Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapies (BROOKLYN): A Placebo-Controlled, Double-Blind, Randomized, Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With a History of HeFH and LDL C >= 70 mg/dL Who are Not Adequately Controlled by Their Lipid Modifying Therapies

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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 fasting apolipoprotein B (ApoB), non-…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON53451

Source
ToetsingOnline

Brief title
BROOKLYN

Condition

- Lipid metabolism disorders

Synonym
Familial hypercholesterolemia, high cholesterol

Research involving
Human

Sponsors and support

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

Intervention

Keyword: dyslipidemia, heterozygous familial hypercholesterolemia, high cholesterol, LDL-cholesterol

Outcome measures

Primary outcome

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

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

Secondary outcome

Secondary efficacy endpoints: 1. Percent change from Baseline to Days 180 and 365 in fasting LDL-C in the obicetrapib group compared to the placebo group; 2. Percent change from Baseline to Days 84, 180, and 365 in fasting ApoB in the obicetrapib group compared to the placebo group; 3. Percent change from Baseline to Days 84, 180, and 365 in fasting non-HDL-C in the obicetrapib group compared to the placebo group; 4. Percent change from Baseline to Days 84, 180, and 365 in fasting HDL-C in the obicetrapib group compared to the placebo group; 5. Percent change from Baseline to Days 84 and 365 in fasting Lp(a) in the obicetrapib group compared to the placebo group; 6. Percent change from Baseline to Days 84, 180, and 365 in fasting TC in the obicetrapib group compared to the placebo group; and 7. Percent change from Baseline to Days 84, 180, and 365 in fasting TG in the obicetrapib group compared to the placebo group. The exploratory efficacy endpoints include the following: - Individual responsiveness defined as the number of participants reaching on treatment fasting LDL-C levels of <40 mg/dL (<1.04 mmol/L), <55 mg/dL (<1.42 mmol/L), <70 mg/dL (<1.81 mmol/L), and <100 mg/dL (<2.59 mmol/L) at Days 84 and 365; - Individual responsiveness defined as the number of participants reaching on treatment fasting non-HDL-C levels of <85 mg/dL (<2.20 mmol/L), <100 mg/dL (<2.59 mmol/L), and <130 mg/dL (<3.37 mmol/L) at Days 84 and 365; - Individual responsiveness defined as the

number of participants reaching on treatment fasting ApoB levels of <65 mg/dL (<0.65 g/L), <80 mg/dL (<0.80 g/L), and <130 mg/dL (<1.30 g/L) at Days 84 and 365; - Percent change from Baseline to Days 84 and 365 in fasting ApoA1 in the obicetrapib group compared to the placebo group; and - Trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group.

Study description

Background summary

HeFH is a genetic condition that increases the levels of *bad cholesterol* (LDL-C) in your blood.

A high level of bad cholesterol is a major risk factor for the development of disease of the heart and blood vessels. Lowering the *bad cholesterol* has been shown to reduce the risk of death, heart attack, and other major heart and blood vessel problems

Your *bad cholesterol* blood level remains high despite use of the maximum tolerated dose of the medication you currently take, or you are unable to take *bad cholesterol* lowering medication because you cannot tolerate statins or other medicines that lower your *bad cholesterol*.

People with high *bad cholesterol* levels often have low levels of *good cholesterol* (HDL-C, in their blood. This can be the consequence of a specific protein which can reduce the good cholesterol and increase the *bad cholesterol*. Obicetrapib, the study medicine, is designed to block this specific protein, which should lead to lower *bad cholesterol* levels. This may help lower the risk of cardiovascular problems, though this has yet to be proven.

Study objective

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 fasting 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 fasting LDL-C levels at Days 180 and 365;
- To evaluate the effect of obicetrapib on fasting lipoprotein (a) (Lp[a]) at

Days 84 and 365; and
- To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with HeFH, 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 Number of participants reaching prespecified fasting LDL-C, non-HDL-C, and ApoB
levels at Days 84 and 365; and
o Fasting apolipoprotein A1 (ApoA1) at Days 84 and 365.
- To evaluate trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group.

Study design

This study will be a multisite, placebo-controlled, double-blind, randomized, Phase 3 study in approximately 300 participants with a history of HeFH 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 300 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. At least 70% of the participants enrolled into this study must be taking HISs. HeFH diagnosis is defined by existing confirmation via genetic testing, WHO Criteria/Dutch Lipid Clinical Network Criteria with a score of >8 points, and/or Simon Broome Register Diagnostic Criteria. 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. An End of Study (EOS) Visit will be conducted approximately 35 days after the participant*s last dose of study drug, during which vital signs; limited serum chemistry, hematology, and coagulation parameters; pharmacokinetics; concomitant medications; and AEs will be assessed. The study will be governed by a Steering Committee, and a Data and Safety Monitoring Board will provide independent oversight of participant safety. The responsibilities, procedures, and workflow for these committees will be defined in separate charters outside of the protocol.

Intervention

The study drugs used in this study are as follows:
- 10 mg obicetrapib tablet; or
- Placebo tablet.
All study drugs will be administered by the participant orally, once daily at approximately the same time on Days 1 to 365. Study drug should be administered with water.

Study burden and risks

The primary pharmacology in in vitro, ex vivo, and in vivo studies has demonstrated that obicetrapib has the ability to inhibit CETP, decrease LDL-C levels, increase HDL-C levels, and importantly, reduce the number of atherogenic ApoB-containing particles in a way that is useful in the treatment of dyslipidemia.

In clinical studies in healthy volunteers, obicetrapib was generally well tolerated in single doses up to 150 mg and multiple doses up to 25 mg/day for 21 days. In clinical studies in patients, obicetrapib was also well tolerated after daily dosing of 10 mg for 12 weeks, both alone and in combination with 2 different statins. Near maximal effects were observed with the 10 mg obicetrapib dose. At this dose level, CETP activity was reduced, and HDL-C levels were increased while LDL-C levels decreased. There were no dose-related AEs identified and no clinically significant changes in vital signs, ECGs, or hematology or biochemistry parameters in any clinical studies. A statistically significant reduction in Lp(a) levels from Baseline was also observed at the 10 mg obicetrapib dose level. Therefore, the present study will utilize a dose of 10 mg obicetrapib in participants with a history of HeFH who are not adequately controlled by their maximally tolerated lipid-modifying therapy.

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. 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 and >=18 years of age at Screening; o 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. o Females of childbearing potential must have a negative urine pregnancy test at Screening. 3. Have a history of HeFH as defined by at least 1 of the following: o Genotyping by a central laboratory; o Clinical assessment using the WHO Criteria/Dutch Lipid Clinical Network Criteria with a score of >8 points; and/or o Meet the Simon Broome Register Diagnostic Criteria for definite or possible Familial Hypercholesterolemia (FH). 4. Are on maximally tolerated lipid-modifying therapy, as an adjunct to diet, defined as follows: o A statin at a maximally tolerated stable dose; o Ezetimibe for at least 8 weeks with or without maximally tolerated statin prior to Screening; o Bempedoic acid for at least 8 weeks in combination with maximally tolerated statin prior to Screening; o A proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeted therapy alone or in combination with other lipid-modifying therapy for at least 4 stable doses prior to Screening; 5. Have a fasting serum LDL-C >=70 mg/dL (>=1.81 mmol/L) at Screening; 6. Have fasting TG <400 mg/dL (<4.52 mmol/L) at Screening; and 7. Have an estimated glomerular filtration rate >=30 mL/min/1.73 m2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening. Other protocol-defined criteria apply.

Exclusion criteria

1. Have current or any previous history of New York Heart Association class III or IV heart failure (HF) or left ventricular ejection fraction <30%; 2. Have been hospitalized for HF within 5 years prior to Screening; 3. Have had any of the following clinical events within 3 months prior to Screening: o Non-fatal myocardial infarction; 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 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 FH; 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; 7. Have glycosylated

hemoglobin >=10.0% (>=0.100 hemoglobin fraction) or a fasting glucose >=270 mg/dL (>=15.0 mmol/L) at Screening; 8. Have thyroid-stimulating hormone >1.5 X ULN at Screening; 9. Have creatine kinase >3 x ULN at Screening; 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; 11. Have a known history of alcohol and/or drug abuse within 5 years prior to Randomization; 12. Have received treatment with other investigational products or devices within 30 days of Screening or 5 half-lives of the previous investigational product, whichever is longer; 13.Are taking gemfibrozil; 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:	Recruiting
Start date (anticipated):	24-01-2023

Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Obicetrapib
Generic name:	Obicetrapib

Ethics review

Approved WMO Date:	20-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-09-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-03-2023

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2023
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	EUCTR2021-005064-22-NL
ClinicalTrials.gov	NCT05425745
CCMO	NL81010.100.22