A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension

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Primary Objective:To assess the effect of UT-15C sustained release (SR) tablets on exercise capacity compared to placebo (as measured by the change in 6-Minute Walk distance from Baseline to Week 16) in subjects with PAH.Secondary objective:To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON35674

Source
ToetsingOnline

Brief title
FREEDOM-C2

Condition

- Pulmonary vascular disorders

Synonym
high blood pressure in the small circulation; Pulmonal Arterial Hypertension

Research involving

Human

Sponsors and support

Primary sponsor: United Therapeutics Europe Ltd.
Source(s) of monetary or material Support: United Therapeutics Corporation

Intervention

Keyword: Double-Blind, PLacebo-controlled, Pulmonary Arterial Hypertension, UT-15C Sustained release

Outcome measures

Primary outcome

The efficacy endpoints are as follows:

* 6-Minute Walk Distance (6MWD) (i.e., distance traversed during the 6-

Minute Walk Test) [Primary Endpoint]

Secondary outcome

The efficacy endpoints are as follows:

* Clinical Worsening, as defined by:

1. Death (all causes excluding accident)

2. Transplantation

3. Atrial septostomy

4. Hospitalization as a result of right heart failure

5. Greater than or equal to a 20% decrease in 6-Minute Walk distance

from Baseline (or too ill to walk) AND addition of an inhaled

prostacyclin analogue, ERA, or PDE-5 inhibitor.

6. Initiation of parenteral prostacyclin therapy (i.e., epoprostenol,

iloprost, or treprostinil) for the treatment of PAH

United Therapeutics Corp. TDE-PH-308

* Combined ranking of distance walked and Borg Dyspnea Score from the 6-

Minute Walk Test

* N-terminal pro-BNP

* WHO Functional Class for PAH

* Borg Dyspnea Score from the 6-Minute Walk Test

* Quality of life (as measured by the CAMPHOR questionnaire)

* Dyspnea-Fatigue Index

* Symptoms of PAH (fatigue, dyspnea, edema, dizziness, syncope, chest

pain, orthopnea)

* Biomarkers (specific targets to be determined)

The safety endpoints are as follows:

* Adverse Events

* Clinical Laboratory Parameters (see Section 15.5 for parameters to be

assessed)

* Vital Signs

* Electrocardiogram findings

Study description

Background summary

Remodulin (treprostinil sodium) is a chemically stable, longer acting prostacyclin
analogue that has shown clinical effectiveness when administered by the continuous SC and IV routes. Subcutaneously or intravenously delivered Remodulin is approved in many countries for the treatment of various forms and classes of PAH. An oral formulation of treprostinil may not only allow patients

suffering from PAH to benefit from the simplicity of an oral dosage form, but may
also facilitate the treatment of either previously untreated conditions or improve
the treatment of conditions that are not adequately controlled with current therapies.

Study objective

Primary Objective:To assess the effect of UT-15C sustained release (SR) tablets on exercise capacity compared to placebo (as measured by the change in 6-Minute Walk distance from Baseline to Week 16) in subjects with PAH.

Secondary objective:
To assess the effect of UT-15C SR on the following:
* Clinical Worsening*
* Combined Walk Distance / Borg Dyspnea Score
* N-terminal pro-Brain Natriuetic Peptide (BNP)
* World Health Organization (WHO) Functional Class
* Borg Dyspnea Score
* Quality of Life (as measured by the CAMPHOR questionnaire where validated in the local language)
* Dyspnea-Fatigue Index
* Symptoms of PAH
* Biomarkers (specific targets to be determined)
* Safety (adverse events, clinical laboratory parameters, vital signs, electrocardiogram (ECG) findings)

*Definition of clinical worsening requires one of the following:
1. Death (all causes excluding accident)
2. Transplantation
3. Atrial septostomy
4. Hospitalization as a result of right heart failure
5. Greater than or equal to a 20% decrease in 6-Minute Walk distance from Baseline (or too ill to walk) AND addition of an inhaled prostacyclin analogue, endothelin receptor antagonist (ERA), or phosphodiesterase type-5 (PDE-5) inhibitor.
6. Initiation of parenteral prostacyclin therapy (i.e., epoprostenol, iloprost, or treprostinil) for the treatment of PAH

Study design

Multi-center, randomized, double-blind, placebo-controlled, 16-week study in subjects with PAH. Stratification of the population will occur by type of background therapy (approved ERA, PDE-5 inhibitor, or the combination) and

Baseline 6-Minute Walk distance (* 350 meters and > 350 meters)

Intervention

Active treatment is UT-15C SR tablets provided as 0.125, 0.25, 0.5, and 1 mg strengths for the 16-week Treatment Phase. Placebo is identical in size, shape, and color to the respective active tablets.

Treatment will be initiated at 0.25 mg twice daily (every 12 hours +/- 1 hour) with dose escalation of an additional 0.25 to 0.5 mg twice daily every 3 days if clinically indicated according to protocol-defined guidelines. If available, 0.125 mg tablets may be utilized for dose titration.All study drug should be administered immediately following (~10 minutes) breakfast and dinner.

Study burden and risks

Subjects who remain on study drug and successfully complete all assessments during the 16-week Treatment Phase may be enrolled into an open-label extension trial (TDE-PH-304). Additionally, subjects who experience clinical worsening and are withdrawn from study drug prior to Week 16 should continue to return to the clinic for scheduled visits to be eligible for the open-label study. If participating in the open-label study, the treatment assignment for each subject will be provided at the Week 16 visit after completion of all study assessments. Those subjects who experience clinical worsening while receiving UT-15C will not be eligible for the open-label study while those who experience clinical worsening while receiving placebo will be eligible for the open-label study.

Efficacy Assessments: Exercise capacity (including 6-Minute Walk distance and Borg Dyspnea Score) measured approximately 3 to 6 hours after administration of the morning dose of study drug and background therapy(ies); Clinical Worsening; Dyspnea-Fatigue Index; WHO Functional Class; Symptoms of PAH; N-terminal pro-BNP; collection of blood sample for biomarker testing (optional) and quality of life (as measured
Study Visit Schedule: Subjects will be assessed during Screening and Baseline Phases to determine eligibility for the study. Once randomized, four Treatment Phase visits to the clinic will be required at 4, 8, 12 and 16 weeks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects are between 18 and 75 years of age, have a minimum weight of 40 kg and a Body Mass Index (BMI) <45kg/m2 , have a diagnosis of idiopathic or familial PAH, PAH associated with collagen vascular disease or human immunodeficiency virus (HIV) infection, or PAH associated with appetite suppressant or toxin use or PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired >5 years). The baseline 6-minute walk distance must be between 150 and 425 meters, inclusive. Subjects are receiving an approved ERA and/or an approved PDE-5 inhibitor for at least 90 days prior to randomization and are on a stable dose for 30 days.

Exclusion criteria

1)The subject is pregnant or lactating
2)The subject has received epoprostenol, treprostinil, iloprost, beraprost or any other prostacyclin therapy within 30 days of baseline (Except if used during acute vasoreactivity testing)
3)The subject has previously used UT-15C SR
4)The subject has had previous intolerance or significant lack of efficacy to an oral or parenteral prostacyclin analogue that resulted in discontinuation or inability to effectively

titrate that therapy
5)The subject has any disease associated with PAH other than collagen vascular disease, HIV infection, or apetite suppressant/toxin use or repaired congenital systemic-to-pulmonary shunts (repaired >5 years) (e.g. portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease etc) or has had an atrial septostomy
6)The subject has a current diagnosis of uncontrolled sleep apnea as defined by their physician
7)The subject has chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL or the requirement for dialysis
8)The subject has liver function tests (AST or ALT) greater than three times the upper limit of normal at Screening
9)Has anemia as defined by a Screening hemoglobin value of less than 10g/dL, active infection, or any other condition that would interfere with the interpretation of study assessments
10)The subject has musculoskeletal disorder
11)The subject is receiving an investigational drug, has an investigation device in place or has participated in an investigational drug or device study within 30 days prior to screening

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Treprostinil Diethanolamine

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-009366-13-NL
Other	n/a
CCMO	NL29283.029.09