A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low density lipoprotein cholesterol (LDL-C)

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Primary :The primary objective is to evaluate the effect of inclisiran treatment on:* LDL-C levels at Day 510.* Time adjusted percent change in LDL-C levels from baseline after Day 90 up to Day 540 levelsSecondary:The secondary objectives are to...

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

Summary

ID

NL-OMON48935

Source
ToetsingOnline

Brief title
MDCO-PCS-17-03 (ORION-9)

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: The Medicines Company
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: - double-blind, - heterozygous familial hypercholesterolemia (HeFH), - Placebo-controlled

Outcome measures

Primary outcome

Primary Endpoints:

* Percentage change in LDL-C from baseline to Day 510

* Tine adjusted percentage change in LDL-C from baseline after Day 90 up to Day

540. This is the average percentage change in LDL-C from baseline over the

period after Day 90 up to Day 540.

Secondary outcome

Key Secondary Endpoints:

* Absolute change in LDL-C from baseline to Day 510

* Time adjusted absolute change in LDL-C from baseline after Day 90 up to Day

540

* Percentage change from baseline to Day 510 in PCSK 9, total cholesterol,

ApoB, and non-HDL-C

Other Secondary Endpoints:

* Mean maximum percentage change in LDL-C

* Absolute change from baseline to Day 510 in PCSK9, total cholesterol, ApoB and non-HDL-C

* Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540

* Individual responsiveness defined as the number of subjects reaching on treatment LDL C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510

* Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline

* Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540

* Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk

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 al, 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 2005].
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

Primary :
The primary objective is to evaluate the effect of inclisiran treatment on:
* LDL-C levels at Day 510.
* Time adjusted percent change in LDL-C levels from baseline after Day 90 up to Day 540 levels

Secondary:
The secondary objectives are to evaluate the effect of inclisiran on:
* Proprotein convertase subtilisin/kexin type 9 (PCSK9), total cholesterol, ApoB, and non-high-density lipoprotein cholesterol (HDL-C) at Day 510
* LDL-C and PCSK9 levels over time to Day 540
* Mean maximum reduction in LDL-C levels
* LDL-C and PCSK9 levels over time in individual subjects
* Other lipids, lipoproteins, apolipoproteins
* Proportion of subjects achieving prespecified LDL-C targets
* Safety and tolerability profile of inclisiran

Exploratory:
The exploratory objectives are to collect/evaluate the effect of inclisiran on the following:
* Cardiovascular (CV) events such as CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), and non-fatal stroke (ischemic and hemorrhagic)
* Response of LDL-C reduction by underlying causal mutations of HeFH

Study design

This study is a Phase III, placebo-controlled, double-blind, randomized study in 400 subjects with HeFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of subcutaneous inclisiran injection(s).
Subjects will be screened and approximately 400 eligible subjects will be randomized: 200 subjects will be randomized to inclisiran sodium 300 mg and 200 subjects randomized to placebo. Treatment allocation will be stratified by

country and by current use of statins or other lipid-modifying therapies. Each subject will receive four subcutaneous injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450.
On Day 1, all eligible subjects will be randomized and will receive the first subcutaneous (SC) injection of investigational product (inclisiran or placebo). After the first SC injection, the subject will be observed in the clinic for at least 4 hours post injection in order to have additional laboratory assessments and vital signs completed before being discharged. Subjects will return on Day 90, Day 270, and Day 450 to receive additional investigational product. During these subsequent dosing visits, subjects will be observed in the clinic for at least 30 minutes after administration of each injection and have additional laboratory assessments completed if needed. Subjects will also have in clinic visits on Day 30, Day 150, Day 330, and Day 510 for follow-up and limited laboratory assessments. The end of study (EOS) visit will be conducted on Day 540.
Pharmacodynamic assessments will be collected at various visits and include LDL-C levels as well as other lipids and lipoproteins (eg, total cholesterol, triglycerides, HDL-C, non HDL-C, very low-density lipoprotein cholesterol [VLDL-C], apolipoprotein A1 [Apo-A1], apolipoprotein B [ApoB], lipoprotein(a) [Lp(a)], high sensitivity C-reactive protein [hsCRP], and PCSK9).
All subjects will be invited to consent to pharmacogenetic analyses, unless underlying causal mutations of HeFH are well documented by a validated specialized laboratory. A blood sample will be collected, preferably during screening, only from subjects who sign a separate consent for pharmacogenetics.
Safety assessments including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and safety laboratory parameters will also be collected during the study. In addition, formation of anti-drug antibodies (ADA) and further characterization of ADA will be evaluated.
End of study evaluations will be conducted at the Day 540 visit.
Subjects who have completed the study to Day 540 will be given the opportunity to enroll in a separate open label long-term extension study to collect long-term safety and efficacy data for inclisiran.
The independent Data Monitoring Committee (IDMC) will review safety data after the first 40 subjects receive the first SC injection of inclisiran or placebo and have completed 1 month follow-up. Thereafter the IDMC will review safety data every 3 months until theend of study EOS unless requested otherwise by the IDMC. A recommendation may be taken to stop or amend the study at any of these reviews.

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, and Day 450.
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

Inclisiran
In a previous study in subjects with high LDL-C (*bad* cholesterol), 51 subjects received single or multiple doses of inclisiran. In this study inclisiran at various doses was well tolerated with no serious side effects. The most common side effects in people who received one dose were cough, nasopharyngitis (cold-like symptoms), and musculoskeletal (muscle and bone) pain. One mild local injection site reaction occurred at a dose of inclisiran that is higher than the doses planned for the study you are being asked to join. The most common side effects in subjects who received more than one dose of inclisiran were headache, back pain, diarrhea, nasopharyngitis (cold-like symptoms) and nausea. Three subjects had mild, local reactions at the site where they were injected. The total dose given in the previous study was more than you will receive in this study.

Since the study drug is investigational when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.

Placebo
If you are receiving placebo there is a possibility that symptoms of your disease may return or get worse.

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 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. In the previous study around 5% of all patients receiving treatment had an injection site reaction. These were usually mild and localized and did not require any specific treatment, resolving usually within 1-2 weeks.

Allergic reactions
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. These severe reactions have not been seen in animals who received inclisiran at much higher

doses than are planned in this trial or in clinical trials with inclisiran or 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 ECG
Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.

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. It is not known if the medicines could affect male sperm. There is no information on the long-term effects of inclisiran on fertility.

Benefit
If the patiënts 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

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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 in the study if they meet all of the following criteria:
1. Male or female subjects *18 years of age.
2. History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease may indicate FH
3. Stable on a low-fat diet (eg, NCEP)
4. Serum LDL-C *2.6 mmol/L (*100 mg/dL) at screening
5. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
6. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized clinical methodology.
7. Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF)
8. Subjects not receiving statin must have documented evidence of intolerance to all doses of at least two different statins
9. Subjects on lipid-lower therapies (such as a statin and/or ezetimibe) should be on a stable dose for *30 days before screening with no planned medication or dose change during study participation.
10. Subjects must be 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 prior to randomization:
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] 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. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%.
4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
5. Major adverse cardiovascular event within 3 months prior to randomization.
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
7. 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 >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.
8. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 2 years.
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
10. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of highly effective contraception (failure rate less than 1% per year) (eg, combined oral contraceptives, barrier methods, approved contraceptive implant, longterm injectable contraception, or 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 last menstrual period) AND more than 55 years of age.
b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomization.
c. Women who are surgically sterilized at least 3 months prior to enrollment.
11. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
12. Known history of alcohol and/or drug abuse within the last 5 years.
13. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
14. Planned use of other investigational products or devices during the course

of the study.
15. 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.
16. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.Subjects excluded for any of the above reasons may not be re-screened for participation at any time even if the exclusion characteristic has changed.font>

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:	Recruitment stopped
Start date (anticipated):	22-01-2018
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	09-10-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-03-2018
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:	09-11-2018
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:	11-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2019
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:	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)

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	EUCTR2017-002472-30-NL
CCMO	NL63081.000.17

Study results

Date completed: 27-08-2019

Actual enrolment: 38

Summary results
Trial is onging in other countries