A long term extension trial of the Phase III lipid-lowering trials to assess the effect of long term dosing of inclisiran given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C (ORION-8)

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The primary objectives are to evaluate:-The effect of inclisiran treatment on the proportion of subjects achieving prespecified low densitylipoprotein cholesterol (LDL-C) targets at end of study (EOS)-The safety and tolerability profile of long term...

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

Summary

ID

NL-OMON55497

Source
ToetsingOnline

Brief title
MDCO-PCS-17-05 (CKJX839A12306B) (ORION-8)

Condition

- Cardiac disorders, signs and symptoms NEC
- Cardiac and vascular disorders congenital
- Lipid metabolism disorders

Synonym
Hypercholesterolemia and elevated levels of cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: The Medicines Company (industry)

Intervention

Keyword: - Atherosclerotic cardiovascular disease (ASCVD), - Elevated LDL-C, - High cardiovascular risk, - Long-term dosing of inclisiran

Outcome measures

Primary outcome

The primary endpoint of this study is:

a.Proportion of subjects who attain global lipid targets (entry criterion from

respective

previous study) for their level of ASCVD risk at EOS.

Secondary outcome

The secondary endpoints of this study are:

a.Absolute change and percentage change in LDL-C from baseline (defined as

baseline in

feeder study) to EOS

b.Absolute change and percentage change in other lipids and lipoprotein from

baseline

(defined as baseline in feeder study) to EOS

The safety endpoint of this study is:

a.To evaluate the safety and tolerability profile of long term use of

inclisiran

Study description

Background summary

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually [WHO, 2016]. Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated low-density lipoprotein associated cholesterol (LDL-C) is a major risk factor for the development of CVD [Grundy et all 2004; Go et al, 2014]. Lowering LDL-C has been shown to reduce the risk of death or heart attack and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction [Baigent et al 20051
Recently developed and approved PCSK9-blocking monoclonal antibodies reduce circulating PCSK9 levels and lower LDL-C levels. Preliminary reports indicate that treatment with such antibodies can lead to reduction of cardiovascular events compared with placebo
The data from PCSK9 blocking antibodies such as Repatha@ (evolocumab) and Praluent@ (arilocumab) are very encouraging.
However, these products are dosed SC every 2 to 4 weeks necessitating up to 26 injections per year [Hooper et al, 2005; Navarese et al, 2015; Zhang et al, 2015]. In contrast, one injection of inclisiran is anticipated to be given three times in the first year and every 6 months thereafter.

Study objective

The primary objectives are to evaluate:
-The effect of inclisiran treatment on the proportion of subjects achieving prespecified low density
lipoprotein cholesterol (LDL-C) targets at end of study (EOS)
-The safety and tolerability profile of long term use of inclisiran

Secondary:
The secondary objectives are to evaluate the effect of inclisiran on:
-LDL-C levels
-Other lipids and lipoproteins

Study design

This study will be a long-term extension study in up to 3300 subjects with

atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia), or heterozygous or homozygous familial hypercholesterolemia (HeFH or HoFH) and elevated low density lipoprotein cholesterol (LDL-C) despite treatment with LDL-C lowering therapies who have completed the Phase II trial MDCO-PCS-16-01 (ORION-3, also referred to as CKJX839A12201E1) or Phase III lipid lowering studies: MDCO-PCS-17-03(ORION-9 also referred to as CKJX839A12303), MDCO-PCS-17-04 (ORION-10, also referred to as CKJX839A12304, or MDCO-PCS-17-08(ORION-11, also referred to as CKJX839A12305) The purpose of this extension study is 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. The EOS visit in the previous study will be Day 1 in ORION-8
Subjects who received placebo in the previous Phase III feeder study will receive blinded inclisiran and subjects who received inclisiran in the previous feeder study will receive blinded placebo at this visit, in order to maintain the blinding of the feeder study until database lock of those studies . This dosing regimen is to enable former placebo subjects to start ORION-8 with the same starting dosing-regimen as subjects in the inclisiran arms of the feeder studies i.e. an initial dose, followed by a dose after 90 days and then followed by doses every six months. Subjects who previously received inclisiran only require dosing every six months. All subjects will return at Day 90 for the next visit and will receive open label inclisiran sodium 300 mg which is equivalent to 284 mg inclisiran. Subjects will then return for open label drug administration of inclisiran sodium 300 mg every 180 days until EOS and be observed for 30 minutes at each visit.
The study duration for each subject is expected to be a maximum of 3 years.

Intervention

Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) will be administered as a single SC injection on Day 1, Day 90, Day 270, Day 450, Day 630, Day 810, Day 990.
Placebo will be administered as SC injections of saline solution. Placebo volume will be matched to test product volume within each dose and injection ie, the 300 mg dose will be administered as 1.5 mL of placebo.

Study burden and risks

Most drugs have side effects, which some people may experience, and others may not. Since the study drug is investigational when taken alone or in combination with other medications, not all of the possible side effects of the study treatment are known at this time. It is very important that you tell the Study Doctor if you have any complaints, side effects, or had other doctor visits or hospitalizations outside of the study. Ask the study doctor if you have any questions about the signs or symptoms of any side effects that you read about

in this consent form.
Inclisiran was safe and well tolerated in all previously completed studies. Safety data from three large studies that included a total of 1833 patients treated with inclisiran for up to 18 months (mean treatment duration on inclisiran was 526 days) showed that patients treated with inclisiran had a similar number of adverse events compared to patients receiving placebo. Injection site reactions were found to be the only events related to inclisiran treatment.

Injection Reactions
Inclisiran will be given under your skin 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, rash, 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. During the study, the study staff will check the site of injection for any reactions. In the overall research program, fewer than 1 in 10 people (8.2%) noticed reactions where the injection was given.. These were usually mild, occasionally moderate and localized and did not require any specific treatment, resolving usually within 1-2 weeks.

Allergic reactions
No general allergic reactions or signs or symptoms suggestive of general allergic reactions have been seen following administration of inclisiran in any of the completed clinical studies. However there is a remote chance that inclisiran (like any investigational drug) may cause an allergic reaction, which in some cases can be severe. This severe reaction may be characterized by sudden shortness of breath, decreased consciousness, and rash, and may require emergency treatment. If you think, you are having an allergic reaction, call the study Doctor right away and/or seek medical attention.

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.

Fasting Risks
Fasting could cause dizziness, headache, stomach discomfort, or fainting
Reproductive risks
It is not known if the study treatment by inclisiran may affect an unborn child or nursing infant. There is no information on the long-term effects of inclisiran on fertility.
Benefit
If the patients are placed on inclisiran, they may benefit from treatment with inclisiran and it may prove as safe or safer and as effective as or more effective due to its unique effects on lowering the 'bad' cholesterol than other treatment you might have previously received. In the future, other people with elevated cholesterol may benefit from the information we learn from this

study

Contacts

Public
Novartis

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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

Subjects may be included if they meet all of the following inclusion criteria prior to entry into this study: 1.Completion of a previously qualifying inclisiran Phase II trial MDCO-PCS-16-01 (ORION-3), or Phase III lipid-lowering ORION feeder study [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10) MDCO-PCS-17-08 or (ORION-11),], meaning the subject received the last dose of study drug and completed the final study visit per applicable protocol. 2.On current lipid-lowering therapies (such as a statin and/or ezetimibe) from previous study with no planned medication or dose change during study participation. 3.Willing and able to give informed consent before initiation of

any study-related procedures and willing to comply with all required study procedures

Exclusion criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply immediately prior to entry into the study:
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.Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 3 years.
4.Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin (TBIL) elevation >2x ULN at last recorded visit in the feeder study prior to study entry visit.
5.Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least one method of acceptable effective 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.Planned use of other investigational medicinal products other than inclisiran or devices during the course of the study.
7.Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
a.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.Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the

study
e.Persons directly involved in the conduct of the study

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-07-2019
Enrollment:	152
Type:	Actual

Ethics review

Approved WMO Date:	31-01-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2019
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2019
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:	25-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2022
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	EUCTR2017-003092-55-NL
CCMO	NL68504.000.18

Study results

Date completed: 02-02-2023

Results posted: 03-11-2023

First publication
26-10-2023