Multi-center, blinded, randomized, PaRAllEl-group, Phase 3 study with aproCItentan in Subjects with Resistant HypertensiON (RHT)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON48671

Source
ToetsingOnline

Brief title
PRECISION

Condition

- Cardiac arrhythmias
- Vascular hypertensive disorders

Synonym
Increased blood pressure insusceptible for 3 or more blood lowering drugs, Resistant hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Idorsia Pharmaceuticals
Source(s) of monetary or material Support: Bedrijf

Intervention

Keyword: aprocitentan, blood pressure lowering, Resistant hypertension

Outcome measures

Primary outcome

The primary efficacy endpoint is the change from baseline to Week 4 of DB

treatment in mean trough sitting SBP measured by AOBPM.

Baseline is defined as the last available measurement before the start of DB

treatment.

Secondary outcome

The key secondary efficacy endpoint is the change from Week 36 to Week 40 of

double blind withdrawal treatment in mean trough sitting SBP measured by AOBPM.

Study description

Background summary

Hypertension is a *silent* killer that rarely causes symptoms. Hypertension is defined in adults by (office) systolic/diastolic blood pressure >= 140/90 mmHg. This condition represents a significant global public health concern, as it contributes to vascular and renal morbidity, cardiovascular mortality, and economic burden.
Despite current knowledge on the management of hypertension and the availability of numerous effective antihypertensive drugs, hypertension remains inadequately controlled in many patients. A number of these uncontrolled patients are considered to have so called *resistant hypertension* or *difficult-to-control hypertension*, which is defined as uncontrolled blood pressure in patients adhering to lifestyle modifications and to an appropriate regimen of three or more antihypertensive drugs from different pharmacological classes, including a diuretic, in the absence of secondary cause of

hypertension.
The estimated prevalence of resistant hypertension varies from 2 to 30% of the hypertensive population. This broad range of the estimate is mainly due to the different sources of information (e.g., insurance healthcare systems, registries, well-controlled therapeutic clinical trials). It is not always clear from these reports whether the prevalence is for *apparent* or *true* resistant hypertension.
A critical characteristic of most *true* resistant hypertension patients is their complex medical condition.
Compared to the hypertensive population, resistant hypertension patients are more likely to be older (> 75 years), to be of black race, to have a higher body mass index, albuminuria, reduced renal function, self-reported co-morbidities of diabetes mellitus, coronary heart disease, and sleep apnea. Chronic kidney disease and diabetes mellitus, in particular, amplify the resistant hypertension patients* vulnerability and increase the complexity of resistant hypertension treatment. In addition, in resistant hypertension patients, the risk of cardiovascular events is much higher than in the rest of the hypertensive population. This has been consistently shown in different settings (i.e., clinical trials, observational studies, and international registries) comparing resistant hypertension vs non- resistant hypertension patients. Consequently, it is important to control BP in the resistant hypertension population.

Study objective

The primary objective of the study is to demonstrate the BP lowering effect of aprocitentan when added to standard-of-care in true resistant hypertension subjects.

The secondary objectives of the study are
• to demonstrate that the effect of aprocitentan on BP is durable when added to standard-of-care in true resistant hypertension subjects
• to evaluate the long-term safety and tolerability of aprocitentan in true resistant hypertension subjects during 48 weeks of treatment.

Other objectives:
• Evaluate steady-state trough plasma concentrations of aprocitentan after 4 weeks of treatment.
• Evaluate the endothelin system activity and the effect of aprocitentan on micro- and macrovascular complications based on specific biomarkers.

Study design

This is a prospective, multicenter, randomized, parallel-group, blinded Phase 3 study with aprocitentan in subjects with true resistant hypertension.
Approximately 4000 subjects are expected to be screened, in order to enroll

about 1500 subjects with diagnosis of resistant hypertension into the SB placebo Randomized I period. At least 600 subjects will be randomized and at least 300 subjects are expected to complete the study (i.e., the 30 day safety follow-up period). The study will be conducted in approximately 100 sites in approximately 20 countries.
The study comprises the following consecutive periods: screening period, placebo run-in period, randomized treatment period and safety follow-up. Subject participation in the study will be up to 68 weeks.

Intervention

During the screening period, subjects will be switched to the standardized background antihypertensive therapy.
In the run-in period all subjects will receive placebo in a single blinded fashion.
At Visit 4 the subjects are randomized to aprocitentan 12.5 mg, aprocitentan 25 mg or placebo in a 1:1:1 ratio.
At the end of the double blind part (Week 4) all subjects will be assigned to 25 mg aprocitentan.

Study burden and risks

Based on the mechanism of action of aprocitentan, current nonclinical data, and clinical data from the Phase 1 studies and Phase 2 study in adult subjects with essential hypertension on mono-therapy, it is anticipated that aprocitentan will reduce the blood pressure of subjects participating in this study in a durable and safe manner.
During the study subjects will be carefully followed at regular visits for up to 68 weeks in hypertension specialized hospital departments. All visit assessments (e.g., blood pressure measurement, blood sampling, electrocardiogram [ECG]) are part of the routine standard-of-care for subjects with resistant hypertension, although their frequency may be higher in the study. The most invasive procedure repeated at each visit will be blood sampling.

An Independent Data Monitoring Committee (IDMC) has overall responsibility for safeguarding the interests of subjects by monitoring the relationship between benefits and risks and by giving the appropriate recommendations on the basis of all reported data. This ensures that the IDMC ensures that the research is carried out in compliance with the highest scientific and ethical standards.
The IDMC will be fully operational before the first subject is included in the study. The composition and operation of the IDMC are described in the IDMC charter.

An independent Clinical Adjudication Committee assesses and confirms in a blinded way, all reported cases of Major Adverse Cardiac Events.

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

- Screening criteria:
Signed and dated ICF prior to any study-mandated procedure;
Male and female subjects; 18 years (or year of country specific majority) or older;
Historical documentation in the subject*s medical records on uncontrolled BP despite at least 3 background antihypertensive medications within 1 year before screening visit;
Treated with at least 3 antihypertensive therapies of different pharmacological classes including a diuretic for at least 4 weeks before the screening visit (Visit 1);
Mean SiSBP >= 140 mmHg measured by AOBPM;
Women of childbearing potential are eligible only if the following applies;

Negative pregnancy test at screening and at baseline (i.e., end of RI period);
Agreement to undertake pregnancy tests during the study and up to 30 days after randomized study treatment discontinuation;
Agreement to use methods of birth control from Screening up to at least 30 days after randomized study treatment discontinuation., - Run-in entry criteria:
Switched to the standardized background antihypertensive therapy at least 4 weeks before the first RI visit;
Mean trough SiSBP >= 140 mmHg measured by AOBPM., - Randomization criteria:
Stable dose of the standardized background antihypertensive therapy since the start of the RI period;
Mean trough SiSBP >= 140 mmHg measured by AOBPM.

Exclusion criteria

- Apparent/pseudo RHT due to white coat effect, medical inertia, poor therapeutic adherence, or secondary causes of hypertension (except sleep apnea);
- Confirmed severe hypertension (grade 3) defined as SiSBP >= 180 mmHg and/or SiDBP >= 110 mmHg as measured by AOBPM at two different time points.;
- Pregnant or lactating subjects;
- Clinically significant unstable cardiac disease in the opinion of the investigator;
- Severe renal insufficiency;
- N-terminal pro-brain natriuretic peptide (NT-proBNP) >= 500 pg/mL;
- Any known factor, disease or clinically relevant medical or surgical conditions that, in the opinion of the investigator, might put the subject at risk, interfere with treatment compliance, study conduct or interpretation of the results

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:	Completed
Start date (anticipated):	29-11-2018
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	aprocitentan
Generic name:	aprocitentan
Product type:	Medicine
Brand name:	Exforge HCT
Generic name:	amlodipine/□valsartan/□hydrochloorthiazide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	05-11-2018
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2021
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	EUCTR2017-004393-33-NL
CCMO	NL65338.018.18

Study results

Date completed:	25-04-2022
Results posted:	08-05-2023

First publication

01-01-1900