Dose response and safety of an oral PCSK9i, NNC0385-0434, in patients with established atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction

Published: 15-06-2021
Last updated: 05-04-2024

Primary objective:To demonstrate superiority of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52178

Source
ToetsingOnline

Brief title
Oral PCSK9i studie

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Cardiovascular disease; heart disease

Research involving
Human

Sponsors and support

Primary sponsor: Novo Nordisk
Source(s) of monetary or material Support: Novo Nordisk

Intervention

Keyword: Dose-response, NNC0385-0434, Oral PCSK9i

Outcome measures

Primary outcome

Change in LDL-cholesterol From baseline (week 0) to visit 9 (week 12) %

Secondary outcome

Supportive secondary endpoints

% Change in total cholesterol From baseline (week 0) to visit 9 (week 12)

% Change in HDL-cholesterol From baseline (week 0) to visit 9 (week 12)

% Change in VLDL-cholesterol From baseline (week 0) to visit 9 (week 12)

% Change in triglycerides From baseline (week 0) to visit 9 (week 12)

% Change in total Apo B From baseline (week 0) to visit 9 (week 12)

% Change in total Apo CIII From baseline (week 0) to visit 9 (week 12)

Ratio Change in total Lp(a) From baseline (week 0) to visit 9 (week 12)

Number of adverse events: Treatment-emergent adverse events From baseline (week

0) to visit 10 (19 weeks + 4 days)

Number of events

Study description

Background summary

The LDL-receptor is located on liver cells and involved in the removal of LDL-C from the circulation. When LDL-C binds to the LDL-receptor, this complex moves into the cell. The LDL-receptor releases LDL-C in the endosome for degradation whilst the LDL-receptor is recycled back to the cell surface. If PCSK9 binds to the LDL-receptor on its epidermal growth factor-like repeat A (EGF-A) domain, the LDL-receptor is no longer recycled back to the cell surface but degraded along with the bound LDL-C. Therefore, when inhibiting PCSK9, more LDL-receptors will be recycled to the cell surface and more LDL-C can be taken up by the liver cells, reducing LDL-C in the circulation.

Study objective

Primary objective:
To demonstrate superiority of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

Secondary objectives
To compare the effect on lipid/lipoprotein parameters excluding LDL-C of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the effect on lipid/lipoprotein parameters of three dose levels of oral NNC0385-0434 versus s.c. evolocumab in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the safety and tolerability of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

Study design

This is a randomised, multicentre, multinational, seven-armed, parallel group, dose finding trial. The trial will be double-blinded within dose level of oral NNC0385-0434 and size-matched placebo arm. The s.c. evolocumab arm will be open label. The trial population includes patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction. A PK sub-study in Japanese and non-Japanese patients will be performed following the 12 weeks of treatment.

Patients will be randomised 3:1:3:1:3:1:3 according to the following treatment arms:
* Oral NNC0385-0434 15 mg
* Oral placebo (size-matched to oral NNC0385-0434 15 mg)
* Oral NNC0385-0434 40 mg
* Oral placebo (size-matched to oral NNC0385-0434 40 mg)
* Oral NNC0385-0434 100 mg
* Oral placebo (size-matched to oral NNC0385-0434 100 mg)
* S.c. evolocumab

Randomisation will be stratified according to participation in the PK sub-study, country and population (inclusion criteria a/b). Within each stratum, each patient will be randomly allocated to one of the treatment arms. For the main statistical analyses, the 3 placebo arms will be pooled into one placebo group.

Intervention

Patients will be randomised 3:1:3:1:3:1:3 according to the following treatment arms:
* Oral NNC0385-0434 15 mg
* Oral placebo (size-matched to oral NNC0385-0434 15 mg)
* Oral NNC0385-0434 40 mg
* Oral placebo (size-matched to oral NNC0385-0434 40 mg)
* Oral NNC0385-0434 100 mg
* Oral placebo (size-matched to oral NNC0385-0434 100 mg)
* S.c. evolocumab

Study burden and risks

Currently, there are no identified risk with evidence of a causal association with NNC0385-0434.

Potential risk:
Hypersensitivity/allergic reaction
As with all protein-based pharmaceuticals, patients treated with NNC0385-0434 are at risk of developing immunogenic and allergic reactions.

As a precaution, patients with known or suspected hypersensitivity to trial product or related products are excluded. In addition, patients will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.

Considering the measures taken to minimise risk to patients participating in this trial, the potential risks identified in association with NNC0385-0434 are justified by the anticipated benefits that may be afforded to patients with

established ASCVD or ASCVD risk.

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

- Male patient or female patient of non-childbearing potential.
- Established atherosclerotic cardiovascular disease (ASCVD) (criteria a) or ASCVD risk (criteria b):
a)Age greater than or equal to 40 years at the time of signing informed consent and history of ASCVD
b)Age greater than 50 years at the time of signing informed consent and with ASCVD risk
- Serum LDL-C greater than or equal to1.8 mmol/L (greater than or equal to 70 mg/dL) as measured by the central laboratory at screening.

Japanese patients: Serum LDL-C greater than or equal to 2.6 mmol/L (greater than or equal to 100 mg/dL) for patients of greater than or equal to 40 years of age and with a history of coronary heart disease, and serum LDL-C greater than or equal to 3.1 mmol/L (greater than or equal to 120 mg/dL) for all other Japanese patients
- Patients must be on maximally tolerated dose of statins.
- Patients not receiving statin must have documented evidence of intolerance to all doses of at least two different statins.

Exclusion criteria

- Treatment with PCSK9i therapy (alirocumab or evolocumab within 90 days prior to screening) or PCSK9 siRNA therapy (inclisiran within 12 months prior to screening).
- Fasting triglyceride greater than 4.52 mmol/L (greater than 400 mg/dL) as measured by the central laboratory at screening.
- Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
- Renal impairment with eGFR below 30 ml/min/1.73 m^2 as measured by the central laboratory at screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-10-2021
Enrollment:	45

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet bekend
Generic name:	NNC0385-0434
Product type:	Medicine
Brand name:	Repatha
Generic name:	Evolocumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-07-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2020-002630-32-NL
CCMO	NL77330.041.21
Other	U1111-1252-3392