



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Subjects could voluntarily withdraw or be withdrawn from the study by the Investigator at any time for reasons including, but not limited to, the following: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 full range (min-max) | 1.569 -1.64 to 34.47 | - | |
| 6-Minute Walk Distance (6MWD) Units: Meters median full range (min-max) | 366.0 30 to 705 | - | |
| Borg Score Units: Numerical Score median full range (min-max) | 3.00 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) | 129 / 894 (14.43%) 142 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 94 / 894 (10.51%) 119 | | |
| Fluid overload subjects affected / exposed occurrences (all) | 44 / 894 (4.92%) 58 | | |
| Fluid retention subjects affected / exposed occurrences (all) | 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: