Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-16)

Published: 20-11-2020
Last updated: 31-12-2024

Study CKJX839C12301 (ORION-16) is a pivotal phase III study designed to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (aged 12 to 130 mg/dL (3.4 mmol/L). The use of inclisiran (as an adjunct to stable, optimal background...

Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54301

Source
ToetsingOnline

Brief title
CKJX839C12301 ORION-16

Condition

- Cardiac and vascular disorders congenital
- Vascular hypertensive disorders

Synonym
elevated LDL-cholesterol, heterozygous familial hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: - elevated LDL-cholesterol, - heterozygous familial hypercholesterolemia, - inclisiran

Outcome measures

Primary outcome

The primary objective is to demonstrate superiority of inclisiran compared to

placebo in reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents

(aged 12 to <18 years) with HeFH and elevated LDL-C

Secondary outcome

- Demonstrate superiority of inclisiran compared to placebo in reducing LDL-C

[time-adjusted percent change] over Year 1

- Demonstrate superiority of inclisiran compared to placebo in reducing LDL-C

[absolute change] at Day 330 (Year 1)

- Demonstrate superiority of inclisiran compared to placebo in reducing Apo B,

lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C),

and total cholesterol [percent change] at Day 330 (Year 1)

- Evaluate the effect of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and PCSK9 over time

- Evaluate the safety and tolerability profile of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HeFH

Study description

Background summary

Familial hypercholesterolemia (FH) is a genetic disorder that causes high levels of LDL-C in the blood and is characterized by premature cardiovascular (CV) disease. Current treatment options are still limited for children with FH, and the known limitations of contemporary therapies are particularly relevant among children with FH who are at the highest risk of future CV events, and thus require the most intensive and aggressive management of hypercholesterolemia. There remains a clear unmet medical need for treatments that will lower LDL-C, especially in pediatric populations.
Inclisiran is a medication made to reduce the level of LDL-cholesterol in the blood. Inclisiran works in a way that makes the liver produce less of a substance called *PCSK9*. PCSK9 reduces the ability of the liver to remove LDL-cholesterol from the blood. By lowering the production of PCSK9, inclisiran leads to more LDL-cholesterol being removed by the liver from the blood. By that, the level of LDL-cholesterol in the blood is reduced.
Inclisiran may improve the treatment of children/adolescents with HeFH, with a low injection burden given the only twice yearly dosing.

Study objective

Study CKJX839C12301 (ORION-16) is a pivotal phase III study designed to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (aged 12 to <18 years) with HeFH and LDL-C >130 mg/dL (3.4 mmol/L). The use of inclisiran (as an adjunct to stable, optimal background lipid-lowering therapy) for the treatment of HeFH in adolescent patients who require additional lipid-lowering will be investigated in order to obtain needed pediatric information on inclisiran. The follow-up period (Part 2/Year 2) serves to collect longer-term data on inclisiran and also allows access of study

participants to a potentially effective treatment.

Study design

This study is a two-part (double-blind, placebo-controlled / open-label) multicenter study in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C (>130 mg/dL / 3.4 mmol/L) on stable, individualized, optimal SoC background lipid-lowering therapy (including maximally tolerated statin treatment).

- Part 1 (Year 1): 12 months double-blind, parallel group period in which participants will be randomized to receive either inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) s.c. or placebo (given at Days 1, 90 and 270).
- Part 2 (Year 2): 12 months single arm, open-label follow-up period with all participants receiving inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) s.c. Participants randomized to placebo in Part 1 will receive inclisiran starting on Day 360 (*Switch* Day 360). Participants randomized to inclisiran in Part 1 will receive placebo on Day 360. This dose of inclisiran/placebo on Day 360 will remain blinded in order to maintain the blind for Part 1 of the study. All participants will receive subsequent doses of open-label inclisiran on Days 450 and 630.

Intervention

Participants will be randomized 2:1 to double-blind s.c. injections of inclisiran sodium 300 mg or placebo in Part 1 (Year 1) of the study, and subsequently all participants will receive open-label s.c. injections of inclisiran sodium 300 mg in Part 2 (Year 2) of the study.

Study burden and risks

- Injection site reactions: itching, pain, rash, redness, changes of the color of the skin, ulcers, swelling, sensitive skin, or other reactions near the injection site.
- Allergic reactions. Frequently seen allergic reactions are rash, itching, skin problems, swelling of the face and throat and problems with breathing. So far no general allergic reactions have been reported with inclisiran and no symptoms have been seen which matches an allergic reaction.
- Blood sampling can cause some pain and/or bruising.

Contacts

Public

Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

• Heterozygous Familial Hypercholesterolemia (HeFH) diagnosed either by genetic testing or on phenotypic criteria
• Fasting LDL-C > 130 mg/dL (3.4 mmol/L) at screening
• Fasting triglycerides < 400 mg/dL (4.5 mmol/L) at screening
• On maximally tolerated dose of statin (investigator*s discretion) with or without other lipid-lowering therapy; stable for >= 30 days before screening
• Estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m2 at screening
Other inclusion criteria are listed in the protocol

Exclusion criteria

• Homozygous familial hypercholesterolemia (HoFH)
• Active liver disease
• Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome
• Major adverse cardiovascular events within 3 months prior to randomization

• Previous treatment with monoclonal antibodies directed towards PCSK9 (within 90 days of screening)
• Recent and/or planned use of other investigational medicinal products or devices

Other exclusion criteria are listed in the clinical study protocol

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:	Completed
Start date (anticipated):	23-04-2021
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	20-11-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-02-2021

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2023
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	EUCTR2020-002757-18-NL
ClinicalTrials.gov	NCT04652726
CCMO	NL75440.000.20