

A 2-Part, Phase 1, Multicenter, Single Dose, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of CSL889 in Adult Patients with Sickle Cell Disease

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Primary Objective: To assess the safety and tolerability of single doses of CSL889 administered by IV infusion in subjects with stable SCD and in subjects with SCD in VOC
Secondary Objectives: 1. To characterize the PK profile of CSL889 after single IV...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON52183

Source

ToetsingOnline

Brief title

CSL889_1001 (2102/0113)

Condition

- Blood and lymphatic system disorders congenital

Synonym

Sickle cell disease

Research involving

Human

Sponsors and support

Primary sponsor: CSL Behring LLC

Source(s) of monetary or material Support: By the study sponsor CSL Behring.

Intervention

Keyword: CSL889, Hemopexin, Sickle Cell Disease

Outcome measures

Primary outcome

Primary Endpoints:

Frequency, nature and severity of TEAEs from start of infusion until 32 days after infusion in subjects with stable SCD and in subjects with SCD in VOC

Secondary outcome

Secondary Endpoints:

1. Serum PK parameters of CSL889, with and without adjustment for baseline hemopexin: C_{max}, AUC from time 0 to the last measurable concentration (AUC_{0-last}), AUC_{0-inf}, time of maximum concentration (t_{max}), terminal half-life (t_{1/2}), clearance (CL), volume of distribution during the elimination phase (V_z)
2. Anti-CSL889 antibodies

Study description

Background summary

The study drug CSL889 is being developed for the treatment of vaso-occlusive crisis (also known as pain crisis) that occurs in patients with severe sickle cell disease. CSL889 is a human protein called hemopexin. All humans have hemopexin. However, patients with sickle cell disease may have very little hemopexin. A main job of hemopexin is to combine with a substance in blood called heme and to clear heme from the blood. The heme comes from red blood cells when red blood cells die. Research suggests that heme may play a role in

pain crisis. If CSL889 combines with heme, similar to the way hemopexin found in the body does, it may help clear heme from the blood.

Study objective

Primary Objective:

To assess the safety and tolerability of single doses of CSL889 administered by IV infusion in subjects with stable SCD and in subjects with SCD in VOC

Secondary Objectives:

1. To characterize the PK profile of CSL889 after single IV doses of CSL889 in subjects with stable SCD and in subjects with SCD in VOC
2. To assess immunogenicity of CSL889 after single IV doses of CSL889 in subjects with stable SCD and in subjects with SCD in VOC

Study design

This is a 2-part phase 1, first-in-human, multicenter, open label, cohort study to evaluate the safety and tolerability, pharmacokinetics (PK), exploratory pharmacodynamics (PD), and biomarkers of target engagement of CSL889 following single intravenous (IV) doses of CSL889 in subjects with stable SCD and in subjects with SCD in vaso-occlusive crisis (VOC), requiring parenteral opioids and admission to hospital for management. The study includes 2 parts.

Part A: To evaluate single dose administration of CSL889 in subjects with stable SCD

Part B: To evaluate single dose administration of CSL889 in subjects with SCD in VOC.

This study will be conducted in the United States, the United Kingdom, The Netherlands, and possibly other countries.

Study Part A involves sequential dose escalation of cohorts with between group assessments of safety, PK, exploratory PD, and biomarkers of target engagement, and consists of a 21-day Screening Period, CSL889 administration on Day 1, and a Safety Follow-up Period of 32 days after CSL889 administration for each subject. The study includes an inpatient period and outpatient visits, some of which may be performed as home care visits.

In Part A, eligible subjects receive a single IV dose of CSL889 in an open label manner at the study site on Day 1 and remain in the clinic for inpatient monitoring until approximately 24 hours after end of CSL889 infusion, during which blood samples for scheduled assessments of safety, PK, exploratory PD, and biomarkers of target engagement will be obtained. Subjects will be followed up in scheduled study site and home care visits for 32 days for safety, PK, exploratory PD, and biomarkers of target engagement.

In Part A, it is planned to assess 6 ascending single doses at 3, 10, 30, 60, 120, and 200 mg/kg CSL889 in 4 subjects per dose cohort. These doses are putative, and based on emerging safety and PK data, dose levels by cohort may be adjusted, and intermediate dose cohorts may be added. Sentinel dosing will

be used for the first subject of each dose cohort (sentinel subject), with a 24-hour monitoring period for the sentinel subject and dosing of the remaining subjects ≥ 72 hours after the start of CSL889 infusion in the sentinel subject. Study Part B assesses safety, PK, exploratory PD, and biomarkers of target engagement in subjects with SCD in VOC, and will enroll 1 cohort of 4 subjects in VOC to receive a single IV dose of CSL889 at a dose selected based on emerging safety and PK data from Part A. An additional cohort of up to 4 subjects may be included if necessary to adequately characterize safety and / or PK and / or exploratory PD and biomarkers of target engagement. In Part B, informed consent and Screening will be conducted only in the context of a hospital admission for VOC. The process of obtaining informed consent may be initiated once the decision has been made to admit the subject for ongoing treatment of VOC per local standard of care (eg, in the Emergency Department), even if the subject has not yet been admitted to an inpatient facility. Potential subjects for Part B may be preidentified while in stable SCD, based on their medical history.

The duration of the study for an individual subject is expected to be approximately 8 weeks in Part A and approximately 5 weeks in Part B. The overall study duration globally (first subject's first visit to last subject's last visit) will be approximately 17 months.

Intervention

Study product:

CSL889 is a human 60 kilodalton glycoprotein that is purified from human plasma using a Kistler Cohn Fraction IV-4 as the starting material for the manufacturing process. CSL889 will be supplied as a sterile liquid formulation at a concentration of 100 mg/mL in 50 mL vials, formulated with commonly used stabilizers including citric acid, sodium phosphate dihydrate, and sodium chloride, pH 6.9 to 7.5.

Dose:

Part A: It is planned to assess 6 ascending single doses at 3, 10, 30, 60, 120, and 200 mg/kg CSL889 in 4 subjects per dose cohort. These doses are putative, and based on emerging safety and PK data, dose levels by cohort may be adjusted, and intermediate dose cohorts may be added.

Part B: The proposed dose for Cohort B1 is 60 mg/kg, provided it has been shown to be safe and well tolerated in subjects with stable SCD in Part A. The dose level may be adjusted based on emerging safety and PK data from Part A. The decision to study a second dose level in Part B will be determined based on emerging data from Cohort B1. The dose would be selected from those studied in Part A.

Dosing regimen:

Single dose administration.

Administration:

IV infusion at a constant rate into the left or right arm contralateral to the blood sampling site.

Study burden and risks

Please refer to section 6. 'Possible side effects and discomforts' in the subject information sheet for an overview of the risks and side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

- Diagnosis of SCD as documented in the subject's medical record
- Aged 18 to 60 years, inclusive

- Stable SCD for at least 30 days before Day 1. Stable SCD is defined as the subject being at his or her medical baseline, with no evidence of worsening of disease over the last 30 days (including VOC, recent major surgery, hospitalization, serious infection, significant bleeding, cerebrovascular accident, seizures, or IV opioids)(Part A)
- Uncomplicated VOC requiring parenteral opioid treatment and admission to hospital for management
Uncomplicated VOC is defined as sickle cell pain without the following associated clinical features (Part B):
 - o Fever ($> 38.5^{\circ}\text{C}$)
 - o Hypotension ($< 90/60$ mmHg)
 - o Hypoxia ($< 90\%$ oxygen saturation on room air, or requiring oxygen therapy to maintain oxygen saturation above 90%)
 - o New neurological signs and / or symptoms clinically suggestive of stroke or transient ischemic attack
 - o Signs and / or symptoms of Acute Chest Syndrome, accompanied by any new pulmonary infiltrate on chest radiography (chest X-ray to be performed if clinically indicated and according to local clinical guidelines)
- Subject is either not taking one of the study permitted SCD therapies (hydroxyurea, L-glutamine, L-glutaminecrizanlizumab, and/or voxelotor) or subject has been taking one or more of those for at least 30 days before Day 1 and is on a stable, well tolerated regimen that is planned to continue without change throughout the study

Exclusion criteria

- History of primary hemorrhagic stroke
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk for bleeding
- Hospitalization for vaso-occlusive crisis (VOC) or treated with parenteral pain medications in other medical settings such as the emergency department or day hospital for VOC during the past 30 days before Day 1
- Blood transfusion within the 90 days before Day 1, or expecting blood transfusion during the study
- Weight >110 kg (242 lbs)
- Surgery within 30 days before Day 1 or any preplanned surgeries during the study (minor surgeries may be permitted under local anesthesia before screening, with permission of the medical monitor)
- Female subjects who are pregnant or breastfeeding
- Female subject of childbearing potential or fertile male subject either not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 30 days after receipt of CSL889.
- Treatment with any other drug / biologic that is newly approved for SCD during the conduct of this study within 90 days before Day 1.
Exceptions: crizanlizumab [Adakveo®] and voxelotor [Oxbryta®] are permitted

(where prescribed).

- Treatment with another investigational product within 30 days or within 5 half-lives of the product (whichever is greater) before Day 1
- Vaccination within 30 days before Day 1, or planned vaccination during the study
- Body-mass index < 16 kg/m² or weight < 50 kg (110 lbs)
- History of anaphylactic-type reactions, transfusion related reaction, asthma, or autoimmune disease

Study design

Design

Study type: Interventional

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Treatment

Recruitment

NL

Recruitment status: Recruitment stopped

Start date (anticipated): 21-06-2021

Enrollment: 10

Type: Actual

Medical products/devices used

Product type: Medicine

Brand name: CSL889

Generic name: Hemopexin

Ethics review

Approved WMO

Date: 28-09-2020

Application type: First submission

Review commission: METC Amsterdam UMC

Approved WMO
Date: 08-02-2021
Application type: First submission
Review commission: METC Amsterdam UMC

Approved WMO
Date: 18-03-2021
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 25-03-2021
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 26-11-2021
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 21-03-2022
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 23-03-2022
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 22-04-2022
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-05-2022
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-06-2022
Application type: Amendment
Review commission: METC Amsterdam UMC

Approved WMO

Date: 08-11-2022
Application type: Amendment
Review commission: METC Amsterdam UMC
Approved WMO
Date: 23-12-2022
Application type: Amendment
Review commission: MEC Academisch Medisch Centrum (Amsterdam)

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Approved WMO
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Application type: Amendment
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Approved WMO
Date: 30-08-2023
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
EudraCT	EUCTR2019-001870-27-NL
ClinicalTrials.gov	NCT04285827
CCMO	NL74968.018.20

Study results

Date completed:	08-02-2023
Results posted:	18-03-2024
Actual enrolment:	5

Summary results

Trial is ongoing in other countries

First publication

26-02-2024