A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group-sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension.

Published: 20-12-2018
Last updated: 25-03-2025

To explore the efficacy and safety of an oral IP receptor agonist in an inoperable or persistent/recurrent CTEPH population treated with standard of care.

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

Summary

ID

NL-OMON49441

Source
ToetsingOnline

Brief title
SELECT

Condition

- Pulmonary vascular disorders

Synonym
Chronic Thromboembolic Pulmonary Hypertension; CTEPH

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Actelion Pharmaceuticals Ltd (a Janssen Pharmaceutical Company of Johnson and Johnson)

Intervention

Keyword: Chronic trombobembolic pulmonary, hypertension, Interventional clinical trial, Prostacyclin receptor agonist, Pulmonary hypertension

Outcome measures

Primary outcome

Primary efficacy endpoint(s):

PVR (pulmonary vascular resistance) at Week 20, assessed at rest, within 2-5

hours post dose, expressed as a percent of baseline PVR.

Timepoint(s) of evaluation of this end point

Assessed at rest in screening period (Day -60 to Day -14; baseline) and

assessed at rest within 2-5 hours post-dose at Week 20 during

treatment period.

Secondary outcome

Secondary efficacy endpoints

1 Change from baseline in 6MWD to Week 26 (key secondary endpoint).

2 TTCW: Time to clinical worsening (according to the CHMP definition, (key secondary endpoint) up to Week 52, defined as at least one of the following components confirmed by the CEC when applicable:

All-cause death;

Non-planned PH-related hospitalization;

PH-related deterioration identified by at least one of the following:

Increase from baseline in WHO FC4

Deterioration by at least 15% in exercise capacity as measured by the 6MWD;

New Signs or symptoms of right heart failure defined as a reported AE with one of the following preferred terms: *CTEPH*, *pulmonary hypertension*, *right ventricular failure*, *right ventricular dysfunction* and *acute right ventricular failure*.

The investigation of a composite endpoint that reflects the TTCW has been encouraged by the European Medicines Agency.

3 All cause death or hospitalisations related to PH worsening

4 Proportion of subjects with improvement in WHO FC from baseline to Week 26.

5 Change from baseline to Week 26 in PAH-SYMPACT* cardiopulmonary symptom domain and cardiovascular symptom domain.

6 Change from baseline to Week 26 in the Borg dyspnea index (BDI)/Borg CR10.

7 Change from baseline to Week 26 in NT-proBNP.

Safety endpoints

- Treatment-emergent adverse events (AEs)2 up to 3 days after study treatment discontinuation at each analysis time point.

- Serious adverse events (SAEs) up to 30 days after study treatment discontinuation at each analysis time point.
- AEs leading to premature discontinuation of study treatment at each analysis time point.
- Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study at each analysis time point.
- Treatment-emergent marked laboratory abnormalities up to 3 days after study treatment discontinuation as detailed in Appendix 2 at each analysis time point.
- Treatment-emergent AEs2 of special interest (e.g., hypotension, anemia, hyperthyroidism) up to 3 days after study treatment discontinuation at each analysis time point.

Timepoint(s) of evaluation of this end point

1. Week 26, 2. end of double blind treatment period, 3. end of double blind treatment period, 4. Week 26, 5. Week 26, 6. Week 26, 7. Week 26

Study description

Background summary

CTEPH is an important cause of severe Pulmonary Hypertension and is associated with significant deterioration of quality of life and increased mortality/morbidity. This study will be the first global, randomized, controlled study to explore the efficacy and safety of an oral IP receptor agonist in an inoperable (i.e. technically inoeprable) or persistent/recurrent after surgical and/or interventional treatment CTEPH population treated with standard of care. This study will provide insight into the long-term outcomes of an IP receptor agonist, in particular when added sequentially to therapies

acting on other pathogenic pathways.

The histopathologic findings, including endothelial cell dysfunction and distal pulmonary arterial remodeling, between PAH and CTEPH closely resemble each other [Humbert 2010, see reference in the protocol]. The rationale for this study is therefore based on efficacy of PH-specific therapies such as riociguat and macitentan in inoperable and persistent/recurrent CTEPH. Selexipag is an orally available, selective and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) having the unique advantage to target the prostacyclin pathway for the treatment of PAH and may also be beneficial in patients with CTEPH. The purpose of the study is to evaluate the efficacy of selexipag in CTEPH.

Study objective

To explore the efficacy and safety of an oral IP receptor agonist in an inoperable or persistent/recurrent CTEPH population treated with standard of care.

Study design

A prospective, multi-center, randomized, double-blind, placebo controlled, add-on to standard of care, parallel-group, group sequential, adaptive Phase 3 study with an open-label extension period.
Up to 280 subjects will be randomized in a 1:1 ratio to receive either selexipag or placebo during the DB period. Subjects completing the DB period will enter the open-label extension period and will receive selexipag.
Subjects will be recruited in two sequential cohorts. Approximately the first 90 randomized subjects will constitute the hemodynamic cohort who, in addition to the overall study assessments, will undergo an RHC (and left heart catheterization *LHC*, if needed) at Week 20. The remaining subjects will constitute the non-hemodynamic cohort. Both cohorts are combined for the evaluation of secondary efficacy endpoints, which do not require a post-baseline hemodynamic assessment. Treatment allocation will be stratified by treatment with PH-specific therapies (ie, endothelin receptor antagonists [ERAs], phosphodiesterase type-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator [riociguat]; one versus two versus naive [naive capped at 40%]) and by CTEPH population (inoperable [with or without BPA] versus persistent/recurrent after PEA [including PEA followed by BPA]).
The database will be locked and analyzed at five time points during the study:
• Time point 1: when approximately 90 randomized subjects, the hemodynamic cohort, have completed the Week 20 RHC (and LHC, if needed) or prematurely discontinued from the study, the final analysis for the PVR endpoint will be performed by an Independent Statistical Analysis Center (ISAC) for the IDMC.
• Time point 2: when approximately 160 randomized subjects have completed the Week 26 6MWD assessment or prematurely discontinued from the study, an interim

analysis (IA) for the 6MWD endpoint and the TTCW endpoint will be performed by the ISAC for the IDMC.
• Time point 3: when all (up to 280) randomized subjects have completed the Week 26 6MWD assessment or prematurely discontinued from the study, the final analysis for the 6MWD endpoint and an IA for the TTCW endpoint will be performed by the ISAC for the IDMC.
•Time point 4: when all (up to 280) randomized subjects have completed the DB treatment period or the post-treatment observation period (PTOP) or prematurely discontinued from the study, the DB database will be locked, the data extract will be performed and unblinding will occur. The final analysis for all endpoints will be performed by the sponsor.
• Time point 5: when all (up to 280) randomized subjects have performed their End-of-Study (EOS) visit, an analysis including OL period data will be performed by the sponsor.

Intervention

Investigational treatment:
Double-blind and open-label selexipag 200 µg, oral tablets in childproof bottles, up-titrated to allow each subject to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to 1600 µg twice daily (b.i.d.). Depending on the iMTD, a single dose of double-blind and open-label study treatment will consist of 1 to 8 tablets (200 µg to 1600 µg).

Comparator and/or placebo:
Matching placebo, b.i.d.

Study burden and risks

The histopathologic findings, including endothelial cell dysfunction and distal pulmonary arterial remodeling, between PAH and CTEPH closely resemble each other [Humbert 2010, see reference in the protocol]. The rationale for this study is therefore based on efficacy of PH-specific therapies such as riociguat and macitentan in inoperable and persistent/recurrent CTEPH. Selexipag is an orally available, selective and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) having the unique advantage to target the prostacyclin pathway for the treatment of PAH and may also be beneficial in patients with CTEPH. The purpose of the study is to evaluate the efficacy of selexipag in CTEPH.

Side effects standard of care, side effects lumicitabine, side effects assessments, unknown risks may occur. Safety and tolerability will be evaluated throughout the study from signing of the informed consent form onwards until the last study-related activity (end of study/early withdrawal).
An IDMC will be established to monitor the safety of subjects and will review data in an unblinded manner on a regular basis to ensure the continuing safety

of the subjects enrolled in this study and to evaluate whether efficacy objectives are met. The IDMC will review the data and make recommendations to the Sponsor Committee, which will be responsible for identifying appropriate actions based on the recommendations of the IDMC.
Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and other safety evaluations.

Contacts

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Scientific
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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. Signed and dated ICF.
2. Male and female subjects >=18 (or the legal age of consent in the jurisdiction in which the study is taking place) and <= 85 years old at screening (visit 1)
3. Subjects with diagnosis of CTEPH and inoperability confirmed by the corresponding adjudication committee (AC; country-specific adjudication committee [CSAC] or
central adjudication committee [CAC]), defined as one of the following options:
a) Inoperable CTEPH (i.e., technically non-operable) with:
- Diagnosis of CTEPH based on at least two of the following assessments performed in the 14-month period prior to randomization (Visit 2): ventilation/perfusion (V/Q) scan; pulmonary angiography (PA); computed tomography pulmonary angiogram (CTPA) and/or magnetic resonance angiography (MRA).
- RHC (and LHC if needed) 1 performed at least 90 days after start of full anticoagulation showing: PVR at rest >= 400 dyn.sec/cm5 or >= 5 Wood units for the hemodynamic cohort and PVR at rest >= 300 dyn.sec/cm5 or >=3.75 Wood units for the non-hemodynamic cohort
- mean pulmonary arterial pressure (mPAP) >= 25 mmHg;
- Pulmonary arterial wedge pressure (PAWP) <= 15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) <= 15 mmHg.
b) Persistent/recurrent CTEPH after BPA and deemed inoperable, with:
- Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last interventional (BPA) treatment: V/Q scan, PA, CTPA or MRA.
- RHC (and LHC if needed)performed at least 90 days after last interventional (BPA) treatment and at least 90 days after start of full anticoagulation, showing:
PVR at rest >= 400 dyn.sec/cm5 or >= 5 Wood units for the hemodynamic cohort and PVR at rest >=300 dyn.sec/cm5 or >=3,75 Wood units for the non-hemodynamic cohort;
mPAP >= 25 mmHg;
PAWP <= 15 mmHg, or, if not available or unreliable, an LVEDP <= 15 mmHg.
c) Persistent/recurrent CTEPH after PEA (including PEA followed by BPA) with:
- Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last surgical (PEA) or interventional (BPA) treatment: V/Q scan, PA, CTPA or MRA.
-RHC (and LHC if needed) performed at least 90 days after last surgical (PEA) or interventional (BPA) treatment and at least 90 days after start of full anticoagulation, showing: PVR at rest >= 400 dyn.sec/cm5 or 5 Wood units for the hemodynamic cohort and PVR at rest >=300 dyn.sec/cm5 or >=3,75 Wood units for the non-hemodynamic cohort;
mPAP >= 25 mmHg;

PAWP <= 15 mmHg, or, if not available or unreliable, an LVEDP <= 15 mmHg.
4. PH in WHO FC I-IV.
5. Subject able to perform the 6MWT with a minimum distance of 100 m and a maximum distance of 450 m at screening visit (Visit 1).
6. A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if all the following applies:
a. Negative serum pregnancy test at Screening and a negative urine pregnancy test at randomization.
b. Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.
c. Agreement to use one of the methods of birth control described in Section 4.5 from Screening visit up to at least 30 days after study treatment discontinuation

Exclusion criteria

1. Planned BPA within 26 weeks after randomization.
2. Change in dose or initiation of new PH-specific therapy within 90 days prior to the baseline RHC (and LHC if needed) qualifying for enrollment for the hemodynamic cohort and within 90 days prior to randomization (Visit 2) for the non-hemodynamic cohort
3. Treatment with prostacyclin (epoprostenol), prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e., selexipag/Uptravi) within 90 days prior to randomization (Visit 2), except those given at vasodilator testing during RHC
4. Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC (and LHC if needed).
Exclusion criteria related to comorbidities
5. Severe coronary heart disease or unstable angina as assessed by the investigator.
6. Myocardial infarction within the last 6 months prior to screening.
7. Decompensated cardiac failure if not under close supervision.
8. Severe arrhythmias as assessed by the investigator.
9. Cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months prior to screening.
10. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.
11. Known or suspicion of pulmonary veno-occlusive disease. Exclusion criteria related to selexipag use
12. Known and documented severe hepatic impairment.
13. Severe renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m2 or serum creatinine > 2.5 mg/dL) at screening.
14. Known or suspected uncontrolled thyroid disease as per investigator judgment.
15. Pregnant, planning to be become pregnant or lactating.

16. Treatment with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil) within 14 days prior to randomization.
17. Systolic blood pressure < 90 mmHg at screening (Visit 1) or at randomization (Visit 2).
18. Known hypersensitivity to selexipag or drugs of the same class, or any of their excipients.
19. Planned or current treatment with another investigational treatment up to 3 months prior to randomization.
20. Any co-morbid condition that may influence the ability to perform a reliable and reproducible 6MWT, including use of walking aids (cane, walker, etc.).
21. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease.
22. Known concomitant life-threatening disease with a life expectancy < 12 months.

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:	Recruiting
Start date (anticipated):	06-02-2020
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Uptravi
Generic name:	Selexipag
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2021
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	EUCTR2018-002823-41-NL
ClinicalTrials.gov	NCT03689244
CCMO	NL67626.029.18

Study results

Results posted: 01-06-2023

Actual enrolment: 0

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File