (4.03%)		
occurrences causally related to treatment / all	4 / 43		
deaths causally related to treatment / all	0 / 7		
Right ventricular failure			
subjects affected / exposed	129 / 894 (14.43%)		
occurrences causally related to treatment / all	16 / 188		
deaths causally related to treatment / all	1 / 31		
Nervous system disorders			
Syncope			

subjects affected / exposed	30 / 894 (3.36%)		
occurrences causally related to treatment / all	6 / 33		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 894 (3.13%)		
occurrences causally related to treatment / all	5 / 32		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	28 / 894 (3.13%)		
occurrences causally related to treatment / all	1 / 33		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	41 / 894 (4.59%)		
occurrences causally related to treatment / all	10 / 51		
deaths causally related to treatment / all	0 / 4		
Pulmonary hypertension			
subjects affected / exposed	129 / 894 (14.43%)		
occurrences causally related to treatment / all	20 / 147		
deaths causally related to treatment / all	2 / 28		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	37 / 894 (4.14%)		
occurrences causally related to treatment / all	8 / 48		
deaths causally related to treatment / all	0 / 4		
Infections and infestations			
Pneumonia			
subjects affected / exposed	63 / 894 (7.05%)		
occurrences causally related to treatment / all	1 / 76		
deaths causally related to treatment / all	0 / 11		

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

Non-serious adverse events	Oral Treprostinil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	890 / 894 (99.55%)		
Vascular disorders			
Flushing			
subjects affected / exposed	416 / 894 (46.53%)		
occurrences (all)	499		
Hypotension			
subjects affected / exposed	79 / 894 (8.84%)		
occurrences (all)	91		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	201 / 894 (22.48%)		
occurrences (all)	228		
Oedema peripheral			
subjects affected / exposed	192 / 894 (21.48%)		
occurrences (all)	240		
Chest pain			
subjects affected / exposed	135 / 894 (15.10%)		
occurrences (all)	180		
Pain			
subjects affected / exposed	97 / 894 (10.85%)		
occurrences (all)	102		
Pyrexia			
subjects affected / exposed	83 / 894 (9.28%)		
occurrences (all)	100		
Chest discomfort			
subjects affected / exposed	57 / 894 (6.38%)		
occurrences (all)	70		
Asthenia			
subjects affected / exposed	51 / 894 (5.70%)		
occurrences (all)	64		
Oedema			

subjects affected / exposed	43 / 894 (4.81%)		
occurrences (all)	44		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	207 / 894 (23.15%)		
occurrences (all)	294		
Pulmonary hypertension			
subjects affected / exposed	190 / 894 (21.25%)		
occurrences (all)	215		
Cough			
subjects affected / exposed	159 / 894 (17.79%)		
occurrences (all)	202		
Nasal congestion			
subjects affected / exposed	98 / 894 (10.96%)		
occurrences (all)	103		
Epistaxis			
subjects affected / exposed	77 / 894 (8.61%)		
occurrences (all)	88		
Haemoptysis			
subjects affected / exposed	45 / 894 (5.03%)		
occurrences (all)	57		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	95 / 894 (10.63%)		
occurrences (all)	98		
Anxiety			
subjects affected / exposed	57 / 894 (6.38%)		
occurrences (all)	60		
Depression			
subjects affected / exposed	56 / 894 (6.26%)		
occurrences (all)	59		
Investigations			
Weight decreased			
subjects affected / exposed	47 / 894 (5.26%)		
occurrences (all)	49		
Cardiac disorders			

Dizziness subjects affected / exposed occurrences (all)	248 / 894 (27.74%) 320		
Palpitations subjects affected / exposed occurrences (all)	145 / 894 (16.22%) 175		
Right ventricular failure subjects affected / exposed occurrences (all)	136 / 894 (15.21%) 202		
Cardiac failure subjects affected / exposed occurrences (all)	42 / 894 (4.70%) 54		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	698 / 894 (78.08%) 994		
Syncope subjects affected / exposed occurrences (all)	101 / 894 (11.30%) 141		
Presyncope subjects affected / exposed occurrences (all)	51 / 894 (5.70%) 55		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	84 / 894 (9.40%) 112		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	592 / 894 (66.22%) 808		
Nausea subjects affected / exposed occurrences (all)	505 / 894 (56.49%) 673		
Vomiting subjects affected / exposed occurrences (all)	349 / 894 (39.04%) 485		
Abdominal pain			

subjects affected / exposed	121 / 894 (13.53%)		
occurrences (all)	144		
Abdominal pain upper			
subjects affected / exposed	97 / 894 (10.85%)		
occurrences (all)	111		
Abdominal distension			
subjects affected / exposed	92 / 894 (10.29%)		
occurrences (all)	102		
Dyspepsia			
subjects affected / exposed	92 / 894 (10.29%)		
occurrences (all)	95		
Constipation			
subjects affected / exposed	65 / 894 (7.27%)		
occurrences (all)	74		
Gastrooesophageal reflux disease			
subjects affected / exposed	46 / 894 (5.15%)		
occurrences (all)	48		
Abdominal discomfort			
subjects affected / exposed	45 / 894 (5.03%)		
occurrences (all)	48		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	79 / 894 (8.84%)		
occurrences (all)	87		
Pruritus			
subjects affected / exposed	43 / 894 (4.81%)		
occurrences (all)	50		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	52 / 894 (5.82%)		
occurrences (all)	69		
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	313 / 894 (35.01%)		
occurrences (all)	360		
Pain in extremity			

subjects affected / exposed	255 / 894 (28.52%)		
occurrences (all)	337		
Arthralgia			
subjects affected / exposed	140 / 894 (15.66%)		
occurrences (all)	163		
Myalgia			
subjects affected / exposed	123 / 894 (13.76%)		
occurrences (all)	143		
Back pain			
subjects affected / exposed	105 / 894 (11.74%)		
occurrences (all)	127		
Muscle spasms			
subjects affected / exposed	64 / 894 (7.16%)		
occurrences (all)	71		
Musculoskeletal pain			
subjects affected / exposed	42 / 894 (4.70%)		
occurrences (all)	44		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	222 / 894 (24.83%)		
occurrences (all)	334		
Nasopharyngitis			
subjects affected / exposed	185 / 894 (20.69%)		
occurrences (all)	316		
Bronchitis			
subjects affected / exposed	103 / 894 (11.52%)		
occurrences (all)	153		
Pneumonia			
subjects affected / exposed	94 / 894 (10.51%)		
occurrences (all)	118		
Urinary tract infection			
subjects affected / exposed	89 / 894 (9.96%)		
occurrences (all)	115		
Sinusitis			
subjects affected / exposed	80 / 894 (8.95%)		
occurrences (all)	108		

Influenza subjects affected / exposed occurrences (all)	54 / 894 (6.04%) 64		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Fluid overload subjects affected / exposed occurrences (all) Fluid retention subjects affected / exposed occurrences (all)	 129 / 894 (14.43%) 142 94 / 894 (10.51%) 119 44 / 894 (4.92%) 58 43 / 894 (4.81%) 54		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2007	Amendment 1 - Introduced 0.5 mg tablet, added several administrative changes/clarifications and added the study entry criteria clarifications highlighted in Amendment A.1UK (dated 19-Dec-2006).
13 December 2007	Amendment 2 - Removal of the 10 mg strength and the addition of the 0.25 mg strength when available. Altering the timing of the 6-Minute Walk Test relative to the last dose of study drug to 3 to 6 hours post-dose to coincide with peak plasma concentrations. Lowering the starting dose to 0.5 mg for subjects randomized to placebo in Studies TDE-PH-301 (FREEDOM–C) or TDE-PH-302 (FREEDOM–M). Altering the dosing schedule to 0.5-mg increments every 3 days and allowing 0.25-mg dose increases if needed. Clarifying subjects participating in additional oral treprostinil protocols will also be eligible for the extension study. Clarifying subjects receiving placebo in FREEDOM-C or -M should be followed more closely via frequent telephone contacts, and if necessary, clinic visits in the first several months of the extension study to ensure subject safety. Clarifying additional information regarding concomitant medications will be captured.
28 April 2008	Amendment 3 - Removal of the 5 mg strength tablet and the addition of the 2.5 mg tablet. Subjects receiving placebo in Studies TDE-PH-301 or TDE-PH-302 must be contacted weekly by telephone during the first 12 weeks of the open-label study. Monthly calls must be made for all subjects regardless of their study drug allocation. All subjects must be seen in the clinic no less than once every 6 months for routine standard of care.
02 March 2009	Amendment 4 - Study TDE-PH-308 included as a source for subjects to enter the open-label study, which increased the total sample size to ~900. The starting dose changed to 0.25 mg with a dose titration to occur in 0.25- or 0.5-mg increments every 3 days. The 0.125 mg strength tablet added if available. The duration of the study increased from 3 years until the drug becomes commercially available or the Sponsor discontinues development of the drug with yearly study visits to occur beyond Visit 5.
20 March 2013	Amendment 5 - Added Studies TDE-PH-203 and TDE-PH-205 to allow subjects to enroll into Study TDE-PH-304 from these protocols. Description of procedures related to optional transition from BID to TID regimen.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: