An open label, active comparator extension trial to assess the effect of long term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL C (ORION-3)

Published: 14-03-2017
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Primary:• To evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 210 compared to Day 1 of this extension study. Secondary:• To evaluate the effects of inclisiran on the following: LDL-C levels...

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

Summary

ID

NL-OMON55880

Source
ToetsingOnline

Brief title
Effect of long term treatment with inclisiran compared to evolocumab

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherosclerosis, cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis (Industry)

Intervention

Keyword: Atherosclerosis, Extension trial, Open label

Outcome measures

Primary outcome

Parameters to be assessed will include: total cholesterol (TC), triglycerides,

LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very

low-density lipoprotein (VLDL), apolipoprotein A1 (Apo-AI), apolipoprotein B

(Apo-B), lipoprotein(a) [Lp(a)], C-reactive protein (CRP), and PCSK9.

Secondary outcome

n/a

Study description

Background summary

This is an open-label comparator study in male and female subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated dose of LDL-C lowering therapies. This study is an extension trial to the ORION-1 study (MDCO-PCS-15-01, EudraCT: 2015-003772-74) and will evaluate the efficacy, safety and tolerability of the investigational product, inclisiran (formerly known as ALN-PCSSC) in comparison with evolocumab.
The overall safety data from inclisiran in nonclinical studies and clinical data from the Phase I ALN-PCSSC-001 study, the ALN PCS02-001 study (ALN-PCS02 2014), and multiple PCSK9 antibody studies demonstrated that potent lowering of PCSK9 is well-tolerated in human subjects and support the dose and dosing schedule proposed in this Phase II extension study. A comparator arm has been

added to this long-term extension to evaluate safety, tolerability and patient reported outcomes (PRO) compared to an active comparator (evolucumab).

Study objective

Primary:
• To evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 210 compared to Day 1 of this extension study.
Secondary:
• To evaluate the effects of inclisiran on the following:
LDL-C levels over time
PCSK9 levels over time
Other lipids, lipoproteins, and apolipoproteins over time
Proportion of subjects achieving target levels prespecified in global lipid guidelines
Proportion of subjects at least 50% LDL-C reduction from Day 1 over time
Individual responsiveness to inclisiran
Duration of lipid-lowering effect
• To compare the effects of inclisiran and evolocumab at Day 210 on the proportion of subjects achieving prespecified global lipid guidelines
• To compare the effects of switching from evolocumab to inclisiran on the proportion of subjects achieving prespecified global lipid guidelines after 210 days of treatment (Day 570) (LDL-C beta quantification)
• To evaluate the long term safety and tolerability of inclisiran
• To collect/evaluate (and compare where applicable) patient reported outcomes (PRO)
Treatment Satisfaction Questionnaire for Medications (TSQM)
Patient reported adherence to self injectable evolucumab

Exploratory:
• To collect/evaluate the effect of inclisiran on the following:
Cardiovascular (CV) events
Anti-drug antibodies (ADA) to the investigational product
• To compare the effects of inclisiran and evolocumab from Day 1 to 360 on the following:
LDL-C levels over time
PCSK9 levels over time
Other lipids, lipoproteins, and apolipoproteins over time
Proportion of subjects with at least 50% LDL-C reduction from Day 1
• To compare the effects of switching from evolocumab to inclisiran from Day 360 to End of study (EOS) on the following:
LDL-C levels over time
PCSK9 levels over time
Other lipids, lipoproteins, and apolipoproteins over time
Proportion of subjects with at least 50% LDL-C reduction from Day 1 over time

Study design

This study will be an open label, long term extension trial with an active comparator (evolocumab) in up to 490 subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies who have completed study MDCO-PCS-15-01 (ORION-1), to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. Informed consent will be obtained from subjects before the initiation of any study-specific procedures.
Subjects completing study MDCO-PCS-15-01 and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran or evolocumab, based on the treatment received in study MDCO-PCS-15-01. Those subjects who received inclisiran in MDCO-PCS-15-01 will receive inclisiran 300 mg throughout this study, and those subjects who received placebo in MDCO-PCS-15-01 will receive evolocumab as comparator for 1 year, and then switch to inclisiran for the remainder of the study. Until study drug is available, subjects will have monthly observation visits until study drug administration commences.
Day 1 is the day when eligible subjects will receive the first SC administration of inclisiran or evolocumab. After first study drug administration, all subjects will be observed in the clinic for at least 4 hours post injection before being discharged. Subjects will return for follow up at Day 30, Day 90 and Day 180. Thereafter all subjects will return 30 and 90 days after study drug administration on Days 180, 360 and 540 and then every 90 days from Day 720 until the end of the study. Subjects receiving inclisiran will receive the second injection at the Day 180 visit and every 180 days thereafter.
Subjects receiving evolocumab will receive the first dose on Day 1, administered by the investigator, and after that point will self administer drug every 14 days until Day 336. At Day 360 these subjects will switch to and receive inclisiran. From Day 360 onwards, all subjects will receive inclisiran every 180 days until the EOS.
Efficacy assessments will measure the effects of inclisiran on levels of LDL-C lipids and lipoproteins including total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], C-reactive protein (CRP), and PCSK9.
At each visit, adverse events (AEs), serious adverse events (SAEs), concomitant medications, and safety laboratory assessments will be collected.
Formation of ADA will be assessed on Day 1 of inclisiran treatment (prior to and 4 hours after the injection) and on Days 90, 180, 270, 360, and then every 90 days until EOS for those subjects taking inclisiran.
Patient reported outcomes (PRO) questionnaires will assess satisfaction with treatment in all subjects during the first year of inclisiran treatment, andadherence to self injection for those subjects who take evolocumab for the first year.

A Safety Review Committee (which includes Data Monitoring Committee [DMC] members) will review safety data every 2 months until the end of the trial. A recommendation may be taken to stop or amend the study at any of these reviews.
All subjects will receive study drug for approximately 4 years (or until the investigator's recommendation of discontinuation, sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, until an administrative decision is made to end the study, or until inclisiran has received regulatory approval in the respective country, whichever occurs first). At this time EOS evaluations will be conducted at the EOS visit.
An interim analysis of lipids and PCSK9 will be conducted upon completion of Day 210 by all subjects, and a further interim analysis will be conducted at Day 720 to support an assessment of PRO.

Intervention

Subjects completing study MDCO-PCS-15-01 and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran or evolocumab, based on the treatment received in study MDCO-PCS-15-01. Those subjects who received inclisiran in MDCO-PCS-15-01 will receive inclisiran 300 mg throughout this study, and those subjects who received placebo in MDCO-PCS-15-01 will receive evolocumab as comparator for 1 year, and then switch to inclisiran for the remainder of the study. Until study drug is available, subjects will have monthly observation visits until study drug administration commences.

Study burden and risks

Reactions at injection site
Inclisiran will be given under your skin (subcutaneous) in your abdomen and like with any injection given under the skin, you could develop a reaction at the site of the injection. You could develop pain, tenderness, redness, swelling, itching, formation of sores, skin color changes, or other reactions around an injection site. If you have a reaction, you may undergo an examination by a doctor or other health care professional and have photographs taken of the area of interest. The photographs will, whenever possible, be taken in such a way as to prevent disclosure of your identity. During the study, the study staff will check the site of injection for any reactions.
Allergic reactions
There is a remote chance that inclisiran (like any pharmaceutical product) may cause an allergic reaction, which in some cases can be severe - otherwise known as an anaphylactic reaction. This anaphylactic reaction may be characterized by sudden shortness of breath, decreased consciousness, and rash, and may require emergency treatment. Anaphylactic reactions have not been seen in animals who received inclisiran or in clinical trials where similar drugs to those used in this study were given to humans.
Risks associated with blood draws
There is a risk of minor discomfort, bruising, bleeding, swelling, or (rarely)

infection at the site of needle insertion for blood drawing.

Risks associated with evolocumab (for patients in the comparator arm)
Evolocumab will be injected under the skin (subcutaneously) and like all medicines, this medicine may cause side effects, although not everybody gets them.
Common side effects: may affect up to 1 in 10 people
• Flu (high temperature, sore throat, runny nose, cough and chills)
• Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory
tract infections)
• Feeling sick (nausea)
• Back pain
• Joint pain (arthralgia)
• Injection site reactions, including rash, redness, bruising or pain

Uncommon side effects: may affect up to 1 in 100 people
• Hives, red itchy bumps on your skin (urticaria)
Risks associated with ECG
Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
Risks associated with Fasting
Fasting could cause dizziness, headache, stomach discomfort, or fainting.
Reproductive Risks
Inclisiran & Evolocumab
The effects of inclisiran and evolocumab on the unborn child are unknown. It is not known if the medicines could affect male sperm. There is no information on the long-term effects of inclisiran and evolocumab on fertility.
In order to reduce the risk of pregnancy, female subjects of child-bearing potential must use two effective methods of birth control while participating in this study. If you are already using a method of birth control, the study doctor or study staff will discuss with you whether your current method of birth control is acceptable for use during this study.
Acceptable birth control methods include, but are not limited to, oral contraceptives, barrier methods (diaphragm), approved contraceptive implant, long-term injectable contraception,intrauterine device (IUD) and tubal litigation (tubes tied).
Male subjects must agree to use an effective method of birth control during the entire study (ie, condom with spermicide).

Contacts

Public

Novartis

Lichtstrasse 35
Basel 4056
CH
Scientific
Novartis

Lichtstrasse 35
Basel 4056
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Completion of study MDCO-PCS-15-01 and no contraindications to receiving inclisiran or evolucumab.
2. Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.
3. Willing to self-inject

Exclusion criteria

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator*s [or delegate*s] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with

interpretation of the clinical study results.
3. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses).
4. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >2x the upper limit of normal (ULN), or total bilirubin elevation >1.5x ULN at study entry visit, confirmed by a repeat abnormal measurement at least 1 week apart.
5. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of contraception (eg, oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions from this criterion:
a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age
b. Postmenopausal women (as defined above) and less than 55 years old with a negative pregnancy test within 24 hours of enrollment
c. Women who are surgically sterilized at least 3 months prior to enrollment
6. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
7. Treatment with investigational medicinal products other than inclisiranor devices within 30 days or five half*lives, whichever is longer.
8. Planned use of other investigational medicinal products other than inclisiranor devices during the course of the study.
9. Subjects with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients.
10. Previous or current treatment (within 90 days of study entry) with monoclonal antibodies directed towards PCSK9.
11. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
a. Inappropriate for this study, including subjects who are unable to communicate or to cooperate with the investigator.
b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
c. 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).
d. Involved with, or a relative of, someone directly involved in the conduct of the study.
e. Any known cognitive impairment (eg, Alzheimer*s disease).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-08-2017
Enrollment:	168
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Repatha
Generic name:	Evolocumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-07-2017
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	03-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	07-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-07-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2016-003815-37-NL
CCMO	NL60283.000.17

Study results

Date completed: 15-12-2021

Results posted: 04-08-2022

First publication
07-06-2022