A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel group
Study to Investigate the Efficacy and Safety of CSL112
in Subjects with Acute Coronary Syndrome

Published: 14-06-2018
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The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) from the time of randomization through 90 days in subjects with ACS (diagnosed with STEMI or NSTEMI).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON54553

Source
ToetsingOnline

Brief title
AEGIS II study

Condition

- Coronary artery disorders

Synonym
Heart attack; Coronary

Research involving
Human

Sponsors and support

Primary sponsor: CSL Behring GmbH
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Acute Coronary Syndrome, CSL112, Major Adverse Cardiovascular Events (MACE)

Outcome measures

Primary outcome

The primary endpoint is the time to first occurrence of any component of the composite MACE, defined as CV death, MI, or stroke from the time of randomization through 90 days.

The primary endpoint will include all MI's.

Secondary outcome

1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days.

2. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days.

3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days.

1. Time to first occurrence of each individual component of the composite primary efficacy endpoint from the time of randomization through 90 days:

• CV death.

• MI.

• Stroke.

2. Time to occurrence of all-cause death from the time of randomization through

365 days.

Study description

Background summary

Cardiovascular (CV) disease is the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. There are more deaths annually from CV disease causes than all forms of cancer combined [Mozaffarian et al, 2016]. The disease process responsible for the majority of CV disease related deaths is atherosclerosis, which can lead to a variety of acute presentations depending on the arterial bed affected and severity; the 2 most common are acute coronary syndrome (ACS) and ischemic stroke [Mahoney et al, 2008].
Acute coronary syndrome is a life-threatening condition, which most commonly occurs when an atherosclerotic plaque ruptures or erodes, leading to thrombus formation within a coronary artery. A thrombus within a coronary artery can result in unstable angina, a myocardial infarction (MI) (heart attack), or sudden death. Even after recovery from an acute episode of ACS, patients continue to be at heightened risk. The short-term morbidity and mortality associated with both the index coronary event and recurrent CV events can be as high as 20% per year [Morrow, 2010]. In the PLATO Study, which was conducted in ACS patients, approximately 50% of recurrent CV events (CV death, MI, or stroke) occurred within the first 30 days of a 1-year follow-up period in all ACS subgroups [NDA 22-433/S015 Brilinta®, 2015].
Despite advances in therapeutic strategies for ACS, patients remain at heightened risk for recurrent ischemic events, particularly in the immediate weeks to months following the event. Consequently, effective and safe therapies that provide clinically relevant reductions in recurrent CV events beyond current secondary prophylaxis are needed for patients with ACS.
High-density lipoprotein (HDL) exerts a protective effect in experimental models of atherosclerotic CV disease. While the proposed atheroprotective properties of HDL are multifaceted [Remaley et al, 2008; Tardif et al, 2009], HDL is believed to bring about beneficial effects mainly by reverse cholesterol transport, whereby excess cholesterol is removed from arteries containing atherosclerotic plaques and transported back to the liver for excretion. This removal of cholesterol is mediated by the dominant protein of HDL, apolipoprotein A-I (apoA-I) [Tall, 1998], and removal of cholesterol from the

artery wall reduces the size of the plaque. Cholesterol efflux capacity, an ex vivo measure of HDL function, evaluates the ability of HDL to remove excess cholesterol from atherosclerotic plaque for transport to the liver. The measure is a correlate of major adverse CV events (MACE) endpoints that is independent of HDL cholesterol [Khera et al, 2011; Rohatgi et al, 2014; Saleheen et al, 2015; Liu et al, 2016; Zhang et al, 2016]. It has been suggested that pharmacotherapies that elevate cholesterol efflux capacity may be more likely to yield benefit to patients than those which raise HDL cholesterol [Siddiqi et al, 2015]. The central hypothesis of the program is that elevation of cholesterol efflux by infusion of CSL112 will reduce recurrent events in the period of high risk following an MI.

Study objective

The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) from the time of randomization through 90 days in subjects with ACS (diagnosed with STEMI or NSTEMI).

Study design

This is a phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of CSL112 on reducing the risk of MACE in subjects with ACS (diagnosed with STEMI or NSTEMI) who are receiving evidence-based medical therapy.

Intervention

Treatment 1 - Study drug

The active component of CSL112 is apoA-I, which is purified from human plasma. Apolipoprotein A-I is formulated with PC and stabilized with sucrose and cholate as excipients.
Reconstituted CSL112 (dose 6 g; approximately 170 mL) will be IV infused in a vein (peripheral or central) over 2 hours.
Weekly infusion of the study drug and this during 4 weeks.
This makes a total of 4 infusions.
Each infusion is to be given at least 5 days apart. All 4 infusions should be administered within 30 days of you receiving your first infusion.

Treatment 2 - Placebo (albumine)

The placebo solution will comprise 30 mL of 25% albumin solution diluted with 140 mL dextrose 5% in water.
An equivalent amount of placebo (approximately 170 mL) to CSL112 will be IV

infused in a vein (peripheral or central) over 2 hours.
Weekly infusion of Placebo (albumine) and this during 4 weeks.
This makes a total of 4 infusions.
Each infusion is to be given at least 5 days apart. All 4 infusions should be administered within 30 days of you receiving your first infusion.

Study burden and risks

The overall study duration will be approximately 50 months.

Disadvantages of participation in the study may be:
- possible side effects/complications of the intervention
- possible adverse effects/discomforts of the evaluations in the study.

Participation in the study also means:
- additional time;
- additional or longer hospital stays;
- additional tests;
- instructions you need to follow;

The patient may or may not have direct medical benefit. They may receive information about their health from physical examinations and medical tests done in this study

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
Male or female at least 18 years of age at the time of providing written informed consent.
Evidence of myocardial necrosis in a clinical setting consistent with type I (spontaneous) MI (STEMI or NSTEMI) caused by atherothrombotic coronary artery diseaseas defined by the following:
a. Detection of a rise and / or fall in cardiac troponin I or T with at least 1 value above the 99th percentile upper reference limit.
AND
b. Any 1 or more of the following:
i. Symptoms of acute myocardial ischemia (ie, resulting from a primary coronary artery event).
ii. New (or presumably new) significant ST/T wave changes or left bundle branch block.
iii. Development of pathological Q waves on electrocardiogram.
iv. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality in a
pattern consistent with an ischemic etiology.
v. Identification of intracoronary thrombus by angiography.
Note: Electrocardiograms obtained as part of standard of care can be used to support or confirm the index MI.
No suspicion of acute kidney injury at least 12 hours after IV contrast agent administration (subjects who have undergone angiography) or after first medical contact for the index MI (subjects who have not undergone angiography). There must be documented evidence of stable renal function defined as no more than an increase in serum creatinine < 0.3 mg/dL (~27 µmol/L) from pre-contrast serum creatinine value.
Evidence of multivessel coronary artery disease defined as meeting 1 or more of the following criteria:
c. At least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery
territories (left anterior descending, left circumflex,

right coronary artery) on catheterization performed during the index hospitalization.
d. Prior cardiac catheterization documenting at least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery territories or left anterior descending, left circumflex, right coronary artery.
e. Prior percutaneous coronary intervention and evidence of at least 50% stenosis of at least 1 epicardial coronary artery territory different from prior revascularized artery territory .
f. Prior multivessel coronary artery bypass grafting.
Presence of established cardiovascular risk factor(s), defined as:
a. Diabetes mellitus on pharmacotherapy.
OR
b.2 or more of the following :
g. Age >= 65 years.
h. Prior history of MI.
Peripheral arterial disease.

Exclusion criteria

* Ongoing hemodynamic instability
* Evidence of hepatobiliary disease
* Evidence of severe chronic kidney disease
* Plan to undergo scheduled coronary artery bypass graft surgery after randomization, as determined at the time of screening.
* Body weight < 50 kg.
* Allergy to soy bean or peanuts
* Known or suspected hypersensitivity to the investigational product, or to any excipients of the investigational product or placebo (albumin)
* A known history of IgA deficiency or antibodies to IgA
* Other severe comorbid condition, concurrent medication
For a complete list refer to p41, 42 and 43 of the 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):	08-01-2019
Enrollment:	1650
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CSL112-3001
Generic name:	Apolipoprotein A-I

Ethics review

Approved WMO Date:	14-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 13-03-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-03-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-05-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 29-07-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 15-08-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 29-11-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 06-01-2020

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 08-04-2020

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 09-04-2020

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	20-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	10-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	15-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000996-98-NL
ClinicalTrials.gov	NCT03473223
CCMO	NL65261.029.18