Effects of ziltivekimab versus placebo on cardiovascular outcomes in participants with established atherosclerotic cardiovascular disease, chronic kidney disease and systemic inflammation

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This study has been transitioned to CTIS with ID 2023-506926-35-00 check the CTIS register for the current data. The primary objective is to demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly in reducing the risk of MACE (as defined...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54148

Source
ToetsingOnline

Brief title
ZEUS

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC
- Renal disorders (excl nephropathies)

Synonym
Atherosclerotic cardiovascular disease and chronic kidney disease

Health condition

systemische ontstekingen

Research involving
Human

Sponsors and support

Primary sponsor: Novo Nordisk
Source(s) of monetary or material Support: Novo Nordisk

Intervention

Keyword: Atherosclerotic Cardiovascular Disease (ASCVD), Chronic Kidney Disease (CKD), Inflammation, subcutaneous injection once monthly

Outcome measures

Primary outcome

The primary endpoint is time from randomisation to first occurrence of a major

adverse cardiovascular event, a composite endpoint consisting of:

cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke.

Secondary outcome

The confirmatory secondary endpoints are:

• Time from randomisation to first occurrence of an expanded MACE endpoint

consisting of:

CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable

angina pectoris requiring urgent coronary revascularisation

• Number of hospitalisations for heart failure or urgent heart failure visit

• Time to occurrence of all-cause mortality

• Time to first occurrence of a composite CKD endpoint consisting of: onset of

persistent >= 40% reduction in estimated glomerular filtration rate

(eGFR)(CKD-EPI) compared with baseline, kidney failure defined as kidney death,

onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m2 or initiation of chronic

kidney replacement therapy (maintenance dialysis or kidney transplantation)

Study description

Background summary

Atherosclerotic CV disease (ASCVD) is the leading cause of morbidity and mortality in patients worldwide. ASCVD represents a major burden for patients and society, underscoring the need for therapies that lower the risk of CV events in patients with established ASCVD.
There is a major unmet medical need to improve the treatment of patients with established ASCVD, especially those with chronic kidney disease (CKD), and thereby reduce their risk of cardiovascular (CV) events. Inflammation is an additional important risk factor to address in patients with ASCVD at high risk of major adverse cardiovascular events (MACE). Ziltivekimab is a fully human monoclonal antibody directed against the interleukin 6 (IL-6) ligand and currently available clinical data supports that ziltivekimab oncemonthly reduces inflammation as measured by high-sensitivity C-reactive protein (hs-CRP), and thereby has the potential to reduce cardiovascular risk. The aim of the current study is to demonstrate the efficacy of ziltivekimab in reducing the risk of MACE in adult patients with established ASCVD, CKD and systemic inflammation at high risk of CV events.

Study objective

This study has been transitioned to CTIS with ID 2023-506926-35-00 check the CTIS register for the current data.

The primary objective is to demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly in reducing the risk of MACE (as defined by the primary endpoint) compared to placebo, both added to standard of care, in participants with established ASCVD, CKD and systemic inflammation.

Key secondary objectives are to demonstrate the superiority of ziltivekimab 15 mg s.c. oncemonthly compared to placebo, both added to standard of care, in participants with established ASCVD, CKD and systemic inflammation, with regards to the following:
• reducing the risk of expanded MACE
• reducing the risk of heart failure
• reducing all-cause mortality
• delaying the progression of CKD

Study design

This is an interventional, randomised, parallel-group, double-blind, placebo-controlled, multicentre, multi-national CVOT designed to evaluate the effects of 15 mg ziltivekimab versus placebo (randomised 1:1), both administered s.c. once-monthly and added to standard of care, on CV outcomes in participants with established ASCVD, CKD and systemic inflammation.

The study is event driven; therefore, end-of-study will be scheduled according to projected study closure. Study duration is expected to be up to 48 months following randomisation of the first participant.

Intervention

Oncemonthly ziltivekimab/placebo subcutaneous injection, single-use pre-filled syringe (1 mL) or pen-injector (0.5 mL).

Study burden and risks

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimize the risks and inconveniences of participation in the trial. Additionally standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk to minimise the risk. Currently, there are no identified risks with ziltivekimab.
In other medicines similar to ziltivekimab the below side effects have been seen. We do not know if these side effects will happen with ziltivekimab or how often (Infections, low levels of a type of white blood cells (neutropenia), low levels of the blood cells called *platelets* (thrombocytopenia), elevated levels of liver enzymes, allergic reactions, skin problem where the injection is given, stomach ulcers).
One argument that we have seen a very beneficial safety profile for ziltivekimab in our phase II study is, that the dose used in order to lower the low grade inflammation in ASCVD, is much lower than the doses used in order to lower the inflammatory state of autoimmune diseases. This leads us to expect that the safety profile we have seen in our phase II study is translationable to our phase III study.
No data are available yet on the safety profile with longer-term exposure. Hence, the safety of the participants will be monitored closely throughout the study with specific focus on potential risks of ziltivekimab, the patient population included in the study and the endpoints defined for the study. Furthermore, an independent DMC will monitor the safety of participants enrolled in the study, and thereby protect the safety of the participants and ensure a positive benefit-risk balance. In completed clinical studies ziltivekimab has shown a reduction in systemic inflammation, as assessed by hs-CRP, in participants with CKD. Ziltivekimab may reduce the risk of MACE in patients with established ASCVD, CKD and systemic inflammation, providing

further benefits to ziltivekimab-treated participants in the study. Considering the measures taken to minimise risk and burden to study participants, the potential risks identified in association with ziltivekimab are justified by the anticipated benefits that may be afforded to participants with established ASCVD, CKD and systemic inflammation at high risk of CV events.

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

•Chronic kidney disease defined by one of the below:
eGFR >=15 and < 60 mL/min/1.73 m2 (using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation) or UACR >200 mg/g and eGFR>60 mL/min/1.73 m2 (using the CKD-EPI creatinine equation).
•Serum hs-CRP *2 mg/L

•Evidence of ASCVD by one or more of the following:
a) Coronary heart disease defined as at least one of the following:
i. Documented history of MI
ii. Prior coronary revascularisation procedure
iii. >=50% stenosis in major epicardial coronary artery documented by cardiac catheterisation or CT coronary angiography
b) Cerebrovascular disease defined as at least one of the following:
i. Prior stroke of atherosclerotic origin
ii. Prior carotid artery revascularisation procedure
iii. >=50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound.
c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
i. Intermittent claudication with an ankle-brachial index (ABI) <= 0.90 at rest
ii. Intermittent claudication with a >=50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound
iii. Prior peripheral artery (excluding carotid) revascularisation procedure
iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis).

Exclusion criteria

•Clinical evidence of, or suspicion of, active infection at the discretion of the investigator.
•Myocardial infarction, stroke, hospitalisation for unstable angina pectoris, or transient ischaemic attack within 60 days prior to randomisation (visit 2).
•Planned coronary, carotid or peripheral artery revascularisation known on the day of randomisation
•Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure (thoracoscopic or laparoscopic) within the past 60 days prior to randomisation (visit 2) or any major surgical procedure planned at the time of randomisation (visit 2).

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):	05-11-2021
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet bekend
Generic name:	ziltivekimab

Ethics review

Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
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Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)

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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	CTIS2023-506926-35-00
EudraCT	EUCTR2020-004853-59-NL
CCMO	NL77706.018.21