An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema

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This study has been transitioned to CTIS with ID 2024-510777-18-00 check the CTIS register for the current data. The primary objective of the study is to evaluate the long-term safety of SC administration of CSL312 in the prophylactic treatment of...

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

Summary

ID

NL-OMON54235

Source
ToetsingOnline

Brief title
CSL312-3002

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;CSL Behring LLC

Intervention

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

Outcome measures

Primary outcome

The primary objective of the study is to evaluate the long-term safety of SC administration of CSL312 in the prophylactic treatment of subjects with C1-INH HAE.

Secondary outcome

The secondary efficacy endpoints are:

• Time-normalized number of HAE attacks

• 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 secondary safety endpoints are:

• Serious adverse events (SAEs)

• Deaths

• Related TEAEs

• TEAEs leading to study discontinuation

• TEAEs by severity

• Anti-CSL312 antibodies

• Laboratory findings reported as adverse events (AEs)

• Adverse events of special interest (AESIs) (ie, thromboembolic events [TEEs],

abnormal bleeding events, severe hypersensitivity, including anaphylaxis events)

• TEAEs (for nC1-INH subjects only)

The secondary endpoint for the reported assessment of response to therapy is:

• Subject*s Global Assessment of Response to Therapy (SGART)

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, antifibrinolytics), 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.

The efficacy and safety of CSL312 in patients with HAE has been demonstrated in a phase 2 study. This phase 3b is to evaluate long-term safety and efficacy of CSL312 200 mg when administered once a month for at least 12 months.

Study objective

This study has been transitioned to CTIS with ID 2024-510777-18-00 check the CTIS register for the current data.

The primary objective of the study is to evaluate the long-term safety of SC administration of CSL312 in the prophylactic treatment of subjects with C1-INH HAE.

The secondary objectives of this study are to evaluate the long-term efficacy, safety and patient reported assessment of response to therapy.

Study design

This phase 3b study will evaluate long-term safety and efficacy of CSL312 (also known as garadacimab) when administered subcutaneously (SC) once monthly for at least 12 months. Subjects entering CSL312_3002 will be from 3 sources:
• Subjects who participated in Study CSL312_2001
• Subjects who participated in Study CSL312_3001
• CSL312-naïve HAE subjects who have not participated in either of the above studies

The study will consist of screening, run-in (for CSL312-naïve subjects), open label treatment, and follow-up periods. For subjects naïve to CSL312, there will be up to 1 month Screening Period followed by a Run-In Period, which may last at least 1 month and up to 2 months.

CSL312-naïve subjects who meet all eligibility criteria during the Run-In Period will then enter the at least 12-month Treatment Period. Subjects rolling over from Studies CSL312_2001 or CSL312_3001 will enter directly into the Treatment Period.

Subjects who reach the end of treatment or terminate the study early will have a follow-up phone call 2 months after the End of Treatment Visit.

A Pharmacokinetic (PK) subgroup analysis will be conducted in adult CSL312-naïve subjects to further characterize the PK of CSL312 following the SC loading dose. A target number of 12 CSL312-naïve adult subjects will be included in the subgroup analysis.

Per Amendment 1, administration of the study drug, CSL312, will be done with the use of an autoinjector.

Intervention

Subjects will be treated with CSL312 a minimum of 1 years.

CSL312 will be administered as 1 dose (200 mg) SC once monthly for a total minimum of 12 doses (ie, 12 months of treatment). For CSL312-naïve subjects, a loading dose of 400 mg (two 200 mg doses) will be administered SC on the first month, then 200 mg once monthly for at least 11 months.

Per Amendment 1, administration of the study drug, CSL312, will be done with the use of an autoinjector, The dose, 200 mg, and the injection frequency, once a month, will continue to be the same.

Study burden and risks

The subjects participation in this study will last a minimum of 12 month. In total the subject will visit the hospital approximately 9-13 times. Ech visit will take between 30 minutes and 2 hours to complete.

The study will consist of screening, run-in (for CSL312-naïve subjects), open label treatment, and follow-up periods. For subjects naïve to CSL312, there will be up to 1 month Screening Period followed by a Run-In Period, which may last at least 1 month and up to 2 months.

Please refer to page 16-25 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

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

Public

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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

1. Males and females aged >= 12 years
2. Diagnosed with clinically confirmed C1-INH HAE
3. Experienced >= 3 HAE attacks during the 3 months before Screening
4. Participated in the Run-in Period for at least 1 month (CSL312-naïve subjects only)
5. Experienced at least an average of 1 HAE attack per month during the Run-in Period"

Exclusion criteria

1. Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema or recurrent angioedema associated with urticaria
2. Use of C1-INH products, androgens, antifibrinolytics or other small molecule

medications for routine prophylaxis against HAE attacks at least 2 weeks before the first day of the Run-in Period
3. Use of monoclonal antibodies such as lanadelumab (Takhzyro®) 3 months before the first day of the Run-in Period.
4. Female subjects use estrogen-containing oral contraceptives or hormone replacement therapy within 4 weeks prior to screening
5. Female or male subjects who are fertile and sexually active 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 the last dose of CSL312
6. Pregnant, breastfeeding, or not willing to cease breastfeeding

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2021
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Factor XIIa inhibitor monoclonal antibody
Generic name:	garadacimab

Ethics review

Approved WMO Date:	21-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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Approved WMO Date:	06-09-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	17-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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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
EU-CTR	CTIS2024-510777-18-00
EudraCT	EUCTR2020-003918-12-NL
CCMO	NL77110.018.21