A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-groupStudy to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Moderate Renal Impairment and Acute Myocardial Infarction

Published: 04-01-2017
Last updated: 11-04-2024

The primary objective of this study is to assess the renal safety of CSL112 in subjects with moderate RI and AMI after administration of up to 4 weekly infusions of CSL112.The secondary objectives of the study are:1. To further characterize the...

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

Summary

ID

NL-OMON43079

Source
ToetsingOnline

Brief title
CSL112_2001

Condition

- Myocardial disorders

Synonym
heart infarction, moderate renal impairment

Research involving
Human

Sponsors and support

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

Intervention

Keyword: acute myocardial infarction, renal impairment, safety, tolerability

Outcome measures

Primary outcome

The renal safety profile of CSL112 in subjects with moderate RI and AMI who receive up to 4 weekly administrations of CSL112 will be assessed by co-primary endpoints of the incidences of treatment-emergent (1) renal SAEs as defined below, and (2) AKI, defined as an absolute increase in serum creatinine from baseline * 0.3 mg/dL (26.5 *mol/L) during the Active Treatment Period that is sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained [due, for example, to loss of follow-up or protocol violation], a single serum creatinine value that is increased from baseline * 0.3 mg/dL (26.5 *mol/L) during the Active Treatment Period
would also fulfil the definition of AKI.
Treatment-emergent is defined as occurring at or after the start of the first infusion. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1.
A renal SAE is defined as any SAE with a MedDRA PT included in the Acute Renal Failure narrow Standard MedDRA Query (SMQ) or a PT of Renal Tubular Necrosis,

Renal Cortical Necrosis, Renal Necrosis, or Renal Papillary Necrosis.

Incidence rates will be based on the number of subjects with at least 1 occurrence of the event of interest; that is, a subject with 2 treatment-emergent renal SAEs or 2 instances of AKI will be counted once.

Secondary outcome

Secondary safety and tolerability endpoints include:

1. The occurrence of any TEAEs throughout the study.

2. The occurrence of treatment-emergent adverse drug reactions or suspected adverse drug reactions defined as:

a. All TEAEs, including local tolerability events, that begin during or within 1 hour after the end of an infusion, or

b. Those TEAEs which the Investigator or Sponsor indicate may be causally related to the administration of the investigational product (CSL112 or placebo), or

c. All TEAEs for which the Investigator's causality assessment is missing or indeterminate, or

d. All TEAEs for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in incidence rates is 1% or more.

3. Changes from baseline (ie, pre-infusion on Study Day 1) through to the end of the Active Treatment Period in renal status defined as:

a. Absolute increases from baseline in serum creatinine as follows:

i. * baseline value

ii. > 0 to < 0.3 mg/dL

iii. * 0.3 to * 0.5 mg/dL

iv. * 0.5 mg/dL

b. Increases in serum creatinine that are sustained for * 24 hours upon repeat measurement as follows:

i. * 1.5 x baseline values

ii. * 2 x baseline value

iii. * 3 x baseline value

iv. serum creatinine * 4.0 mg/dL (353.6 *mol/L)

c. Initiation of renal replacement therapy

d. Decrease in eGFR by * 25% from baseline starting during the Active Treatment Period and that is sustained at the final study visit

4. Change from baseline (ie, pre-infusion on Study Day 1) in hepatic status that occurs during the Active Treatment Period and that is sustained for * 24 hours upon repeat measurement as follows:

a. ALT > 3 x ULN

b. ALT > 5 x ULN

c. ALT > 10 x ULN

d. Serum total bilirubin > 1.5 x ULN (Note: For subjects with a history of Gilbert*s syndrome, this assessment will be based on indirect bilirubin.)

e. Serum total bilirubin > 2 x ULN (Note: For subjects with a history of Gilbert*s syndrome, this assessment will be based on indirect bilirubin.)

f. Possible Hy's Law cases, as defined in the FDA Guidance for Industry: Drug-Induced

Liver Injury: Premarketing Clinical Evaluation (July 2009; see Section 9.1.3.3

for definition of Hy*s Law).

5. The occurrence of treatment-emergent bleeding events as defined by the Bleeding Academic Research Consortium (BARC) criteria (Mehran et al, 2011) from the start of the first infusion until the end of the Safety Follow-up Period.

6. Clinically significant changes in clinical laboratory tests results (serum biochemistry, hematology, and urinalysis), physical examinations findings, body weight, electrocardiograms (ECGs), and vital signs (blood pressure, pulse rate, and body

temperature).

7. The occurrence of binding antibodies specific to apoA-I and/or CSL112.

Study description

Background summary

Acute coronary syndrome (ACS) is a life-threatening condition, that 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 (UA), a
myocardial infarction (MI [ie, 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 cardiovascular
(CV) events can be as high as 20% per year (Fox et al, 2006), and are inversely related to renal function status, such that subjects with mild, moderate, and severe renal impairment (RI) have progressively poorer long-term prognosis as compared with patients with normal
renal function (Gibson et al, 2004; Fox et al, 2010). In patients with ACS and RI, the prognosis, both short- and long-term, is worse than for those with normal renal function, as the risk of CV events and mortality is inversely proportional to the estimated glomerular
filtration rate (eGFR [Nabais et al, 2008; Bhandari and Jain, 2012]). Therefore, the identification of therapies that are safe and effective in patients with concurrent RI and ACS would represent an important advancement in

medical therapy.

Study objective

The primary objective of this study is to assess the renal safety of CSL112 in subjects with moderate RI and AMI after administration of up to 4 weekly infusions of CSL112.
The secondary objectives of the study are:
1. To further characterize the safety and tolerability of CSL112 in subjects with moderate RI and AMI.
2. To characterize the PK of CSL112 after multiple dose administration in subjects with moderate RI and AMI.

Study design

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and tolerability of up to 4 weekly IV administrations of 6 g CSL112 compared with placebo in subjects with moderate RI and AMI.

The main study will enroll approximately 81 subjects who will be randomly assigned in a 2:1 ratio to receive 6 g CSL112 (54 subjects) versus placebo (27 subjects). To ensure that at least one-third of the study population has an eGFR in the Chronic Kidney Disease (CKD) 3b range
(30 to < 45 mL/min/1.73 m2), no more than two-thirds of the study population will have an eGFR in the CKD 3a range (45 to < 60 mL/min/1.73 m2). Randomization of the 81 subjects will be stratified by eGFR (30 to < 45 mL/min/1.73 m2 or 45 to < 60 mL/min/1.73 m2) as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and by medical history of diabetes requiring current treament with any anti-diabetic medication (yes or no). Clinical procedures for these subjects will include assessments for safety (including renal and hepatic), PK, and PD (lipid and CV biomarkers).
A subset of approximately 21 of these subjects will also be asked to participate in a PD substudy, which is intended to characterize the profile of biomarkers of inflammation in response to an ex-vivo inflammatory stimulus in whole blood after CSL112 administration. Subjects will
provide separate informed consent for the additional blood samples to be obtained for this purpose, results of which will be reported separately.

Intervention

The study will consist of screening and 2 study periods: an Active Treatment Period during which patients will receive 4 IV infusions of investigational product (ie, CSL112 or placebo) over approximately 29 days and a Safety Follow-up Period (approximately 30 days from the

Active Treatment Period)

Study burden and risks

In a pharmaceutical study like this one, every risk or side effect cannot be predicted. Each person*s reaction to a test drug may be different.
To date, approximately 102 people (69 healthy adults and 33 patients) have received CSL112 in 3 other completed research studies. In addition, approximately 839 patients with normal renal function or mild renal impairment and MI, 12 healthy adults, and 12 adults with moderate renal impairment have received CSL112 in ongoing studies. Based on the study data available from the completed studies, the following side effects have been reported and may be related to CSL112:
* Injection and infusion site reactions: including pain, redness, swelling, coldness, and inflammation at the IV cannula site
* Venipuncture or catheter site related reactions: including bruising or swelling at the location of a blood draw or IV cannula site
* Headache

You can find more details about possible side effects in Appendix 3 of the subject information form.

Patients should not expect their condition to improve as a result of participating in this research study as they may not get any direct benefit from taking part in this study.
The information we get from this study may help improve the treatment of people with the same medical conditions in the future.

Contacts

Public
CSL Behring GmbH

Emil-von-Behring-Strasse 76
Marburg DE-35041
DE
Scientific
CSL Behring GmbH

Emil-von-Behring-Strasse 76
Marburg DE-35041
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects may be enrolled in the study if all of the following inclusion criteria are met:
1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
2. Males or females aged at least 18 years at the time of providing written informed consent.
3. Evidence of moderate RI (eGFR * 30 and < 60 mL/min/1.73 m2) before randomization, as calculated by the interactive response technology (IRT) using the CKD-EPI equation (Levey et al., 2009; Stevens et al., 2010). The local laboratory serum creatinine value obtained at Visit 2 (Study Day 1) should be used for this calculation.
NOTE: The eGFR calculator on the National Kidney Foundation*s website can be used for pre-screening purposes (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm) and the equation can be found in Appendix I.
4. Evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI as 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 ischemia
ii. New (or presumably new) significant ST/T wave changes or left bundle-branch block (LBBB)
iii. Development of pathological Q waves on ECG
iv. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality
v. Identification of intracoronary thrombus by angiography
5. Documented evidence of stable renal function and no clinical suspicion of AKI at least 12 hours after FMC for the index AMI. For subjects undergoing angiography with or without PCI, stable renal function must be confirmed at least 12 hours after IV contrast

and is defined as a serum creatinine value that is < 0.3 mg/dL increased from the precontrast administration value. If the local laboratory post-contrast serum creatinine value is increased * 0.3 mg/dL from the pre-contrast administration value, the laboratory test may be repeated once at least 24 hours after the initial assessment to assess stable renal function. The repeat serum creatinine value must be increased < 0.3 mg/dL from the pre-contrast administration value and there must be no suspicion of AKI for the subject to be eligible to receive the first infusion (Table 7).
NOTE: If multiple local laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time but before contrast administration should be used as the reference value used to assess stability of renal function.
6. Female subjects must be post-menopausal or with a negative urine pregnancy test at the screening visit and before randomization.
a. Menopause is defined as being over the age of 60 years, or an age 45 to 60 years (inclusive) with amenorrhea for at least 1 year and a confirmatory follicle stimulating hormone (FSH) level > 30 IU/L.
b. Women from the ages 45 to 60 years (inclusive) who are not amenorrheic for at least 1 year or who have a screening FSH * 30 IU/L must use an acceptable method of contraception during the study as described below.
c. Females of childbearing potential must be willing and able to cease breastfeeding, and use an acceptable method of contraception to avoid pregnancy during the study and for 3 months after receipt of the last dose of investigational product.
7. NOTE: Acceptable methods of contraception are: (1) abstinence where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable definitions of abstinence; (2) hormonal method; (3) 2 barrier methods, where 1 method is the male condom; or (4) use of intrauterine device (placed more than 3 months before randomization); or (5) surgical sterilization (more than 3 months before randomization). Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen/progestin vaginal ring, or contraceptive medication implant. Acceptable barrier methods include: female or male condoms, with spermicidal foam or spermicidal jelly, or diaphragm, with spermicidal foam or spermicidal jelly. Female condom and male condom should not be used together.
7. Investigator believes that the subject is willing and able to adhere to all protocol requirements.
8. Willing not to participate in another interventional clinical study until completion of the final study visit.

Exclusion criteria

Subjects are excluded from participating in this study if 1 or more of the following exclusion criteria are met:
1. Symptoms, biomarker elevation or ECG changes other than those of the index event that

are consistent with a diagnosis of AMI but are likely not due to primary myocardial ischemia (eg, PCI or coronary artery bypass graft [CABG]-related MI, stent thrombosis, arrhythmia, heart failure, trauma, renal insufficiency, etc.) (See Third Universal Definition of MI in Appendix II)
2. Ongoing hemodynamic instability defined as any of the following:
a. A history of New York Heart Association (NYHA) Class III or IV Heart Failure within the last year
b. Killip Class III or IV (Appendix III)
c. Sustained and/or symptomatic hypotension (systolic blood pressure < 90 mm Hg)
d. Left ventricular ejection fraction (LVEF) < 30%
3. Planned CABG during the Active Treatment Period
4. Evidence of hepatobiliary disease as indicated by any 1 or more of the following at screening:
a. Current active hepatic dysfunction or active biliary obstruction
b. Chronic or prior history of cirrhosis or of active infectious/inflammatory hepatitis
Note: If subject has a past medical history of recovered hepatitis A, B, or C without evidence of cirrhosis, he/she could be considered for inclusion if there is documented evidence that there is no active infection (ie, antigen and/or polymerase chain reaction [PCR] negative).
c. ALT > 3 x ULN or total bilirubin > 1.5 x ULN at time of randomization. However, subjects with a known or suspected history of Gilbert's syndrome may be eligible for study participation. The medical monitor must be contacted before enrolment of the subject to confirm eligibility (see Section 8.2.2.1, Table 7).
5. History of AKI after previous exposure to an IV contrast agent. Subjects with a history of allergy to IV contrast agent may participate in the study if they have no evidence of serious clinical sequelae at the time of consent. The medical monitor should be contacted to discuss eligibility.
6. History of current nephrotic range proteinuria defined as > 3500 mg/24 hours or > 3000 mg/g creatinine, or 4+ proteinuria on urine dipstick at screening, despite the use of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker therapy.
7. Body weight < 50 kg
8. Known history of allergies, hypersensitivity or deficiencies as follows:
a. Allergy to soybean or peanuts
b. Known or suspected hypersensitivity to the investigational product, or to any excipients of the investigational product
c. A known history of IgA deficiency or antibodies to IgA
9. Other severe comorbid condition, concurrent medication, or other issue that renders the subject unsuitable for participation in the study, including but not limited to:
a. A comorbid condition with an estimated life expectancy of * 6 months
b. Women who are pregnant or breastfeeding
c. Participated in another interventional clinical study or had extensive blood sampling (* 500 mL) within 3 months. Includes administration of any other investigational agents within 3 months before the first administration of current investigational product or at any time during the study
d. Alcohol, drug, or medication abuse within 1 year before consent to this study
e. Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy or gene therapy) within 3 months before the first administration of

investigational product or at any time during the study. Recovery from associated toxicities (eg, hematologic) must be documented in the source document.
NOTE: Use of low dose chemotherapy for treatment of a condition other than cancer (eg, rheumatic disease) may be permissible. The medical monitor should be contacted to discuss eligibility.
f. Previously randomized or participating in this study or previously exposed to CSL112
g. Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study
h. Subjects who are incarcerated, including prisoners or subjects compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
i. Inability or unwillingness to comply with all follow-up, and/or unwilling to allow review of medical records through end of follow-up

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CSL112
Generic name:	CSL112

Ethics review

Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2015-003017-26-NL
ClinicalTrials.gov	NCT02742103
CCMO	NL60082.056.16