A multicenter, double-blind, randomized, placebo-controlled, parallel-arm study to investigate the efficacy and safety of subcutaneous administration of CSL312 (garadacimab) in the prophylactic treatment of hereditary angioedema

Published: 21-10-2020
Last updated: 17-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50841

Source
ToetsingOnline

Brief title
CSL312 (garadacimab) in the prevention of hereditary angioedema attacks

Condition

- Congenital and hereditary disorders NEC

Synonym
HAE, Hereditary angioedema

Research involving

Human

Sponsors and support

Primary sponsor: CSL Behring LLC
Source(s) of monetary or material Support: Industry

Intervention

Keyword: CSL312 (garadacimab), Double Blind, Hereditary angioedema, Phase III

Outcome measures

Primary outcome

The primary endpoint is the time-normalized number of HAE attacks during

treatment from Day 1 through Day 182.

Secondary outcome

The secondary endpoints of the study are:

* The reduction in the attack rate during the Treatment Period compared to the

Run-in Period.

* The time-normalized number of HAE attacks requiring on-demand treatment.

* The time-normalized number of moderate and / or severe HAE attacks.

* The time-normalized number of HAE attacks at various time points during the

treatment period.

* Subject Global Assessment of Response to Treatment (SGART).

* Adverse events (AEs).

* Adverse events of special interest (AESIs).

* Serious adverse events (SAEs).

* CSL312 induced anti-CSL312 antibodies.

* Clinically significant abnormalities in laboratory assessments (ie,

laboratory abnormalities reported as AEs).

Study description

Background summary

In spite of the growing attention to HAE patients by the medical community and stakeholders, the burden of this disease is very high and quality of life is still negatively impacted. Hereditary angioedema negatively impacts a patient*s daily-life, psycho-social health, and productivity both during times of attack and during times of remission [Aygoren-Pursun et al. 2014].

The availability of prophylactic therapies that reduce the frequency and / or severity of attacks has improved, however there are limitations to the treatment armament such as an unfavorable side effect profile (ie, attenuated androgens), a lack of effect (ie, anti-fibrinolytics), or the frequency of administration (intravenous [IV] or subcutaneous [SC] C1-INH). Furthermore, there are currently no therapies specifically developed for treatment or prevention of HAE attacks due to nC1-INH HAE. There remains a medical need for effective and safe therapies that prevent and reduce the disease burden, improve the quality of life, and offer a convenient dosing regimen for patients with HAE [Valerieva 2018].

CSL312 may have the potential to address current unmet needs as a mAb with a novel mechanism of action targeting FXIIa, which is elevated in the serum during acute HAE attacks compared to normal levels observed during times of remission [Cugno et al. 1996]. CSL312 targets FXIIa to inhibit the kallikrein-kinin pathway, thereby inhibiting excessive production of BK, the mediator of swelling in HAE attacks. In addition, the SC route of administration and CSL312 may offer improved patient convenience compared to other products registered for prevention of HAE attacks.

Study objective

The primary objective of this study is to evaluate the efficacy of SC administration of CSL312 as prophylaxis to prevent HAE attacks in subjects with HAE.

The secondary objectives of the study are:
1. To characterize the clinical efficacy of SC CSL312 in the prophylactic treatment of HAE.
2. To evaluate the safety of SC CSL312 in the prophylactic treatment of HAE.

Study design

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of CSL312 (also known as garadacimab) administered subcutaneously (SC) for the prophylaxis to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with C1-esterase inhibitor (C1-INH) HAE. This study will be conducted globally.
Following informed consent, subjects will undergo a Screening Period of up to 1 month to determine eligibility for enrollment into the study. Screened subjects who meet all the inclusion and none of the exclusion criteria will enter a Run-in Period to confirm the required baseline HAE attack rate of * 1 attack per month. Subjects must complete at least 1 month of the Run-in Period. Additionally, subjects must experience at least 2 HAE attacks during the Run-In Period to be eligible to enter the Treatment Period. Subjects who experience at least 2 attacks during the required first month of the
Run-In Period may enter the Treatment Period if they also meet all other criteria as stated in Section 4.1.3 of the protocol.

Subjects who do not meet the screening criteria for entering the Run-in Period within 30 days may be able to rescreen with confirmation from the sponsor. Subjects who do not meet the minimum HAE attack rate during the Run-in Period and / or all other criteria for entering the Treatment Period will be considered Run-in failures and will not be allowed to rescreen. Eligible subjects will be randomized 3:2 to either the CSL312
Active Arm (CSL312 SC) or the Placebo Arm. Randomization will take age (* 17 years, > 17 years) and, for adults, baseline attack rate observed during the Run-in Period (1 to < 3 attacks / month, and * 3 attacks / month) into account. Following the Treatment Period, subjects will either enter a 2-month Follow-up Period (ie, 3 months after last investigational product administration) or may roll-over into an open-label phase 3b study (CSL312_3002).

Intervention

Subjects will be randomly assigned to receive one of the following treatments:
- Group 1 CSL312
- Group 2 placebo

Subjects randomized to the Active Arm will receive CSL312 SC.

Subjects randomized to the Placebo Arm will receive volume-matched placebo SC.

Study burden and risks

The subjects participation in this study will last about 7-11 months In total the subject will visit the hospital approximately 7-9 times. Each visit will take between 30 minutes and 2 hours to complete.
This study is divided in 4 periods; a screening visit, a run-in period, one

treatment period and a follow up period. The run-in period will last between 1 and 2 months. You will not need to come to the hospital during the run-in period and instead run-in visits will be performed by telephone calls of approximately 15 minutes every 15 days. Treatment with CSL312 will start after the run-in period.
Please refer to page 11-15 of the protocol (schedule of events) for more information.

The following tests and procedures will take place during the hospital visits
- questions are asked about the medical history, demographics and eligibility questions
- Measurement of vital signs / physical examination (e.g. blood pressure, heart rate, temperature and respiratory rate), height, weight
- Blood and urine samples are taken
- Pregnancy test for woman of childbearing potential
- ECG

In addition patients are asked to complete the eDiary and questionnaires.

Possible side effects that are already known are described in the Investigator's Brochure and in paragraph 6 of the subject informed consent form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Male or female * 12 years of age; diagnosed with clinically confirmed C1-INH hereditry angioedema; experience * 3 attacks during the 3 months before Screening

Exclusion criteria

Concomitant diagnosis of another form of angioedema such as idiopathic or acquired angioedema, recurrent angioedema associated with urticarial or hereditary angioedema type 3

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:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-04-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Factor XIIa antagonist monoclonal antibody
Generic name:	garadacimab

Ethics review

Approved WMO Date:	21-10-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
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	EUCTR2020-000570-25-NL
CCMO	NL75244.018.20

Study results

Date completed: 03-02-2022

Results posted: 01-11-2022

First publication
06-10-2022