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

Published: 29-08-2012
Last updated: 26-04-2024

To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared to placebo with PAHapproved oral monotherapy on time to first clinical worsening event (adjudicated), as defined by at least one of the events listed below:- Death (all...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON44878

Source
ToetsingOnline

Brief title
Study with UT-15C in PAH-patients

Condition

- Vascular hypertensive disorders

Synonym
increase in blood pressure in the pulmonary arteries, PAH

Research involving

Human

Sponsors and support

Primary sponsor: United Therapeutics Corp.
Source(s) of monetary or material Support: United Therapeutics

Intervention

Keyword: pulmonary arterial hypertension, UT-15C

Outcome measures

Primary outcome

see Objective of the study

Secondary outcome

To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared

to placebo with PAH-approved oral monotherapy on the following:

* Exercise capacity as assessed by 6MWD measured at Week 24

* Plasma N-terminal pro-brain natriuretic peptide (NT proBNP) at Week 24

* Combined 6MWD/Borg dyspnea score at Week 24

* Exercise capacity as assessed by 6MWD measured at each visit up to Week 48

other than Week 24

* Borg dyspnea score

* World Health Organization (WHO) Functional Class

* Right heart catheterization (RHC) hemodynamics at Week 24 (optional)

* Safety (vital signs, adverse events [AEs], clinical laboratory parameters,

electrocardiograms)

Exploratory Objectives:

- optional evaluation of biomarkers

- optional evaluation of pharmacogenomics

Study description

Background summary

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality common to a variety of diseases and syndromes. Elevation in pulmonary arterial pressure causes an increase in right ventricular afterload, impairing right ventricular function and ultimately leading to heart failure and death.
The typical etiologies of PAH include idiopathic, heritable or associated with collagen vascular/connective tissue disease, portal hypertension, infection with the human immunodeficiency virus (HIV), history of cocaine inhalation and exposure to appetite suppressant drugs. An estimated annual incidence of approximately 2 cases per million has been reported for idiopathic PAH [Rich, 1987; Rubin 1997].
There are three major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. There are a number of metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators nitric oxide and prostacyclin (PGI2), and the vasoconstrictor endothelin-1. These substances affect both vascular tone and remodeling leading to their use as pharmacologic targets [Farber, 2004].
Approved pharmacotherapies for PAH include: (1) intravenous PGI2 (epoprostenol sodium or Flolan®, Veletri®); (2) the PGI2 analogues subcutaneous (SC), intravenous (IV), and inhaled treprostinil (Remodulin®, Tyvaso®), oral treprostinil diethanolamine (also referred to as treprostinil diolamine; Orenitram®), oral selexipag (Uptravi®), and inhaled iloprost (Ventavis®); (3) the phosphodiesterase-5 inhibitors (PDE5-I), tadalafil (Adcirca®) and sildenafil (Revatio®); (4) the oral endothelin receptor antagonists (ERA), bosentan (Tracleer®), ambrisentan (Letairis®, Volibris®), and macitentan (Opsumit®), and (5) a soluble guanylate cyclase (sGC) stimulator, riociguat (Adempas®).
Approval of current PAH-specific pharmacotherapies has traditionally been based upon the 6MWT. The 6MWT is an assessment of exercise capacity and remains a standard measure of efficacy for trials of investigational medicines in subjects with PAH. However, recent literature has questioned the clinical relevance, variability, and sensitivity of the 6MWT as a primary endpoint to assess the efficacy of treatments for PAH. Although the 6MWT is still viewed as a valuable tool for measuring clinical efficacy of PAH therapies, a

composite endpoint of *time to clinical worsening* is emerging as an alternative endpoint that allows for assessment of long-term efficacy of investigational drugs for PAH [McLaughlin, 2009].

Study objective

To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared to placebo with PAHapproved oral monotherapy on time to first clinical worsening event (adjudicated), as defined by at least one of the events listed below:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
o Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or
o Lung or heart / lung transplantation; or
o Atrial septostomy
- Initiation of an inhaled or infused prostacyclin for the treatment of worsening PAH
- Disease progression (all criteria required):
o A decrease in six minute walk distance (6MWD) of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by 2 sixminute walk tests (6MWT) performed on different days
o Worsening of PAH symptoms, which must include either:
- An increase in functional class from Baseline or
- Appearance or worsening of symptoms of right heart failure since baseline
- Unsatisfactory long-term clinical response (all criteria required)
o Randomized to receive study drug for at least 24 weeks
o A decrease from Baseline in 6MWD at Week 24 and beyond at two consecutive visits on different days.
o Sustained WHO functional class III or IV symptoms for at least 24 weeks, consecutively

Study design

International, multi-center, randomized, double-blind, placebo-controlled, clinical worsening study in subjects with PAH receiving background oral monotherapy.

Intervention

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Study burden and risks

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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

1. The subject voluntarily gives informed consent to participate in the study.
2. The subject is 18 to 75 years of age (inclusive) at Screening (i.e., date of providing written informed consent).
3. Women of child bearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as

amenorrhea for at least 12 consecutive months). Women of childbearing potential must practice true abstinence from intercourse when it is in line with their preferred and usual lifestyle, or use two different forms of highly effective contraception for the duration of the study, and for at least 30 days after discontinuing study medication. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device (IUD), or (4) partner vasectomy. For women of childbearing potential, a negative urine pregnancy test is required at Screening and Baseline prior to initiating study medication.
4. The subject, if male, must use a condom during the length of the study, and for at least 48 hours after discontinuing study medication.
5. The subject has a diagnosis of symptomatic idiopathic or heritable PAH, PAH associated with CTD, PAH associated with HIV infection, PAH associated with repaired congenital systemic-to-pulmonary shunt (at least 1 year since repair with respect to the date of providing informed consent) or PAH associated with appetite suppressant or toxin use.
6. The subject, if known positive for HIV infection, has a CD4 lymphocyte count of at least 200 cells/mm3 assessed at Screening and is receiving current standard of care anti retroviral or other effective medication for treatment of HIV infection.
7. The subject must have a Baseline 6MWD greater than or equal to 150 meters, in the absence of a concurrent injury, illness (other than PAH or a PAH related condition), or other confounding factor including, but not limited to, use of an aid for ambulation (e.g., use of a cane or walker) or connection to a non-portable machine, that would prevent the accurate assessment of the subject*s exercise capacity.
8. The subject must be optimally treated with conventional pulmonary hypertension therapy (e.g., oral vasodilators, oxygen, digoxin, diuretics, anticoagulants as deemed appropriate by the Investigator) with no additions, discontinuations, or dose changes for a minimum of 10 days prior to randomization. The exceptions are the discontinuation or dose changes of anticoagulants and/or dose change of diuretics.
9. The subject must have been receiving a PAH-approved oral monotherapy at a minimum dose that complies with the approved prescribing information for the product for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization. The subject who previously received two PAH-approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or an sGC stimulator) will be eligible provided they received these medications concomitantly for less than or equal to 90 days cumulatively. The subject must have taken only one PAH-approved therapy for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization.
10. The subject has previously undergone a cardiac catheterization either within three years prior to the start of screening, or during the screening period, and the most recent assessment has documented a mean pulmonary artery pressure (PAPm) of at least 25 mmHg, a pulmonary capillary wedge pressure (PCWP) (or in the event a PCWP cannot be reliably obtained, a left ventricular end diastolic pressure [LVEDP]) less than or equal to 15 mmHg, and absence of unrepaired congenital heart disease (other than patent foramen ovale [PFO]). In the event that a reliable PCWP or LVEDP are unable to be obtained during cardiac catheterization, subjects with clinically normal left heart function and absence of clinically relevant mitral valve disease on echocardiography are eligible for enrollment.
11. The subject has undergone echocardiography with evidence of clinically normal left

systolic and diastolic ventricular function and absence of any clinically significant left sided heart disease (e.g. mitral valve disease). Subjects with clinically insignificant left ventricular diastolic dysfunction due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) are eligible.
12. The subject has a previous ventilation perfusion lung scan, and/or high resolution computerized tomography scan of the chest, and/or pulmonary angiography that are consistent with the diagnosis of PAH (e.g., low probability of pulmonary embolism; absence of major perfusion defects).
13. The subject has pulmonary function tests conducted within 6 months before screening or during the Screening period to confirm the following:
a. Total lung capacity (TLC) is at least 60% (predicted value) assessed by either whole body plethysmography or helium dilution or nitrogen washout technique
b. Forced expiratory volume at one second (FEV1) of at least 50% (predicted value)
14. In the opinion of the Principal Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

Exclusion criteria

1. The subject is pregnant or lactating.
2. The subject has previously received UT-15C.
3. The subject has received a PGI2, (except if used during acute vasoreactivity testing) within 30 days prior to randomization or had previous intolerance or significant lack of efficacy to any PGI2, or PGI2 analogue, that resulted in discontinuation or inability to titrate that therapy effectively.
4. The subject has had any background conventional therapies for PAH added, removed or dose adjusted (including but not limited to oxygen, vasodilators, diuretics, digoxin, anticoagulants) within 10 days prior to randomization. The exceptions are removal or dose adjustments of anticoagulants and/or dose adjustments of diuretics.
5. The subject has received their first dose of a PAH-approved therapy less than 30 days prior to randomization, or has had their PAH-approved oral monotherapy dose changed within 10 days prior to Randomization, or the subject discontinued any PAH-approved therapy within 30 days prior to Screening, or the subject previously received two PAH approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or an sGC stimulator) concomitantly for more than 90 days cumulatively.
6. The subject has any disease associated with PAH other than CTD, HIV infection, repaired (for at least one year) congenital systemic-to-pulmonary shunt, PAH associated with appetite suppressant/toxin use (e.g., portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc.) or has had an atrial septostomy.
7. The subject has a current diagnosis of uncontrolled sleep apnea as defined by their physician.
8. The subject has a history of ischemic heart disease, including a previous myocardial infarction or symptomatic coronary artery disease within 6 months prior to Screening or a history of left sided myocardial disease as evidenced by a mean PCWP (or a left ventricular end diastolic pressure [LVEDP]) greater than 15 mmHg or left ventricular ejection fraction

less than 40% as assessed by either multigated angiogram (MUGA), angiography, or echocardiography.
9. The subject has uncontrolled systemic hypertension as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
10. The subject has ALT or AST levels at least greater than 3 times the upper limit of normal, clinically significant liver disease/dysfunction, or known Child-Pugh Class C hepatic disease (Appendix 15.5) at Screening.
11. The subject has any other disease or condition that would interfere with the interpretation of study assessments.
12. The subject has a musculoskeletal disorder (e.g., arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (e.g. cane or walker), or any disease that is likely to limit ambulation, or is connected to a machine that is not portable.
13. The subject has an unstable psychiatric condition or is mentally incapable of understanding the objectives, nature, or consequences of the trial, or has any condition which in the Investigator*s opinion would constitute an unacceptable risk to the subject*s safety.
14. The subject is receiving an investigational drug, has an investigational device in place, or has participated in an investigational drug or device study within 30 days prior to Screening.
15. The subject has chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 *mol/L) or the requirement for dialysis.
16. Subjects must not have 3 or more of the following left ventricular disease/dysfunction risk factors:
I. Body Mass Index (BMI) *30 kg/m2
ii. History of essential hypertension
iii. Diabetes mellitus * any type
iv. Historical evidence of significant coronary disease established by any one of: history of myocardial infarction or percutaneous coronary intervention or angiographic evidence of coronary artery disease (>50% stenosis in at least one coronary artery), positive stress test with imaging, previous coronary artery bypass graft, stable angina

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):	12-02-2014
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	/
Generic name:	oral treprostinil diethanolamine

Ethics review

Approved WMO Date:	29-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-09-2018
Application type:	Amendment
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	EUCTR2012-000097-26-NL
ClinicalTrials.gov	NCT01560624
CCMO	NL40887.029.12