Obicetrapib on Top of Maximum Tolerated Lipid-ModifyingTherapies (BROADWAY): A Placebo-Controlled, Double-Blind, Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With Underlying HeFH and/or Atherosclerotic Cardiovascular Disease (ASCVD) Who are Not Adequately Controlled by Their Lipid-Modifying Therapies;Protocol v6.0

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Synopsis, page 4-5OBJECTIVES:The primary objective of this study is to evaluate the effect of obicetrapib on LDL-C levels at Day 84.The secondary objectives of this study include the following:• To evaluate the effect of obicetrapib on LDL-C levels...

Ethical review	Approved WMO
Status	Completed
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON53507

Source
ToetsingOnline

Brief title
BROADWAY

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
cardiovascular (CV) disease, hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: NewAmsterdam Pharma BV
Source(s) of monetary or material Support: NewAmsterdam Pharma BV

Intervention

Keyword: Atherosclerosis, Atherosclerotic Cardiovascular Disease, LDL-cholesterol, statins

Outcome measures

Primary outcome

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The primary efficacy endpoint is the percent change from Baseline to Day 84 in

LDL-C in the obicetrapib group compared to the placebo group.

Secondary outcome

The secondary efficacy endpoints include the following:

• Percent change from Baseline to Days 180 and 365 in LDL-C in the obicetrapib

group compared to the placebo group;

• Percent change from Baseline to Days 84, 180, and 365 in ApoB in the

obicetrapib group compared to the placebo group;

• Percent change from Baseline to Days 84, 180, and 365 in non-HDL-C in the

obicetrapib group compared to the placebo group;

• Percent change from Baseline to Days 84, 180, and 365 in HDL-C in the obicetrapib group compared to the placebo group;

• Percent change from Baseline to Day 84 in Lp(a) and ApoA1 in the obicetrapib group compared to the placebo group;

• Percent change from Baseline to Days 84, 180, and 365 in TC in the obicetrapib group compared to the placebo group; and

• Percent change from Baseline to Days 84, 180, and 365 in TG in the obicetrapib group compared to the placebo group.

The exploratory efficacy endpoints include the following:

• Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <70 mg/dL (<1.8 mmol/L) in the obicetrapib group compared to the placebo group;

• Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <55 mg/dL (<1.4 mmol/L) in the obicetrapib group compared to the placebo group;

• Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <40 mg/dL (<1.0 mmol/L) in the obicetrapib group compared to the placebo group;

• Percent change from Baseline to Day 365 in HbA1c in the obicetrapib group compared to the placebo group;

• Percent change from Baseline to Day 365 in HOMA-IR in the obicetrapib group compared to the placebo group;

• Percent change from Baseline to Day 365 in blood glucose in the obicetrapib group compared to the placebo group;

• Trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;

• The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization;

• The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke; and

• The time from Randomization until the first confirmed occurrence of hospitalization for unstable angina and/or chest pain, hospitalization for HF, and TIA.

Study description

Background summary

Atherosclerotic cardiovascular disease (ASCVD) is the build-up of fats, cholesterol and other substances in and on the artery walls (blood vessels).

A high Low Density Lipoprotein Cholesterol (LDL-C) level is a major risk factor for the development of disease of the heart and blood vessels. Lowering LDL-C has been shown to reduce the risk of death, heart attack, and other major heart and blood vessel problems (cardiovascular events).

Your LDL-C blood level remains high despite use of the maximum tolerated dose of the medication you currently take, or you are unable to take LDL-C lowering medication because you cannot tolerate statins or other medicines that lower LDL-C such as ezetimibe (Zetia®) or PCSK9 inhibitors (Praluent® or Repatha®) .

People with high LDL-C levels often have low levels of HDL-C (High Density Lipoprotein Cholesterol, the *good* cholesterol), in their blood. CETP (Cholesteryl ester transfer protein) is a protein found in blood which can reduce HDL-C levels and increase LDL-C levels.

Obicetrapib, the study medicine, is designed to block the CETP protein, which should lead to lower LDL-C levels. This may help lower the risk of cardiovascular events, though this has yet to be proven.

Study objective

Synopsis, page 4-5

OBJECTIVES:
The primary objective of this study is to evaluate the effect of obicetrapib on LDL-C levels at Day 84.

The secondary objectives of this study include the following:
• To evaluate the effect of obicetrapib on LDL-C levels at Days 180 and 365;
• To evaluate the effect of obicetrapib on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non HDL C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG) at Days 84, 180, and 365;
• To evaluate the effect of obicetrapib on lipoprotein (a) (Lp[a]) and apolipoprotein A1 (ApoA1) at Day 84; and
• To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with HeFH and/or ASCVD of all ages, assessed by adverse events (AEs), events of special interest (ESIs), vital signs (including blood pressure), electrocardiogram (ECG) measurements, and clinical laboratory values.

The exploratory objectives of this study include the following:
• To evaluate the effect of obicetrapib on the following:
o Proportion of participants achieving prespecified LDL-C levels at Days 84, 180, and 365; and
o Biomarkers, including glycosylated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and blood glucose at Day 365.
• To evaluate trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;
• To evaluate the effect of obicetrapib on CV death, non fatal myocardial infarction (MI), non fatal stroke, or non elective coronary revascularization; and
• To evaluate the effect of obicetrapib on hospitalization for unstable angina and/or chest pain, hospitalization for heart failure (HF), and transient ischemic attack (TIA).

Study design

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STUDY DESIGN AND DURATION:
This study will be a multisite, placebo-controlled, double-blind, randomized Phase 3 study in approximately 2400 participants with underlying HeFH and/or a history of ASCVD who are not adequately controlled by their lipid-modifying therapy to evaluate the efficacy, safety, and tolerability of obicetrapib. Informed consent will be obtained from participants before the initiation of any study-specific procedures. Approximately 2400 eligible participants will be randomized in a 2:1 ratio, respectively, to the following treatment groups:

• Obicetrapib group: One 10 mg obicetrapib tablet once daily; or
• Placebo group: 1 placebo tablet once daily.

Treatment allocation will be stratified based on CV risk (HeFH or non-HeFH) and Baseline statin dose (HIS or non-HIS). At least 70% of the participants enrolled into this study must be taking HISs. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study. Starting on Day 1, each participant will self-administer their assigned study drug once daily until Day 365. During the Treatment Period, participants will return to the study site for efficacy and safety assessments. Blood samples for pharmacokinetic (PK) assessment will be collected at specified visits throughout the study. An onsite End of Study (EOS) Visit will be conducted 35 days after the participant*s last dose of study drug, during which an assessment of vital signs, concomitant medications, CV events, and AEs will be completed and documented in the participant*s record.The study will be governed by a Steering Committee. A Data and Safety Monitoring Board (DSMB) will provide independent oversight of participant safety. An independent Clinical Events Committee (CEC) will adjudicate all events of death and all potential or suspected CV events.

A subset of approximately 200 participants from selected study sites who consent to participate will be enrolled in an ambulatory blood pressure monitoring (ABPM) substudy. These participants will have a 24-hour ABPM assessment conducted at Screening (Visit 1) and Visit 6 (Day 270). In order to participate in the substudy, participants must provide written informed consent in a substudy-specific informed consent form (ICF) and must be able to provide an acceptable 24-hour ABPM data collection at Screening (Visit 1). Additional details surrounding this substudy, including the definition of an acceptable 24-hour ABPM data collection, are included in a separate study manual.

Intervention

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DOSAGE FORMS AND ROUTE OF ADMINISTRATION:
The study drugs used in this study are as follows:
• 10 mg obicetrapib tablet; or
• Placebo tablet.

All study drug will be administered by the participant orally, once daily at approximately the same time, from Visit 2 (Day 1) to the End of Treatment Visit (Day 365). Study drug should be administered with water and can be taken with or without food.

Study burden and risks

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SAFETY ENDPOINTS:
The safety endpoints include the following:
• Safety and tolerability profile of obicetrapib assessed by AEs, ESIs, vital signs (including blood pressure as assessed by office blood pressure measurements), ECGs, and clinical laboratory values; and.
• Assessment of ABPM measured at Baseline and at Day 270.
All potential or suspected CV events will be reviewed and adjudicated by an independent CEC and reported in the appropriate clinical endpoint eCRF. In addition, these events are subject to normal AE/serious AE reporting procedures.

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.Are willing and able to give written informed consent before initiation of any study-related procedures and willing to comply with all required study procedures;

2.Are male or female >=18 years of age at Screening (Visit 1);
Females may be enrolled if all 3 of the following criteria are met:
- They are not pregnant;
- They are not breastfeeding; and
- They do not plan on becoming pregnant during the study;
Females of childbearing potential must have a negative urine pregnancy test at Screening (Visit 1);

3.Have underlying HeFH and/or a history of ASCVD defined by at least 1of the following conditions:
- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease

4.Are on maximally tolerated lipid-modifying therapy as an adjunct to a lipid-lowering diet and other lifestyle modifications defined as follows:
- A statin at a maximally tolerated stable dose;
- Ezetimibe for at least 8 weeks with or without maximally tolerated statin prior to Screening (Visit 1);
- Bempedoic acid for at least 8 weeks in combination with a maximally tolerated statin prior to Screening (Visit 1); and/or
- A PCSK9-targeted therapy alone or in combination with other lipid-modifying therapy for at least 4 stable doses prior to Screening (Visit 1);

Note: at least 70% of the participants enrolled into this study must be taking HISs. Documentation in the eCRF of the reason why a participant is unable to take HIS is required. HISs include the following:
- Atorvastatin 40 and 80 mg; and
- Rosuvastatin 20 and 40 mg

5.Have a fasting serum LDL-C at Screening (Visit 1) as follows:
- Have a fasting serum LDL-C >=55 mg/dL (>=1.4 mmol/L) to <100 mg/dL (<2.6 mmol/L) OR non-HDL-C >=85 mg/dL (>=2.2 mmol/L) to <130 mg/dL (<3.4 mmol/L) with at least 1 of the following risk enhancers:
- Recent MI (>3 and <12 months prior to Randomization [Visit 2]);
- Type 2 diabetes mellitus;
- Current daily cigarette smoking;
- Age of >60 years;
- High sensitivity C-reactive protein >=2.0 mg/L (>=19.0 nmol/L) at

Screening (Visit 1) or within 6 months prior to Screening (Visit 1);
- Fasting TG >150 mg/dL (>1.7 mmol/L);
- Fasting Lp(a) >30 mg/dL (>70 nmol/L); and/or
- Fasting HDL-C <40 mg/dL (<1.0 mmol/L); OR
- Have a fasting serum LDL-C >=100 mg/dL (>=2.6 mmol/L) OR non-HDL-C >=130 mg/dL (>=3.4 mmol/L).

6.Have fasting TG <500 mg/dL (<5.7 mmol/L) at Screening (Visit 1); and

7.Have an estimated glomerular filtration rate (eGFR) >=30 mL/min/1.73m2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening (Visit 1).

Other protocol-defined criteria apply.

Exclusion criteria

1.Have current or any previous history of New York Heart Association class III or IV HF or left ventricular ejection fraction <30%;

2.Have been hospitalized for HF within 5 years prior to Screening (Visit 1);

3.Have had any of the following clinical events within 3 months prior to Screening (Visit 1):
o Non-fatal MI;
o Non-fatal stroke;
o Non-elective coronary revascularization; and/or
o Hospitalization for unstable angina and/or chest pain;

4.Have uncontrolled severe hypertension, defined as either systolic blood pressure >=160 mmHg or diastolic blood pressure >=100 mmHg prior to Randomization (visit 2) taken as the average of triplicate measurements. One triplicate retest will be allowed during the same visit, at which point if the retest result is no longer exclusionary, the participant may be randomized;

5.Have a formal diagnosis of homozygous familial hypercholesterolemia;

6.Have active liver disease, defined as any known current infectious, neoplastic, or metabolic pathology of the liver; unexplained elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN); or total bilirubin >2 x ULN at Screening (Visit 1);

7.Have HbA1c >=10.0% (>=0.100 hemoglobin fraction) or a fasting glucose >=270 mg/dL (>=15.0 mmol/L) at Screening (Visit 1);

8.Have thyroid-stimulating hormone >1.5 x ULN at Screening (Visit 1);

9.Have creatine kinase >3 x ULN at Screening (Visit 1);

10.Have a history of a malignancy that required surgery (excluding local and wide local excision), radiation therapy, and/or systemic therapy during the 3 years prior to Randomization (Visit 2);

11.Have a known history of alcohol and/or drug abuse within 5 years prior to Randomization (Visit 2);

12.Have received treatment with other investigational products or devices within 30 days of Screening (Visit 1) or 5 half lives of the previous investigational product, whichever is longer;

13. Are taking gemfibrozil or have taken gemfibrozil withing 30 days of Screening (Visit 1);

14.Have planned use of other investigational products or devices during the course of the study;

15.Have participated in any clinical study evaluating obicetrapib;

16.Have a known allergy or hypersensitivity to the study drug, placebo, or any of the excipients in the study drug or placebo; or

17.Have any participant condition that, according to the Investigator, could interfere with the conduct of the study, such as, but not limited to, the following:
o Are unable to communicate or to cooperate with the Investigator;
o Are unable to understand the protocol requirements, instructions and study-related restrictions, and the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency);
o Are unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study);
o Have any medical or surgical condition which, in the opinion of the Investigator, would put the participant at increased risk from participating in the study; or
o Are directly involved in the conduct of the study. Other protocol-defined criteria apply.

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):	28-06-2022
Enrollment:	289
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	TA-8995
Generic name:	Obicetrapib

Ethics review

Approved WMO Date:	01-03-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2022
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	22-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-05-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2021-005065-40-NL
ClinicalTrials.gov	NCT05142722
CCMO	NL80107.100.22