A randomized, double-blind, placebo - controlled, multicenter trial, assessing the impact of inclisiran on major adverse cardiovascular events in participants with established cardiovascular disease (VICTORION-2 PREVENT)

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This study has been transitioned to CTIS with ID 2024-510735-21-00 check the CTIS register for the current data. Study CKJX839B12302 is a pivotal Phase III study designed to test the hypothesis that treatment with inclisiran sodium 300 mg s.c.…

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

Summary

ID

NL-OMON56097

Source
ToetsingOnline

Brief title
CKJX839B12302 (VICTORION-2 PREVENT)

Condition

- Cardiac disorders, signs and symptoms NEC
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Major Adverse Cardiovascular Events (MACE)

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: Cardiovascular disease, Elevated LDL-cholesterol, Inclisiran, Risk reduction

Outcome measures

Primary outcome

Demonstrate the superiority of inclisiran compared to placebo in reducing the risk of 3P-MACE (composite of CV death, non-fatal MI and non-fatal ischemic stroke) in participants with established ASCVD and a LDL-C >=1.8 mmol/L (70 mg/dL) (Endpoint = Time to the first occurrence of 3P-MACE).

Secondary outcome

- Demonstrate the superiority of inclisiran compared to placebo in reducing the risk of CV death (Endpoint = Time to occurrence of CV death)
- Demonstrate the superiority of inclisiran compared to placebo in reducing the risk of 4P-MACE (composite of CV death, non-fatal MI, non-fatal ischemic stroke and urgent coronary revascularization). (Endpoint = Time to the first occurrence of 4P-MACE)
- Demonstrate the superiority of inclisiran compared to placebo in reducing the risk of major limb events (MALE) (Endpoint = time to the first occurence of MALE (including acute lower limb ischemia, or urgent lower limb revascularization for ischemia)

- Demonstrate the superiority of inclisiran compared to placebo in reducing the

risk of all-cause death (Endpoint = Time to the occurrence of all-cause death)

- Evaluate the safety and tolerability of inclisiran compared to placebo.

Study description

Background summary

Inclisiran (KJX839) is the first and only small interfering RNA (siRNA) therapy to reduce low-density lipoprotein cholesterol (LDL-C) levels via an RNA interference (RNAi) mechanism of action and could help improve outcomes for patients with atherosclerotic cardiovascular disease (ASCVD). One key benefit of the mechanism of action of inclisiran is that the duration of its effect is significantly longer than that of currently available lipid-lowering therapy, including PCSK9-blocking mAbs and statins. Inclisiran is approved by EMA based on a on a robust clinical development program demonstrating effective and sustained LDL-C reduction of up to 52% in patients with elevated LDL-C despite maximally tolerated statin therapy. The relationship between LDL-C levels and CV risk has been clearly documented with evidence from >200 studies involving >2 million participants that have shown a dose-dependent log-linear association between the magnitude of exposure to LDL-C and risk of ASCVD. Moreover, evidence has consistently linked therapeutic reductions in LDL-C with reduced risk of CV events. While the strength of this correlation enables regulators to approve LDL-C lowering therapies, a longer and larger trial is needed to confirm the effects on CV outcomes.

This study is planned to investigate if treatment with inclisiran 300 mg (every 6 months) vs placebo, in adjunct to well-tolerated high-intensity statin therapy, reduces major adverse cardiovascular events (MACE) in patients with established ASCVD.

See pages 14-16 of the protocol.

Study objective

This study has been transitioned to CTIS with ID 2024-510735-21-00 check the CTIS register for the current data.

Study CKJX839B12302 is a pivotal Phase III study designed to test the hypothesis that treatment with inclisiran sodium 300 mg s.c. administered on Day 1, Month 3 (Day 90), and every 6 months thereafter taken in addition to well-tolerated high-intensity statin therapy in participants with established

ASCVD will significantly reduce the risk of 3-Point-Major Adverse Cardiovascular Events (3P-MACE) defined as a composite of CV death, non-fatal MI and non-fatal ischemic stroke. This will be compared to placebo in adjunct to well-tolerated high-intensity statin therapy.

Study CKJX839B12302 is specifically aimed at supporting an indication of inclisiran for the reduction of CV risk in participants with established ASCVD who have LDL-C >=1.8 mmol/L (70 mg/dL) mol/L (70 mg/dL) despite being on a background of well-tolerated dose of a high-intensity statin therapy.

Study design

CKJX839B12302 is a randomized, double-blind, parallel group, placebo-controlled, multi-center, event-driven study evaluating inclisiran sodium 300 mg s.c. administered on Day 1, Month 3 (Day 90), and every 6 months thereafter in participants with established ASCVD as evidenced by history of MI, history of ischemic stroke or symptomatic PAD, and elevated levels of LDL-C despite being on a well-tolerated dose of a high-intensity statin therapy.

The study consists of:
• A Statin Optimization Period of approximately 5-7 weeks, applicable only to participants who are not on the minimum doses of the high-intensity statin therapies pre-specified in Section 3.1 at the Statin Optimization Screening Visit,
• A Screening Period of approximately 1-2 weeks for all participants, and
• A double-blind Treatment Period with a minimum of 3 years in approximately 75% of the randomized participants.

The overall trial duration is expected to be approximately 6 years, and the study will continue until at least 1634 participant have experienced a CEC-confirmed primary 3P-MACE endpoint, at least 570 cardiovasular deaths have occurred, and approximately 75% of participants have had at least 3 years of follow-up time (Figure 1-1).

See protocol pages 18-32.

Intervention

Participants will be randomized in a 1:1 ratio to double-blind s.c. injections of inclisiran sodium 300 mg or placebo.

Investigational and control drugs will not be dispensed to the participants but rather administered by qualified healthcare personnel.

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

- Blood sampling can cause some pain and/or bruising.
- Fasting could cause dizziness, headache, stomach discomfort, or fainting.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Male or female >=40 years of age
2) Fasting LDL-C >=1.8 mmol/L (70 mg/dL) at the Screening Visit
3) At the Screening Visit, participants must be on a stable (>=4 weeks) and well-tolerated lipid-lowering regimen (including e.g. with or without Ezetimibe) that must include a high-intensity statin therapy with either atorvastatin >=40 mg QD or rosuvastatin >=20 mg QD
4) Established CV disease, defined as any of the following: Previous myocardial infarction, Previous ischemic stroke, Symptomatic peripheral arterial disease (PAD).

Other inclusion criteria are listed in the clinical study protocol.

Exclusion criteria

1) Acute coronary syndrome, ischemic stroke, peripheral arterial revascularization procedure or amputation due to atherosclerotic disease <4 weeks prior to the first study visit.
2) Planned or expected cardiac, cerebrovascular or peripheral artery surgery or coronary re-vascularization within the 6 months after the first study visit.
3) New York Heart Association (NYHA) class III or IV heart failure
4) Active liver disease
5) Previous exposure to inclisiran or any other non-mAb PCSK9-targeted therapy, either as an investigational or marketed drug within 2 years prior to the first study visit
6) Pregnant or nursing (lactating) women

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:	Recruiting
Start date (anticipated):	10-03-2022
Enrollment:	650
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2022
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)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	21-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-01-2024
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
EU-CTR	CTIS2024-510735-21-00
EudraCT	EUCTR2021-002006-27-NL
ClinicalTrials.gov	NCT05030428
CCMO	NL78939.000.21