A Phase IIB, Randomized, Double blinded, Placebo controlled, Parallel group Study to Evaluate the Efficacy and Safety of MEDI6570 in Participants with a Prior Myocardial Infarction, Persistent Inflammation, and Elevated N terminal Prohormone Brain Natriuretic Peptide

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Ethical review	Approved WMO
Status	Completed
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON52059

Source
ToetsingOnline

Brief title
GOLDILOX

Condition

- Myocardial disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
heart attack, Myocardial Infarction

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: industry

Intervention

Keyword: Elevated NT- pro BNP, GOLDILOX, MEDI6570, Myocardial Infarction

Outcome measures

Primary outcome

To evaluate the effect of MEDI6570 on non-calcified coronary atherosclerotic

plaques compared with placebo

Secondary outcome

Relative change from baseline to Day 253 in NT proBNP.

Change from baseline to Day 253 in:

• LVEF

• GLS

as measured by echocardiography

Change from baseline to Day 253 in:

• LVEF

• GLS

as measured by echocardiography

Change from baseline to Day 253 in:

• Global non-calcified plaque volume

• Low attenuation plaque volume

as measured by CTA imaging

Change from baseline to Day 253 in:

• FAI

as measured by CTA imaging

• ADA incidence

• Titer

as measured in serum during the intervention and follow-up periods

•

MEDI6570 as measured in serum during the intervention and follow up periods

During the intervention and follow up periods:

• AEs

• Clinically important changes in:

Vital signs

ECGs

Safety laboratory assessments

Changes from baseline in:

• hs-CRP

• IL-6

• MPO

• MMP9

• Free sLOX-1

as measured in plasma or serum during the intervention and follow up periods

Changes from baseline to Day 253 in:

• End-diastolic volume index

• End-systolic volume index

• Left atrial volume index

• E/e* ratio

as measured by echocardiography

Change from baseline to Day 253 in:

• Percent atheroma volume

• High-risk plaque features (positive remodeling, napkin ring sign, spotty

calcification

and low attenuation plaque)

as measured by CTA imaging

Change from baseline to Day 253 in:

• FRP

as measured by CTA

Time to MACE (composite of CV death, MI, stroke, or coronary revascularization)

from randomization to Day 253.

Time to CV death or HF hospitalization from randomization to Day 253.

Change from baseline to Day 253 in:

• Time spent in MVPA

• Step count

• Acceleration intensity (MMI)

• Uninterrupted sleep time

as measured by a continuously worn physical activity monitor

Study description

Background summary

Rationale: This Phase IIB, proof-of-concept, dose-range finding clinical study is being conducted to evaluate the anti-inflammatory potential of MEDI6570 and its effect on surrogates for atherosclerotic and heart failure (HF) events in patients with a history of myocardial infarction. The results of the Phase IIB study will inform future clinical development options and precision medicine strategy for future clinical studies.

Study objective

primary
To evaluate the effect of MEDI6570 on non-calcified coronary atherosclerotic plaques compared with placebo

secundary
To evaluate the effect of MEDI6570 on a surrogate biomarker of HF compared with placebo
To evaluate the effect of MEDI6570 on left ventricular systolic function compared with placebo
To evaluate the effect of MEDI6570 on left ventricular systolic function among participants with reduced ejection fraction (defined as < 50%) compared with placebo
To evaluate the effect of MEDI6570 on other measures of non-calcified coronary atherosclerotic plaque compared with placebo
To evaluate the effect of MEDI6570 on coronary inflammation compared with placebo
To evaluate the immunogenicity of MEDI6570
To evaluate the PK of MEDI6570

safety
To assess the safety and tolerability

exploratory
To evaluate the effect of MEDI6570 on inflammatory and target engagement biomarkers compared with placeboy of MEDI6570 compared with placebo
To evaluate the effect of MEDI6570 on systolic and diastolic cardiac structure and function compared with placebo
To evaluate the effect of MEDI6570 on percent atheroma volume and high-risk plaque features compared with placebo
To evaluate the effect of MEDI6570 on coronary inflammatory changes in the perivascular space compared with placebo
To evaluate the effect of MEDI6570 on time to MACE compared with placebo.

To evaluate the effect of MEDI6570 on time to CV death or HF hospitalization
To evaluate the effect of MEDI6570 on activity and sleep among participants with reduced ejection fraction (defined as < 50%) compared with placebo

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter (70 to 100 centers), international study in participants who have recently (within the previous 30 to 180 days) had a myocardial infarction (MI; either ST segment elevation MI or non ST segment elevation MI), with persistent inflammation (high sensitivity C reactive protein [hs CRP] >= 1 mg/L) .
Participants will be randomized in a 2:2 1:1:1 ratio to receive 150, or 400 mg MEDI6570, subcutaneously (SC), or placebo, SC, every 4 weeks (Q4W) for 32 weeks (9 doses in total). The randomization will be stratified by geographic region (North America, Europe, and Japan) and by statin therapy intensity at screening (no, low- or moderate-intensity statin therapy vs high-intensity statin therapy).
Participants will undergo an echocardiogram and computed tomography angiography (CTA) scan before randomization (Day 1; Visit 3) and administration of study intervention. During the follow up period, participants will also undergo an echocardiogram and CTA scan.

Intervention Groups and Duration: The study intervention is MEDI6570, a human Immunoglobulin G1 lambda (IgG1*) triple mutation antibody that binds to human lectin-like oxidized low density lipoprotein receptor 1 (LOX-1). Going forward from amendment 2,the study will include 4 intervention groups: 150, and 400 mg MEDI6570, and 2 injection/volume mathed placebo groups while the participants previously randomized to 50 mg MEDI6570 or its injection/volume-matched placebo will continue their assigned treatment to the end of the study.
Participants will be enrolled in the study for approximately 12 months, comprising a screening and pre randomization period of up to 42 days (6 weeks), an intervention period of 225 days (31 to 32 weeks), and a follow-up period of 100 days (approximately 14 weeks). Doses of MEDI6570 or placebo, will be administered in the clinic SC Q4W for 32 weeks (9 doses in total).

Participants who were randomized to a study intervention under Protocol Version 1.0 or Amendment 1 (when there was also a 50 mg dose group) and were allocated a dosing volume of 0.5 mL will continue on their randomized study intervention (50 mg MEDI6570, or its injection/volume-matched placebo) to the end of the study, and the study blind will be maintained with regard to active versus placebo.

Intervention

Participants will be randomized in a 2:2 1:1:1 ratio to receive, 150, or 400 mg MEDI6570, subcutaneously (SC), or placebo, SC, every 4 weeks (Q4W) for 32 weeks

(9 doses in total). The randomization will be stratified by geographic region (North America, Europe, and Japan) and by statin therapy intensity at screening (no, low- or moderate-intensity statin therapy vs high-intensity statin therapy).
Participants will undergo an echocardiogram and computed tomography angiography (CTA) scan before randomization (Day 1; Visit 3) and administration of study intervention. During the follow up period, participants will also undergo an echocardiogram and CTA scan. In addition, at least 200 participants group will undergo an interim CTA between the fifth and sixth doses (Day 122; Visit 9).

Intervention Groups and Duration: The study intervention is MEDI6570, a human Immunoglobulin G1 lambda (IgG1*) triple mutation antibody that binds to human lectin-like oxidized low density lipoprotein receptor 1 (LOX-1). The study will include 6 intervention groups:, 150, and 400 mg MEDI6570, and matching placebo. Participants will be enrolled in the study for approximately 12 months, comprising a screening and pre randomization period of up to 42 days (6 weeks), an intervention period of 225 days (31 to 32 weeks), and a follow-up period of 100 days (approximately 14 weeks). Doses of MEDI6570 or placebo, will be administered in the clinic SC Q4W for 32 weeks (9 doses in total).

Study burden and risks

Despite improvements made over the last decades in the prevention of secondary MIs, a clinically significant risk of mortality and morbidity remains for up to 5 years post-MI, with the highest risk in the first months post-MI. Plaque progression has also been shown to predict ACS independently. Furthermore, treating the inflammatory pathways associated with MIs results in improved outcomes.
In preclinical models of atherosclerosis and HF, deletion of the LOX-1 receptor has demonstrated decreased atherosclerosis, reductions in myocardial fibrosis, improvements in left ventricular function, and improvements in adverse remodeling of the heart following MI. Post-MI patients have markedly elevated sLOX-1 levels and studies have demonstrated that protein expression of LOX-1 is particularly elevated at the site of human coronary atheromas in vivo. More extreme inflammatory phenotypes, such as patients with psoriasis, who have an increased risk of CHD also have elevated sLOX-1 levels. A recent study demonstrated that treatment with anti-inflammatory therapies in psoriasis decreased sLOX-1 levels and non calcified plaque burden. Moreover, sLOX-1 levels during treatment predicted regression of non calcified plaque burden. In the ongoing Phase I study, MEDI6570 markedly decreases sLOX-1 levels. Given the preclinical and clinical data, MEDI6570 may decrease the severity of atherosclerosis and HF and is a potential future therapy for the secondary prevention of CV death, MI, stroke, HF, and revascularization.

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

1 Participant must provide informed consent before any study specific activities are performed (Appendix A 3), must be able and willing to meet all requirements for randomization within 42 days after signing the full ICF, and must adhere to the schedules of activities.
2 Participant must be >= 40 years of age at the time of signing the ICF.
3 Participant must:
(a) be 30 to 365 days after presumed type-1 (ie, due to plaque rupture or erosion) MI (either STEMI or NSTEMI) at the time of enrollment.
(b) have persistent inflammation, defined as hs CRP >= 1 mg/L, as measured centrally at screening Visit 1.
4 Participant must have body mass index within the range 18 to 40 kg/m2 inclusive.

5 For female participants, the participant must not be pregnant or lactating and must be of non-childbearing potential, confirmed at screening Visit 1 by one of the following:
(a) Postmenopausal, defined as amenorrhea for >= 12 months following cessation of all exogenous hormonal treatments, and with luteinizing hormone and follicle stimulating hormone levels in the postmenopausal range.
(b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. Tubal ligation is not considered as irreversible surgical sterilization.
6 Participant must have an evaluable, pre-randomization CTA with quantifiable, non calcified plaque, as confirmed by the core laboratory.

Participants will be reassessed for study eligibility before study intervention is administered on Day 1 (Visit 3). Participants should be considered for a high-intensity statin based on existing guidelines for long-term management of patients after an MI. Participants should ideally be on a stable dose of lipid-lowering therapy throughout the treatment period of the study; therefore, efforts should be made to maximize statin intensity before randomization.
The proportion of participants with an NT-proBNP value < 125 pg/mL at screening who can be randomized to a study intervention may be capped. If this proportion is capped, a baseline NT proBNP value of >= 125 pg/mL will be required for inclusion in the study. During the study, randomization to an intervention group may also be capped within other specific participant subgroups.
In addition to the inclusion criteria specified above, study participants may elect to take part in the Genomics Initiative; participants who chose to do this must provide written informed consent before samples are collected for the optional genetic research that supports the Genomics Initiative (Appendix D 2).

Exclusion criteria

1 History of any clinically important disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or influence the results or the participant*s ability to participate in the study.
2 Percutaneous coronary intervention [PCI] planned after screening Visit 1. Eligible participants who have a PCI planned after screening Visit 1 may be rescreened after the PCI has been performed (Section 5.4).
3 History of or planned coronary artery bypass grafting.
4 Documented episode of post-MI pericarditis (eg, Dressler*s Syndrome) in the 3 months before enrollment.
5 Ongoing New York Heart Association Class IV (severe) HF.
6 Increased risk of bleeding
(a) Patients with history or presence of any bleeding disorder.
(b) Active bleeding or high risk for major bleeding (eg, gastrointestinal pathology, malignancy with high risk of bleeding, active peptic ulcer).

(c) Need for chronic anticoagulation therapy (prophylactic doses of heparin are allowed).
(d) Known severe liver disease (eg, ascites and/or clinical signs of coagulopathy).
7 History or presence of any of the following:
(a) Ongoing infection or febrile illness that in the opinion of the investigator may be the cause of elevated hs-CRP on screening (Visit 1).
(b) Ongoing atrial fibrillation or flutter.
(c) Cancer within 5 years before randomization (Day 1; Visit 3), with the exception of non melanoma skin cancer.
(d) Alcohol or substance abuse within 6 months before randomization (Day 1; Visit 3), as judged by the investigator.
(e) Known history of hypersensitivity reactions to other biologics, to human IgG preparations, or to any component of MEDI6570, or ongoing severe allergy as judged by the investigator.
(f) Patients with active positive results on screening for serum hepatitis B surface antigen, hepatitis C antibody, or HIV.
8 Any clinically important abnormalities in clinical chemistry, hematology, coagulation parameters, as judged by the investigator, including but not limited to:
(a) Aspartate transaminase (AST) > 2.0 × ULN.
(b) Alanine transaminase (ALT) > 2.0 × ULN.
(c) Total bilirubin (TBL) > 1.5 x ULN (unless due to Gilbert*s syndrome).
(d) Platelet count < 100000 platelets/µl.
9 Blood pressure (BP) values at screening Visit 1:
(a) Systolic BP < 90 mmHg or > 180 mmHg.
(b) Diastolic BP > 100 mmHg.
(c) Participants who are excluded based on elevated BP may be rescreened following adequate treatment.
The eligibility assessment is based on measurements taken starting from after 5 minutes of rest; if the result is outside these limits, additional BP measurements can be taken over the following 5 minutes, ie, up to a total of 10 minutes of rest (repeated a maximum of 3 times). If the result is outside these limits during this period, the participant is considered a screen fail.
10 Participants with any of the following contraindications to CTA:
(a) eGFR < 50 mL/min/1.73 m2 by the Chronic Kidney Disease Epidemiology Collaboration equation, or end stage renal disease treated with kidney transplant or renal replacement therapy.
(b) Allergy to iodinated contrast.
(c) History of contrast-induced nephropathy.
(d) Contraindication to nitroglycerin.
(e) Rapid heart rate that is uncontrolled by medical therapy.
(f) Inability to hold breath for at least 6 seconds.
11 Receipt of any investigational device or therapy within 6 months or 5 half lives before screening (whichever is longer).
This criterion does NOT apply for inactive, non replicating COVID-19 vaccines approved by Health Authorities or under emergency use authorization.

12 Planned participation in an additional study of an intervention or biologic before the end of the follow-up period.
13 Participants who are legally institutionalized.
14 An employee or close relative of an employee of the sponsor, the CRO, or the study site, regardless of the employee or close relative*s role.

Study design

Design

Study phase:	2
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):	24-08-2021
Enrollment:	85
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MEDI6570
Generic name:	MEDI6570

Ethics review

Approved WMO

Date:	21-10-2020
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-02-2022
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-000840-75-NL
CCMO	NL75194.091.20

Study results

Date completed: 03-11-2023

Results posted: 26-06-2024

First publication
01-01-1900