A Phase 3, Prospective, Multicenter, Double-blind, Double-dummy, Randomized, Active-controlled, Parallel-group, Group-sequential, Adaptive, Event-driven Study to Compare Efficacy, Safety, and Tolerability of Macitentan 75 mg Versus Macitentan 10 mg in Patients with Pulmonary Arterial Hypertension, Followed by an Open-label Treatment Period With Macitentan 75 mg

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This study has been transitioned to CTIS with ID 2024-515669-32-00 check the CTIS register for the current data. The purpose of this study is to demonstrate superiority of macitentan 75 milligrams (mg) in prolonging the time to the first clinical...

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

Summary

ID

NL-OMON54353

Source
ToetsingOnline

Brief title
UNISUS

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: sponsor

Intervention

Keyword: Arterial, Hypertension, Pulmonary

Outcome measures

Primary outcome

Double-blind Treatment Period:

Time to First Clinical Events Committee (CEC)-adjudicated Morbidity or

Mortality (M/M) Events.

Secondary outcome

Double-blind Treatment Period: Change From Baseline to Week 24 in 6MWD

Double-blind Treatment Period: Time to First occurrence of either

CEC-adjudicated Death or Hospitalization due to PAH

Double-blind Treatment Period: Change From Baseline to Week 24 in PAH Symptoms

Based on PAH-SYMPACT Questionnaire- Cardiopulmonary Symptom Domain Score

Double-blind Treatment Period: Change From Baseline to Week 24 in PAH Symptoms

Based on PAH-SYMPACT Questionnaire- Cardiovascular Symptom Domain Score

Double-blind Treatment Period: Time to Death Occurring Between Randomization

and End of Double-blind Treatment (EDBT)

Treatment Extension Period: Time to Death Occurring Between Randomization and

End of Study (EOS)

Study description

Background summary

Pulmonary arterial hypertension (PAH) is a syndrome of diverse etiology and pathogenesis, characterized by a persistent increase in pulmonary vascular resistance (PVR) progressing to right heart failure and death. PAH is associated with structural changes in the pulmonary vasculature as well as the right ventricle. The changes in vascular structure involve vasoconstriction, vascular-wall remodeling, and thrombosis in situ.

It remains a severe and incurable disease despite the availability of multiple drugs active by four routes of administration (iv, subcutaneously, orally, and inhaled).
Currently used therapies target three main pathways important in endothelial function: the prostacyclin and nitric oxide (NO) pathways, which are under-expressed in PAH patients, and the endothelin pathway, which is overexpressed in PAH patients.

Published data from the COMPERA registry showed that in a population of treatment-naïve, newly diagnosed PAH patients, mortality rates at 1 year after diagnosis varied from 2.8% in the low-risk cohort to 21.2% in the high-risk cohort according to predefined disease risk criteria comprising the assessment of patient World Health Organization Functional Class (WHO FC), results of the 6 minute walking distance test (6MWT), b-type natriuretic peptide (BNP) or N terminal pro BNP (NT-proBNP) values and hemodynamic values (ie, right atrial pressure, cardiac index and mixed venous oxygen saturation).

Macitentan (JNJ-67896062 [also known as ACT-064992]) is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin-1 (ET-1) to both ETA and ETB receptors. Macitentan 10 mg once daily (qd) is approved worldwide for the treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression and reduce rate of hospitalization for PAH as monotherapy or in combination with other PAH therapies.

Macitentan 10 mg once daily (qd) is approved world-wide for the treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression and reduce rate of hospitalization for PAH as monotherapy or in combination with other PAH therapies. Refer to the local Prescribing Information for more information.

Given the current need to further improve long term outcome (ie, survival), by reducing further occurrence of morbidity events and/or improving patient disease risk status for clinical worsening and death defined by specific criteria (eg, exercise capacity, WHO FC, NT-proBNP), patients may benefit from receiving macitentan at a higher dose in order to further block ETB receptors, which are overexpressed in the lung/vessels of patients with PH related disease.

Study objective

This study has been transitioned to CTIS with ID 2024-515669-32-00 check the CTIS register for the current data.

The purpose of this study is to demonstrate superiority of macitentan 75 milligrams (mg) in prolonging the time to the first clinical events committee (CEC)-adjudicated morbidity or mortality (M/M) event in participants with symptomatic pulmonary arterial hypertension (PAH) compared to macitentan 10 mg.

Study design

This is a Phase 3 prospective, multicenter, double-blind, double-dummy, randomized, active controlled, parallel-group, group-sequential, adaptive, event-driven superiority study in patients with PAH (PH group 1), to evaluate the efficacy, safety, and tolerability of 75 mg macitentan vs 10 mg macitentan.
- Screening period (Max 30 days)
- 4 week run-in period (if applicable)
- randomised dubbel blind period: 1:1 randomisation - 10mg macitentan + matching placebo / or / 75 mg macitentan + matching placebo.
- safety follow-up period / open label period

Intervention

1:1 randomisation period

Group 1: macitentan 10mg + matching placebo
Group 2: macitentan 75mg + matching placebo

Macitentan and matching placebo will be provided as film-coated tablets with a dose strength of 10 mg, 37.5 mg, or 75 mg in childproof bottles. The tablets are administered orally and should be swallowed whole (ie, not crushed, split or chewed) with water during meals. Dosing frequency will be once a day.

Extension period open label:
Macitentan 75mg for all subjects fulfilling the criteria.

Study burden and risks

Overall Benefit/Risk Assessment
The overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:
* There is still a clear unmet medical need to further delay disease progression (and death) and reduce hospitalization for PAH.
* Macitentan 75 mg may offer participants a more potent treatment alternative option than macitentan 10 mg to further delay disease progression and time to death (see Section 4.3).
* Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study, in particular with the requirement for initially restricted exclusion criteria.
* Safety will be closely monitored throughout the study:
* In general, safety evaluations (see Section 8.3) will be performed at scheduled visits during the study, as indicated in the Schedule of Activities. Frequency of visits and planned study assessments are deemed adequate to ensure a close safety monitoring of study participants and assess their disease progression.
* The investigator or the designee will document unsolicited AEs as indicated in Appendix 4.
* Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable condition is reached.
* Safety measures are included in this protocol to minimize the potential risk to participants, including the following:
* Run-in period with macitentan 10 mg for pre-defined participants (see Section 4.1)
* Initially restricted inclusion criteria (see Section 5)
* Initial safety monitoring (see Section 8.3)
* Special attention will be paid to the AEs of special interest as defined in Section 8.4.5
* Specific recommendations are provided for study treatment interruption and discontinuation (Section 7)

* The study will be closely monitored by an external IDMC throughout its conduct.
* Serious hepatic AEs of special interest (HAESIs) will be reviewed by the ILSDRB (see Section 8.4.5)
It is the investigator*s responsibility to monitor the individual benefit/risk of study intervention administration, as well as the degree of distress caused by study procedures at an individual participant level, and to discontinue study intervention or the study if he/she considers that continuation would be detrimental to the participant*s well-being.
More detailed information about the known and expected benefits and risks of macitentan may be found in the IB21 and local Prescribing Information.

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

- Target population: greater than or equal to (><=) 18 (or the legal age of consent in the jurisdiction in which the study is taking place) years of age
- Target population: Symptomatic Pulmonary Arterial Hypertension (PAH) in World Health Organization,Functional Class (WHO FC) II, III, or IV
- Target population: PAH subtype falling in one of the below classifications: Idiopathic; Heritable; Drug- or toxininduced; Related to: Connective tissue disease, HIV infection, Portal hypertension, and Congenital heart disease with small/coincidental cardiac defect with systemic-to-pulmonary shunt (for example atrial septal defect, ventricular septal defect, patent ductus arteriosus, atrioventricular septal defect) which does not account for the elevated pulmonary vascular resistance (PVR) or persistent PAH documented by an Right heart catheterization (RHC) >< = 1 year after simple systemic-to pulmonary shunt repair
- PAH diagnosis confirmed by hemodynamic evaluation at rest at any time prior to screening: Mean pulmonary artery pressure (mPAP) greater than (>) 20 millimeters of mercury (mm Hg), and; Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) less than or equal to (<<=) 15 mm Hg, and PVR >< = 3 Wood Units (that is, >< = 240 dyn*sec/cm^5)
- Able to perform the 6-minute walking test (6MWT) with a minimum distance of 50 meters (m) and maximum distance of 440m at screening. Participants able to walk more than 440m at screening are eligible if they are in WHO FC III or IV and n-terminal prohormone of brain natriuretic peptide or n-terminal pro B-type natriuretic peptide (NT-proBNP) level is ><=300 nanograms per liter (ng/L) at screening, based on central laboratory results

Exclusion criteria

- Known presence of three or more of the following risk factors for heart failure with preserved ejection fraction at screening, based on records that confirm documented medical history: Body mass index (BMI) > 30 kilograms per meter square (kg/m^2), Diabetes mellitus of any type, Essential hypertension (even if well controlled); Coronary artery disease, that is, any of the following: history of stable angina, or known more than 50 percent (%) stenosis in a coronary artery, or history of myocardial infarction, or history of or planned coronary artery bypass grafting and/or coronary artery stenting
- Presence of moderate or severe obstructive lung disease (forced expiratory volume in 1 second [FEV1] / forced vital capacity [FVC] < 70%; and FEV1 < 60% of predicted after bronchodilator administration)) in participants with a known or suspected history of significant lung disease as documented by a spirometry test performed within 1 year prior to screening
- Known moderate to severe hepatic impairment, defined as Child-Pugh Class B or C, based on records that confirm documented medical history

- Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5*upper limit of normal (ULN) at screening
- Hemoglobin < 100 gram per liter (g/L) (< 10 gram per deciliter [g/dL]) at screening

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-12-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opsumit
Generic name:	macitentan
Product type:	Medicine
Brand name:	Opsumit
Generic name:	macitentan 75mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-04-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-06-2021

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-02-2023

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-07-2024

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EU-CTR	CTIS2024-515669-32-00
EudraCT	EUCTR2019-002533-11-NL
ClinicalTrials.gov	NCT04273945
CCMO	NL73393.091.20