CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age
Study Number:	CSL312_3003
Version:	Amendment 3
Study Product:	CSL312 (Garadacimab; Factor XIIa inhibitor monoclonal antibody)
Brief Title:	CSL312_3003 Safety and Pharmacokinetic Study in Subjects 2 to 11 Years of Age with Hereditary Angioedema
Study Phase:	Phase 3
Sponsor Name and Legal Registered Address:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Regulatory Agency Identifier Number(s)	
EudraCT and / or EU Clinical Trial Number:	2022-502386-13-00
IND:	139936
WHO:	To be determined
ClinicalTrials.gov:	To be determined
Protocol Version Date:	09 January 2025

SPONSOR SIGNATORY

Signed by:
PPD

Signing Reason: I approve this document
Signing Time: 13-Jan-2025 | 5:35:50 PM CET

PPD

PPD

, Clinical Research & Development
CSL Behring

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of the personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by the sponsor and provided to the study sites as needed.

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AESIs	Adverse events of special interest
BK	Bradykinin
βFXIIa	Active catalytic fragment of FXII
C1-INH	C1-esterase inhibitor
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRF	Case Report Form (printed, optical, or electronic document)
CSLB	CSL Behring
CSP	Clinical Study Protocol
C_{trough}	Trough plasma concentration
CV%	Percent coefficient of variation
eCOA	Electronic Clinical Outcomes Assessment
eDiary	electronic Diary
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FXII	Factor XII
FXIIa	Activated factor XII
GCP	Good Clinical Practice
HAE	Hereditary angioedema
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous

Abbreviation	Term
LLC	Limited Liability Company
MedDRA	Medical Dictionary for Regulatory Activities
NSD	Needle safety device
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
Q1M	Once monthly
Q2M	Every 2 months
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum plasma concentration
TP1	Treatment Period 1
TP2	Treatment Period 2
WHO	World Health Organization

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

CSP Version	Amendment Type	CSP Date
Amendment 3	Substantial	09 January 2025
Amendment 2	Substantial	26 March 2024
Amendment 1	Substantial	09 November 2023
Administrative Amendment 1	Administrative	01 February 2023
Original	Not applicable	22 September 2022

Amendment 3 (09 January 2025)

Overall Rationale for the Amendment: The primary purpose of Amendment 3 is to facilitate the transition of subjects who complete this study (with at least 12 months of treatment) to the post-study access program or another prophylactic treatment. Subjects who choose to continue treatment with CSL312 within a post-study access program or another prophylactic treatment must complete the End of Treatment Visit for CSL312_3003 as the last study visit. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

Detailed editorial and administrative changes are not identified.

Amendment Summary of Changes

CSP Section Number(s)	Description of Change	Brief Rationale
Section 1.1 Section 4.1	Updated the sentence in the Synopsis and Section 4.1 to state that "At the completion of study participation, subjects will undergo a follow-up consisting of either a study site visit or a phone call 3 months later. Subjects who complete the study have the option to continue treatment with CSL312 or another prophylactic treatment without a scheduled follow-up. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study. Refer to the Follow-up Period for details."	Added for clarification that subjects who complete the study have the option to continue treatment with CSL312 (if they qualify for the post-study access program) or another prophylactic treatment.
Section 1.1 Section 1.3.1 Section 1.3.2	Added a sentence to the Synopsis, Footnote "D" of Sections 1.3.1 and 1.3.2 (Schedules of Assessments), and Section 4.2 to state "Subjects who	Added new information for the subject's option to continue to receive access to CSL312 or another prophylactic treatment

CSP Section Number(s)	Description of Change	Brief Rationale
Section 4.2	complete the study have the option to continue to receive access to CSL312 for a limited duration if they meet the criteria for the post-study access program. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program. For these subjects, the Follow-up Period in this study will not be applicable. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study."	after treatment is completed without a scheduled follow-up in this study.
Section 1.1 Section 6.9	Provided additional clarification to the access of subjects to the investigational product after the end of the study as follows: "Subjects who complete the study (ie, at least 12 months of treatment and the End of Treatment Visit) have the option to continue to receive access to CSL312 (if they meet the criteria for the post-study access program) or another prophylactic treatment. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program or another prophylactic treatment."	Clarified the intention to provide CSL312 in the post-study access program or another prophylactic treatment only to subjects who complete per-protocol Treatment Period with CSL312.
Section 1.2, Figure 1 Section 1.3.1 Section 1.3.2	Updated Figure 1, added Footnote "a" to Section 1.2 (Figure 1), and updated Footnote "B" of Sections 1.3.1 and 1.3.2 (Schedules of Assessments) to include that "The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study."	Updated information to present that "The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 or another prophylactic treatment."

CSP Section Number(s)	Description of Change	Brief Rationale
Section 4.5	Updated the definition of End of Study to "A subject is considered to have completed the study if they have completed 12 months of treatment and the End of Treatment Visit."	Clarified the End of Study definition that, for subjects who continue to receive CSL312 in a post-study access program or another prophylactic treatment, the Follow-up Visit is not required to be considered to have completed the study.
Section 1.3.2 Section 8.3, Table 6 Section 10.3.1	Updated information in Footnote "J" of Section 1.3.2 (Schedule of Assessments), Section 8.3 (Table 6), and Section 10.3.1 to state "adolescent females who had their first menstruation (ie, childbearing potential).''	Clarified that women of childbearing potential are adolescent females who had their first menstruation (ie, childbearing potential).
Section 9.4.2	Updated the efficacy analysis to state "The efficacy endpoints will not be calculated if the subject's observation time for the Treatment Period is less than 30 days, ie, the subject discontinued within 30 days after the Day 1 Visit or the date of the first investigational product administration, if available."	Clarified that the efficacy endpoints will not be calculated if the subject discontinued within 30 days after the Day 1 Visit or the date of the first investigational product administration, if available.
Section 9.4.2.2.1	Updated to include "Additional derived endpoints may be presented, and details will be provided in the SAP."	Reference to the SAP was added for potential additional endpoints.
Section 9.4.3	Updated the safety analysis to state "TEAEs occurring until the Follow-up Visit (or the End of Treatment Visit for subjects continuing into the post-study access program or another prophylactic treatment) will be summarized."	Clarified that TEAEs occurring until End of Treatment Visit for subjects continuing into the post-study access program or another prophylactic treatment will be summarized.
Section 9.4.3.1	Updated the primary safety estimand as follows: "The primary safety interest is to assess whether TEAEs occurred at least once during SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE during treatment from the first investigational product administration at Day 1 Visit through the End of Treatment Visit or	Revised the text "first investigational product administration" in addition to "Day 1 Visit" to define the start more precisely. To take into account the permission to use prophylactic treatment during the Follow-up Period for the primary analysis.

CSP Section Number(s)	Description of Change	Brief Rationale
	the latest available visit or event (whichever is later) for subjects without the End of Treatment Visit while subjects are allowed to treat HAE attacks with on-demand medications."	
Section 9.4.5	Updated the PD analysis to state "The PD data will be summarized with descriptive statistics: n, number and percentage of values below the limit of quantification, mean, SD, CV%, median, minimum, maximum, first and third quartiles for continuous variables, geometric mean and its respective 90% CI, and geometric CV%"	Clarified that the PD data will be summarized with descriptive statistics also including number and percentage of values below the limit of quantification and geometric CV%.
Global	Minor corrections and clarifications, including word modifications and administrative changes.	Administrative changes.

Amendment 2 (26 March 2024)

Overall Rationale for the Amendment: The primary purpose of Amendment 2 is to address queries received from health authorities. Changes to the conduct of the study or updated information that is content-related are shown in the table below. Detailed editorial and administrative changes are not identified.

Amendment Summary of Changes

CSP Section Number(s)	Description of Change	Brief Rationale
Section 1.3.1	Updated the Schedule of Assessments for subjects 2 to 5 years of age, as follows: • Collection of blood for pharmacokinetics / pharmacodynamics was added at Visit Month 4 and removed from Visit Month 10	Per regulatory authority request
Section 8.7 Section 8.8 Section 8.9	Removed previous Section 8.6.1 (Optional Future Research), as it was not applicable Corrected the subsequent section subheading numbers, as follows: • Section 8.7 Pharmacogenomics / Genomics	Formatting correction

CSP Section Number(s)	Description of Change	Brief Rationale
	• Section 8.8 Immunogenicity Assessments • Section 8.9 Medical Resource Utilization and Health Economics	

Amendment 1 (09 November 2023)

Overall Rationale for the Amendment: The primary purpose of Amendment 1 is to address queries received from health authorities. Changes to the conduct of the study or updated information that is content-related are shown in the table below. Detailed editorial and administrative changes including those per the new protocol template are not identified.

Amendment Summary of Changes

CSP Section Number(s)	Description of Change	Brief Rationale
Title Page	Added EudraCT number	Per Administrative Amendment 1, dated 01 February 2023
Section 1.3.1, Section 1.3.2	Inclusion of additional biochemistry assessments Updated the Schedule of Assessments to increase frequency of safety blood draws. Additional time points were added, if feasible, as follows: 2 to 5 Years of Age: • Collection of blood for hematology and / or biochemistry at Visit Months 4 and 10, if feasible 6 to 11 Years of Age: • Collection of blood for hematology and / or biochemistry at Visit Months 3 and 9, if feasible	Per regulatory authority request
Section 2.1.1.2	Provided updated information for Study CSL312_1004 and Study CSL312_3002	Updated information to present current status of clinical studies
Section 1.1 Section 4.1 Section 4.2	Updated target sample size to reflect an enrollment of approximately 20 subjects to ensure that at least 15 subjects complete 12 months of treatment	Per regulatory authority request

CSP Section Number(s)	Description of Change	Brief Rationale
Section 5.2	Updated exclusion criterion #7 to include additional examples of significant illnesses or major comorbidities, eg, a preexisting condition of coagulopathy or thrombotic disorders	Per regulatory authority request
Section 8	Added a statement specifying the maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 61 mL (2 to 5 years old) or 65 mL (6 to 11 years old)	Per sponsor's new protocol template
Section 8.3.2 Section 10.2.2	Added a footnote to Table 7 and reference to the footnote in Section 8.3.2: Note: The assessment of severity of AEs associated with laboratory results will be supplemented by referring to the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table included in the electronic CRF completion guideline.	Per regulatory authority request
Global	Minor corrections and clarifications, including word modifications and administrative changes to incorporate information in new protocol / amendment template and Summary of Changes	Administrative changes harmonized with the sponsor's new protocol template that also provides improved alignment with ICH guidelines and recommendations

AE = adverse event; CRF = Case Report Form; CSP = Clinical Study Protocol; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title	A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age
Development Phase	Phase 3

Study Rationale

There is an evident unmet need in the patient population of children 2 to 11 years of age with hereditary angioedema (HAE) for a safe, efficacious, and convenient treatment, as there are very limited prophylactic options approved. Currently approved prophylactic treatments for children under 12 years of age include C1-esterase inhibitor (C1-INH) plasma-derived products such as Cinryze®, an intravenous plasma-derived medication, which is injected twice a week, and Haegarda®, which lessens the burden associated with intravenous administration with subcutaneous (SC) injections, but dosing is twice a week, and it is only approved in the United States for patients 6 years of age and older. Two other less frequently used, approved prophylactic options include androgens and antifibrinolytics; however, they are not considered the best options for children due to significant side effects and / or poor efficacy [Maurer et al, 2022]. In general, the onset of HAE symptoms occurs in childhood or early in adolescence, and the pathophysiology of HAE is similar across all age groups (adults, adolescents, and children under 12 years of age). HAE attacks are unpredictable regardless of age, and in children, this has a direct impact on their ability to consistently attend school and participate in recreational activities, which negatively affects their quality of life [Caballero, 2013].

CSL312 is an inhibitor of activated factor XII (FXIIa), which has been shown to increase in patients during acute HAE attacks. FXIIa inhibition is a viable target for preventing HAE attacks, and the efficacy and safety of CSL312 in adult patients with HAE have been demonstrated in a phase 2 study and confirmed in a phase 3 study in adult and adolescents with HAE. An ongoing open-label phase 3b study continues to support the efficacy and favorable safety of CSL312 in adolescents and adults.

CSL312 mechanism of action and the similarity of the HAE disease and clinical presentation across all age groups of patients support the study of CSL312 for the prophylactic treatment of HAE in children. Furthermore, the safety and tolerability of CSL312 demonstrated to date support the administration of CSL312 in this age group.

Objective(s)

The primary objectives of the study are to evaluate the safety and pharmacokinetics (PK) of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.

The secondary objectives of this study are to evaluate efficacy, pharmacodynamics (PD), and safety of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.

The exploratory objective of the study is to further evaluate the PD effects of CSL312.

Overall Design

This is a multicenter, open-label, phase 3b pediatric study designed to investigate the safety, PK / PD, and efficacy of SC administered CSL312 in the prophylactic treatment of HAE in children 2 to 11 years of age.

The study schematic is shown in Figure 1.

The following subjects will be eligible to participate in this study if they meet all eligibility criteria:

- CSL312-naïve pediatric subjects with C1-INH HAE type 1 or 2

This phase 3b study is designed to evaluate the safety, PK / PD, and efficacy of CSL312 when administered SC at a dose of 100 mg once monthly (Q1M; subjects 6 to 11 years of age) or every 2 months (Q2M; subjects 2 to 5 years of age) for at least 12 months. The study will consist of a Screening Period, an open-label Treatment Period, and Follow-up Period. Subjects that meet all eligibility criteria during Screening will then enter the Treatment Period. At the completion of study participation, subjects will undergo a follow-up consisting of either a study site visit or a phone call 3 months later. Subjects who complete the study have the option to continue treatment with CSL312 without a scheduled follow-up. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study. Refer to the Follow-up Period for details.

Study Course for Individual Subject

The study schema is presented in Section 1.2, and the Schedule of Activities in Section 1.3.

- The study duration is approximately 3 years.
- After informed consent, subjects will undergo a Screening Period of up to 1 month to determine their eligibility.
- Eligible subjects will enter the Treatment Period. The treatment duration is at least 12 months. Individual subject participation (total duration) is approximately 14 to 15 months.
- Visit frequency is Q2M (subjects 2 to 5 years of age) or every 3 months (subjects 6 to 11 years of age) (see Schedule of Activities).

Study Duration for Individual Subject

The estimated overall study duration for an individual subject will be approximately 14 to 15 months based on the durations of the following study periods:

- Screening Period: Up to 1 month
- Treatment Period: At least 12 months
- Follow-up Period: 1 month (for subjects 2 to 5 years of age) or 2 months (for subjects 6 to 11 years of age). The Follow-up Visit takes place 3 months after last dose of CSL312. Subjects who complete the study have the option to continue to receive access to CSL312 for a limited duration if they meet the criteria for the post-study access program. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program. For these subjects, the Follow-up Period in this study will not be applicable.

Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

Number of Subjects

The target sample size for this study is approximately 20 subjects to ensure that at least 15 subjects complete 12 months of treatment.

Note: Subjects are considered "enrolled" in the study when they, or their legally authorized representative, has agreed to participate in a clinical study after completing the informed consent process and Screening. Potential subjects who are screened to determine their eligibility but fail Screening or do not meet all eligibility criteria are not considered enrolled.

Diagnosis and Main Enrollment Criteria

Key Inclusion Criteria

- Male or female
- Aged 2 to 11 years, inclusive, with body weight ≥ 10th percentile based on age (according to the Centers for Disease Control growth charts [CDC, 2017]), at the time of providing written informed consent / assent
- Diagnosed with clinically confirmed C1-INH HAE
- Experienced ≥ 2 HAE attacks during the 6 months before Screening, as documented in the subject's medical records

Key Exclusion Criteria

- Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticaria, or HAE type 3
- Use of C1-INH products, androgens, antifibrinolytics, approved or future approved medications, or other small-molecule medications for routine prophylaxis against HAE attacks within a minimum of 2 weeks before the Treatment Period
- Participation in another interventional clinical study during the 30 days before the Treatment Period or within 5 half-lives of the final dose of the investigational product administered during the previous interventional study, whichever is longer
- Having laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology or chemistry assessments performed during Screening
- Currently receiving a therapy not permitted during the study, as defined in Section 6.11 (Table 6)
- Being pregnant or breastfeeding

Investigational Product(s), Dosage, and Mode of Administration

Study Product: FXIIa inhibitor monoclonal antibody (CSL312) administered SC

Comparator Product: Not applicable

Dosing Regimen:

Eligible subjects will be assigned to open-label CSL312 with a dosing regimen dependent on their age at the time of consent as follows:

- 2 to 5 years of age: 100 mg SC Q2M
- 6 to 11 years of age: 100 mg SC Q1M

Dose Adjustments: Dose modification is not allowed in this study.

Access to Study Product After End of Study: Subjects will not be provided with CSL312 by the sponsor after withdrawal from the study.

Criteria for Evaluation

Primary Endpoint(s)

- The primary objectives of the study are to evaluate the safety and PK of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.

Secondary Endpoint(s)

- The secondary objectives of this study are to evaluate efficacy, PD, and safety of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.

Exploratory Objective(s)

- The exploratory objective of the study is to further evaluate the PD effects of CSL312.

PK Assessments

Blood samples will be collected on the same day as CSL312 administration for assessment of CSL312 concentrations at time points specified in the Schedule of Activities (Section 1.3).

Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Schedule of Activities (Section 1.3). HAE attacks that are confirmed by investigator or designee will be used for the efficacy analysis and will be recorded on the Case Report Form. All HAE symptoms reported by the subject will be displayed in a by-subject listing.

Safety Assessments

Adverse events, physical examinations, vital signs, pregnancy testing, immunogenicity (development of antibodies [inhibitory and non-inhibitory] specific to FXIIa inhibitor monoclonal antibody [anti-CSL312]), clinical safety laboratory tests, activated partial thromboplastin time / D-dimer / prothrombin time / international normalized ratio, C1-INH functional activity and antigen concentration, and C4 antigen concentration.

PD and Biomarker Assessments

Blood samples will be collected on the same day as CSL312 administration for assessment of FXIIa-mediated kallikrein activity and FXII concentration at time points specified in the Schedule of Activities (Section 1.3).

Data Monitoring / Other Committees

An Independent Data Monitoring Committee (IDMC) will be established to monitor the efficacy and safety data generated during the study. The IDMC will consist of independent clinical specialists in HAE, who also have experience in clinical trials. The IDMC will review accumulating data from the ongoing study. Based on these reviews, the IDMC will advise on the further conduct of the study. No success or futility thresholds will be set for the IDMC reviews. CSL Behring (herein, “the sponsor”) will continue the study unless a safety issue is confirmed that warrants study termination. The composition, activities, analyses, responsibilities, and timing of meetings of the IDMC will be described in the IDMC charter.

Statistical Methods

No formal statistical hypothesis testing will be performed; this study will enroll a prespecified number of subjects as agreed with health authorities.

The primary safety estimand, in line with the primary safety interest of the study, follows the treatment policy strategy and is described as follows:

- Treatment condition: Q1M or Q2M treatment with 100 mg CSL312
- Population: The target patient population, defined by eligibility criteria and who received at least 1 dose of investigational product (Safety Analysis Set)
- Variable: Treatment-emergent adverse events (TEAEs)
- Intercurrent events: The occurrence of an intercurrent event is ignorable. All observed values will be used, regardless of occurrence of any of the following intercurrent events:
  - Administration of on-demand medication in addition to prophylactic treatment with CSL312
  - Prohibited concomitant medications due or not due to Coronavirus disease 2019 (COVID-19) or COVID-19 vaccination
  - Treatment adherence or early treatment discontinuation due or not due to COVID-19
- Population-level summary: TEAE rate per subject year

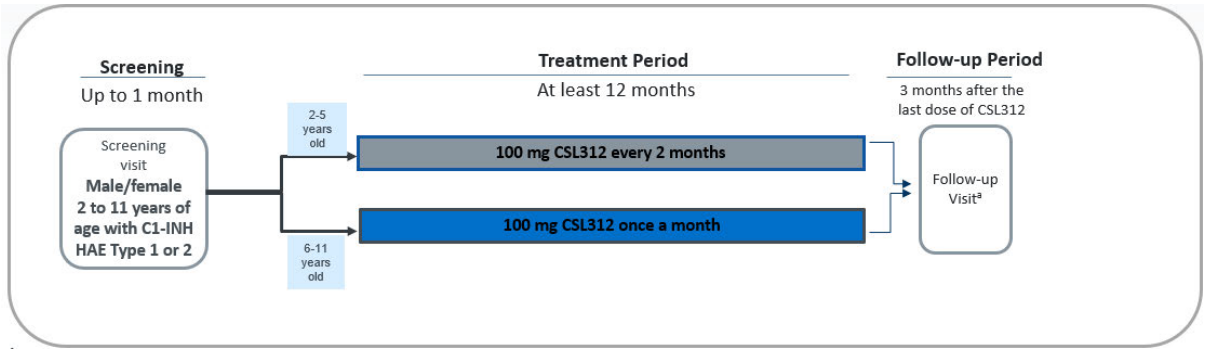
Following the estimand description, the TEAEs will be summarized by event rate per subject year using the Safety Analysis Set. All summary tables described will be by 100 mg Q2M, 100 mg Q1M, and overall. In addition, TEAEs will be summarized by the number of subjects and percentage of subjects experiencing at least 1 TEAE, the number of events, as well as the event rate per injection.

An overview summary of TEAEs as well as a table by system organ class and preferred term will be provided. For the presentation by 3-month time windows, the TEAE will be allocated to the time window based on the TEAE start date.

The PK parameters after SC administration of CSL312 at steady state (maximum plasma concentration [C_{max}], trough plasma concentration (C_{trough}), and time to reach maximum plasma concentration [T_{max}]) are 1 of the 2 primary endpoints in this study. The PK analysis will be performed using the PK Analysis Set.

1.2. Study Schema

Figure 1: Overall Study Schema



C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema.
[a] The Follow-up Visit may be conducted via telephone instead of at study site. Assessments / tests may be omitted if the Follow-up Visit is conducted via telephone. The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study. For further details on post-study access, see Section 6.9.

1.3. Schedule of Activities

1.3.1. Schedule of Assessments: Treatment Period for Subjects 2 to 5 Years of Age

Study Period		Screening Period	Treatment Period							Follow-up / Final Visit [B]
Month		Up to 30 Days [C]		2	4	6	8	10	End of Treatment [D] 12	3 Months After Last Dose of CSL312
Visit Day			1	61	121	181	241	301	361	
Visit Window (Days)				± 4d [E]	± 4d [E]	± 4d [E]	± 4d [E]	± 4d [E]	± 4d [E]	± 7d
Study site visit [A]		X	X	X	X	X	X	X	X	X
Informed consent / IRT registration [F]		X								
Medical history / demographics / HAE history		X								
Inclusion / exclusion criteria		X								
Confirm eligibility for Treatment Period [G]			X							
Physical examination [H]		X	X	X	X	X	X	X	X	X
Vital signs including body weight and height [I]		X	X	X	X	X	X	X	X	X
Blood draws [J]	Hematology / biochemistry / coagulation	X			X	X		X	X	
	Pharmacokinetics / pharmacodynamics		X		X	X			X	
	Immunogenicity		X			X			X	
	Sample collection of C1-INH and C4 [K]	X								
Individual acute treatment plan [L]		X								
Diary training		X								

Study Period	Screening Period	Treatment Period							Follow-up / Final Visit [B]
Month	**Up to 30 Days [C]**		**2**	**4**	**6**	**8**	**10**	**End of Treatment [D] 12**	**3 Months After Last Dose of CSL312**
Visit Day		**1**	**61**	**121**	**181**	**241**	**301**	**361**	
Visit Window (Days)			**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 7d**
Open eDiary access / review eDiary instructions with subject		X							
Review eDiary data and assess / document HAE attacks			X	X	X	X	X	X	X
eDiary deactivation and collection									X
Confirm access to on-demand HAE medication [M]	X	X	X	X	X	X	X	X	
Prior medications and treatment	X								
Dispensation of IP via IRT		X	X	X	X	X	X		
Accountability of IP			X	X	X	X	X	X	
Administration of IP at site [N]		X [O]	X	X	X	X	X		
Concomitant medications	←	←	←	←	←	←	←	←	
Adverse events	←	←	←	←	←	←	←	←	

C1-INH = C1-esterase inhibitor; d = days; eDiary = electronic Diary; HAE = hereditary angioedema; IP = investigational product; IRT = Interactive Response Technology; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous.

[A] Unscheduled visits (for safety evaluations, ie, to follow up on an adverse event) may take place at any point during the study per investigator discretion and / or per subject request.

[B] The Follow-up Visit may be conducted via telephone instead of at study site. Assessments / tests may be omitted if the Follow-up Visit is conducted via telephone. The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

[C] Screening may be extended up to 60 days with permission from the sponsor. If the subject is not eligible for enrollment after 60 days, they will be screen failed or rescreened with permission from the sponsor (each subject may be rescreened a maximum of 1 time).

[D] No CSL312 administration takes place at End of Treatment. The last dose of CSL312 is administered at Month 10 (for subjects ages 2 to 5 years). Subjects who complete the study have the option to continue to receive access to CSL312 for a limited duration if they meet the criteria for the post-study access program. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program. For these subjects, the Follow-up Period in this study will not be applicable. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.
[E] Treatment Period visits have ± 4-day window, with a maximum of 64 days between any 2 consecutive doses.
[F] Written informed consent must be provided before any study-specific assessments or procedures are performed.
[G] Subjects may enter the open-label Treatment Period upon meeting all the inclusion and none of the exclusion criteria.
[H] A full physical examination will be conducted per the study site's standard procedure.
[I] Height will be collected at Screening Visit, Month 6 Visit, and End of Treatment Visit only.
[J] On a dosing day, blood draws should be completed on the same day of IP administration. The + 7 days after each dose PK / PD sample and coagulation blood sample can occur following IP administration at or after any visit following Month 6 Visit (Section 1.3.3). If Screening is extended up to 60 days (with permission from the sponsor), there is no need to repeat the hematology / coagulation / biochemistry assessments. If the subject is not eligible for enrollment after 60 days, they will be screen failed (or rescreened with permission from the sponsor**)**. Collection of blood for hematology and / or biochemistry at Visit Months 4 and 10, if feasible, and provided that the cumulative blood volume to be drawn per visit does not exceed the total volume per visit as provided in the Laboratory Manual.
[K] If clinical confirmation of C1-INH HAE in the medical records is not available, a blood sample to confirm the HAE disease will be collected at Screening.
[L] An individual acute treatment plan will be developed by the investigator to ensure that participating subjects are capable of managing their HAE attacks during the study. The action plan will be reviewed with subjects.
[M] Subjects may use the on-demand medication of their choice to treat HAE attacks experienced during the study if that medication is used according to the product label.
[N] Subjects will be administered a 100 mg dose of CSL312 via SC injection on the first day of the Treatment Period. The parent / caregiver will be trained in IP administration at Visit Day 1 (further training may be provided at any subsequent visits as needed). At the discretion of the investigator, the investigational product may be administered by a trained caregiver at home (including on-site visit days) after completing training and after the first dose is administered at the study site under medical supervision. Subjects 2 to 5 years of age will receive 100 mg CSL312 every 2 months. During administration of CSL312, any device malfunctions should be reported as a suspected Product Technical Complaint. Refer to the Site Investigational Product Manual for additional information.
[O] After the first administration of CSL312, subjects must remain at the site for approximately 2 hours for monitoring for severe reactions / hypersensitivity. Following subsequent administrations of CSL312 at the site, subjects will only remain at the site for monitoring if requested by the investigator. If a subject has an active infectious illness or fever defined as an oral temperature > 38°C (100.4°F), tympanic > 38.5°C (101.3°F), axillary > 38°C (100.4°F), or rectal/core > 38.5°C (101.3°F) within 24 hours before the first dose of IP, the subject will need to return to the site upon resolution of symptoms to start treatment.
Note: Caregiver role during the study must be captured (ie, whether caregiver is completing the eDiary on behalf of the subject, etc).

1.3.2. Schedule of Assessments: Treatment Period for Subjects 6 to 11 Years of Age

Study Period		Screening Period	Treatment Period					Follow-up / Final Visit [B]
Month		Up to 30 Days [C]	1	3	6	9	End of Treatment [D] 12	3 Months After Last Dose of CSL312
Visit Day			1	31	91	181	271	361	
Visit Window (Days)				± 4d [E]	± 4d [E]	± 4d [E]	± 4d [E]	± 4d [E]	± 7d
Study site visit [A]		X	X	X	X	X	X	X	X
Informed consent / IRT registration [F]		X							
Medical history / demographics / HAE history		X							
Inclusion / exclusion criteria		X							
Confirm eligibility for Treatment Period [G]			X						
Physical examination [H]		X	X	X	X	X	X	X	X
Vital signs including body weight and height [I]		X	X	X	X	X	X	X	X
Pregnancy test (local laboratory β-hCG) [J]		X	X	X	X	X	X	X	X
Blood draws [K]	Hematology / biochemistry / coagulation	X			X	X	X	X	
	Pharmacokinetics / pharmacodynamics		X		X	X	X	X	
	Immunogenicity		X			X		X	
	Sample collection of C1-INH and C4 [L]	X							
Individual acute treatment plan [M]		X							
Diary training		X							

Study Period	Screening Period	Treatment Period						Follow-up / Final Visit [B]
Month	**Up to 30 Days [C]**		**1**	**3**	**6**	**9**	**End of Treatment [D] 12**	**3 Months After Last Dose of CSL312**
Visit Day		**1**	**31**	**91**	**181**	**271**	**361**	
Visit Window (Days)			**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 4d [E]**	**± 7d**
Open eDiary access / review eDiary instructions with subject		X						
Review eDiary data and assess / document HAE attacks			X	X	X	X	X	X
eDiary deactivation and collection								X
Confirm access to on-demand HAE medication [N]	X	X	X	X	X	X	X	
Prior medications and treatment	X							
Dispensation of IP via IRT		X	X	X	X	X		
Accountability of IP			X	X	X	X	X	
Administration of IP at site [O]		X [P]	X	X	X	X		
Concomitant medications	←	←	←	←	←	←	←	
Adverse events	←	←	←	←	←	←	←	

β-hCG = beta-human chorionic gonadotropin; C1-INH = C1-esterase inhibitor; d = days; eDiary = electronic Diary; HAE = hereditary angioedema; IP = investigational product; IRT = Interactive Response Technology; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous.

[A] Unscheduled visits (for safety evaluations, ie, to follow up on an adverse event) may take place at any point during the study per investigator discretion and / or per subject request.

[B] The Follow-up Visit may be conducted via telephone instead of at study site. Assessments / tests may be omitted if the Follow-up Visit is conducted via telephone. The Follow-up Period in this study is not applicable for subjects who choose to continue to receive CSL312 (and meet the criteria to participate in a post-study access program) or another prophylactic treatment. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

[C] Screening may be extended up to 60 days with permission from the sponsor. If the subject is not eligible for enrollment after 60 days, they will be screen failed or rescreened with permission from the sponsor (each subject may be rescreened a maximum of 1 time).
[D] No CSL312 administration takes place at End of Treatment. The last dose of CSL312 is administered at Month 11 (for subjects ages 6 to 11 years). Subjects who complete the study have the option to continue to receive access to CSL312 for a limited duration if they meet the criteria for the post-study access program. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program. For these subjects, the Follow-up Period in this study will not be applicable. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.
[E] Treatment Period visits have ± 4-day window, with a maximum of 34 days between any 2 consecutive doses.
[F] Written informed consent must be provided before any study-specific assessments or procedures are performed.
[G] Subjects may enter the open-label Treatment Period upon meeting all the inclusion and none of the exclusion criteria.
[H] A full physical examination will be conducted per the study site's standard procedure.
[I:] Height will be collected at Screening Visit, Month 6 Visit, and End of Treatment Visit only.
[J] A urine test for β-hCG will be performed for adolescent females who had their first menstruation (ie, childbearing potential). A serum pregnancy test will be performed if urine result is inconclusive or if a urine test is unavailable.
[K] On a dosing day, blood draws should be completed on the same day of IP administration. The + 7 days after each dose PK / PD sample and coagulation blood sample can occur following IP administration at or after any visit following Month 6 Visit (Section 1.3.3). If Screening is extended up to 60 days (with permission from the sponsor), there is no need to repeat the hematology / coagulation / biochemistry assessments. If the subject is not eligible for enrollment after 60 days, they will be screen failed (or rescreened with permission from the sponsor). Collection of blood for hematology and / or biochemistry at Visit Months 3 and 9, if feasible, and provided that the cumulative blood volume to be drawn per visit does not exceed the total blood volume per visit provided in the Laboratory Manual.
[L] If clinical confirmation of C1-INH HAE in the medical records is from 5 years or more ago, a blood sample to confirm the HAE disease will be collected at Screening.
[M] An individual acute treatment plan will be developed by the investigator to ensure that participating subjects are capable of managing their HAE attacks during the study. The action plan will be reviewed with subjects.
[N] Subjects may use the on-demand medication of their choice to treat HAE attacks experienced during the study if that medication is used according to the product label.
[O] Subjects will be administered a 100 mg dose of CSL312 via SC injection on the first day of the Treatment Period. Parent / caregiver will be trained in IP administration at Visit Day 1 (further training may be provided at any subsequent visits as needed). At the discretion of the investigator, the investigational product may be administered by a trained caregiver at home (including on-site visit days) after completing training and after the first dose is administered at the study site under medical supervision. Subjects 6 to 11 years of age will receive 100 mg CSL312 once monthly. During administration of CSL312, any device malfunctions should be reported as a suspected Product Technical Complaint. Refer to the Site Investigational Product Manual for additional information.
[P] After the first administration of CSL312, subjects must remain at the site for approximately 2 hours for monitoring for severe reactions / hypersensitivity. Following subsequent administrations of CSL312 at the site, subjects will only remain at the site for monitoring if requested by the investigator. If a subject has an active infectious illness or fever defined as an oral temperature > 38°C (100.4°F), tympanic > 38.5°C (101.3°F), axillary > 38°C (100.4°F), or rectal/core > 38.5 C (101.3°F) within 24 hours before the first dose of IP, the subject will need to return to the site upon resolution of symptoms to start treatment.
Note: Caregiver role during the study must be captured (ie, whether caregiver is completing the eDiary on behalf of the subject, etc).

1.3.3. Schedule of Assessments - Post-dose Pharmacokinetic and Coagulation Sampling (Treatment Period)

Study Period	**Treatment Period**
Sampling Time	**+7 days (± 1 days) after Month 6 administration or thereafter [A]**
Pharmacokinetics / pharmacodynamics	X
Coagulation blood sample	X

[A] Post-dose blood draws to occur after the administration of CSL312 at Visit Month 6 or at site visits thereafter.

2. INTRODUCTION

2.1. Background

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by recurrent and unpredictable episodes of swelling of subcutaneous (SC) tissues throughout the body and / or submucosal edema in the upper airway or gastrointestinal tract. HAE affects approximately 1 in 50,000 individuals, with males and females equally affected. The mean age of onset is 10 years, and most patients experience a worsening of symptoms at the time of puberty. In neonates and infants, symptoms are uncommon. Very little information is available in the literature on the incidence or prevalence of HAE in the pediatric population. However, an unstructured, targeted review of the literature provided some insights into the proportion of individuals with HAE who are under the age of 18. One study out of Italy used data from HAE reference centers and found that across 5 of these centers, 7.3% of patients with HAE were aged 13 years or younger [Cancian et al, 2020]. Another study analyzed data collected out of 29 HAE centers across 5 European countries, the majority of which were in Italy. The authors found that out of 1297 patients with HAE, 11% were under the age of 18 [Zanichelli et al, 2021].

Although HAE attacks can occur at any age, the first HAE attack usually occurs in childhood or adolescence. About 50% of females experienced their first attack before the age of 12 and most by the age of 23; about half of the males with HAE experience their first attack before the age of 13 and most by the age of 25. The severity of the attacks for both adults and children are usually characterized by mild to severe tissue swelling at 1 or more sites in the body (typically the face, hands, feet, airways, and intestinal tract). The most common first attack and most frequent HAE attack in children is angioedema of the skin. Laryngeal HAE attacks pose a risk of death due to asphyxiation [Bork et al, 2016], and this risk is similar in adults and children; however, asphyxia may occur more rapidly in children. The frequency and duration of HAE attacks are highly variable and tend to be less frequent in children. In general, the mean attack frequency increases with age from the onset of disease. On average, HAE attacks can occur every 1 to 2 weeks if left untreated. Swelling from these attacks is self-limited and usually resolves spontaneously in 2 to 5 days.

Clinically, attacks of all symptomatic patients with HAE manifest as painful, potentially life-threatening swelling of SC tissues throughout the body and / or submucosal edema in the upper airway or gastrointestinal tract. These attacks recur with unpredictable frequency, intensity, and duration. Patients with sporadic attacks fear subsequent attacks even during attack-free times.

HAE is classified into 3 disease types [Rosen et al, 1965; Bork et al, 2000]: types 1 and 2 involving deficiency or dysfunction of C1-esterase inhibitor (C1-INH) levels, and a type formerly known as type 3 with normal C1-INH. Type 1 HAE is the most common form, accounting for about 85% of HAE cases, and type 2 accounts for approximately 15% of HAE cases [Zuraw et al, 2010]. The prevalence of normal C1-INH HAE is currently unknown; however, it is estimated to be significantly less prevalent than C1-INH HAE [Cicardi and Zanichelli, 2010; Nasr et al, 2016]. C1-INH is a broad-spectrum major serine protease inhibitor, which regulates 4 proteolytic enzyme cascades: complement, contact, fibrinolytic,

and coagulation pathways. C1-INH is a major inhibitor of the kallikrein kinin system (contact pathway) by inactivating the activated factor XII (FXIIa) and kallikrein.

Throughout development, CSL312 (garadacimab) has been described as an FXIIa antagonist monoclonal antibody and therefore that terminology has been used in all previous corresponding documentation and communications. CSL312 is a fully human immunoglobulin G subclass 4 / lambda recombinant monoclonal antibody, which binds to the catalytic domain of the plasma protein FXIIa and potently inhibits its catalytic activity. As such, CSL312 blocks FXIIa protease activity by binding to its active site; it does not block the effects of an agonist binding to FXIIa. Therefore, it is scientifically more precise for CSL312 to be identified as an inhibitor. This revised terminology does not indicate any change in the activity of the product or a change in the understanding of the mechanism of action. The corrected description for CSL312 as an FXIIa inhibitor monoclonal antibody is used herein. CSL312 is an affinity-matured variant of the parental antibody 3F7, which was isolated following screening against the active catalytic fragment of FXII (βFXIIa). CSL312 is produced in Chinese hamster ovary cells that have been characterized according to applicable international guidelines. A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL312 is provided in the Investigator's Brochure for HAE.

Factor XII (FXII) is the principal initiator of the plasma contact system [Renné et al, 2012]. The contact system is a protease cascade involving the proteins FXII, factor XI, plasma prekallikrein, and the non-enzymatic cofactor high-molecular-weight kininogen. Upon contact with a negatively charged surface, FXII is converted to FXIIa. FXIIa can cleave both factor XI and plasma prekallikrein, which leads to separate pathways that exert procoagulant and proinflammatory effects. Further cleavage of FXIIa releases the 30 kilodalton light chain containing the catalytic domain (βFXIIa), which can activate the classical complement pathway.

During acute HAE attacks, bradykinin (BK) production is increased and is the mediator of swelling in HAE [Nussberger et al, 1998; Nussberger et al, 1999]. Acute and prophylactic treatments for HAE are based on blocking BK production through targeting different proteins in the kallikrein kinin pathway. Plasma levels of FXIIa have been shown to increase in patients during acute HAE attacks compared to levels during remission [Csuka et al, 2015; Cugno et al, 1996]. Given the importance of FXIIa in the initiation of the plasma contact system, it is a novel target for the inhibition of the kallikrein kinin pathway and the excessive production of BK detected during HAE attacks.

The rationale for evaluating CSL312 for prophylaxis to prevent HAE attacks relies on the strong inhibition of FXIIa catalytic activity by CSL312 resulting in the upstream blocking of the contact pathway that produces BK, which feeds the central pathogenic mechanism of HAE.

The efficacy and safety of CSL312 in adult patients with HAE has been demonstrated in a phase 2 study and in a phase 3 study in adult and adolescents with HAE. This phase 3b study is designed to evaluate the safety, pharmacokinetic (PK) / pharmacodynamic (PD), and efficacy of CSL312 in pediatric subjects with HAE (2 to 11 years of age).

2.1.1. Clinical and Nonclinical Experience

2.1.1.1. Nonclinical Evaluation

The nonclinical program conducted to support development of CSL312 included pharmacological, PK, and toxicological studies performed in pharmacologically relevant species that are described in the CSL312 Investigator's Brochure

2.1.1.2. Clinical Experience

2.1.1.2.1. Healthy Subjects

In healthy subjects, 3 phase 1 studies have been completed.

Study CSL312_1001, a phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study, was conducted in healthy volunteers. During this study, the safety, tolerability, and PK of escalating doses of CSL312 were assessed after single intravenous (IV) or SC injections of up to 10 mg/kg in healthy male subjects. CSL312 had an acceptable safety and tolerability profile. During the study, there were no serious adverse events (SAEs); no withdrawals due to adverse events (AEs); no thromboembolic events, bleeding events, or cases of anaphylaxis; no clinically significant abnormal trends in hematology or clinical chemistry assessments. The majority of the AEs were of mild severity. Injection site reactions were more common with SC CSL312 than SC placebo, but there was no apparent dose dependence. Additionally, CSL312 exhibited linear PK with a half-life of approximately 19 days.

Additionally, a phase 1, single-ascending dose study to investigate the PK, PD, safety, and tolerability of CSL312 in healthy Japanese and Caucasian subjects (Study CSL312_1003) was completed. Results from the safety and tolerability assessments demonstrated that CSL312 was well tolerated after a single SC infusion at doses of 200 or 600 mg in Japanese subjects or 200 mg in Caucasian subjects. There were no differences in the safety profiles between healthy Japanese and Caucasian subjects. No deaths, SAEs, adverse events of special interest (AESIs [severe hypersensitivity including anaphylaxis, thromboembolic events, or abnormal bleeding events]), or AEs leading to study discontinuation were reported.

Finally, Study CSL312_1004 is an open-label, phase 1 study to compare the PK and relative bioavailability of single injection of CSL312 administered SC by autoinjector to prefilled syringe assembled to a needle safety device (NSD) in healthy subjects. No deaths, SAEs, AEs leading to study withdrawal, or AESIs were reported. Results from the safety and tolerability assessments demonstrated that CSL312 administered by autoinjector or NSD was safe and well tolerated in healthy adult subjects.

The study results are described in greater detail in the CSL312 Investigator's Brochure.

2.1.1.2.2. Subjects with Hereditary Angioedema

Three clinical studies with CSL312 have taken place in subjects with HAE; 2 studies are completed (CSL312_2001 and CSL312_3001), and 1 study is ongoing (CSL312_3002).

Study CSL312_2001

Study CSL312_2001 is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 dose-ranging (75 mg, 200 mg, and 600 mg) study to investigate the efficacy, PK, and safety of CSL312 SC administered every 4 weeks as prophylaxis to prevent HAE attacks in subjects with C1-INH HAE or FXII / plasminogen HAE. The study consisted of a Screening Period, a Run-in Period, 2 Treatment Periods (Treatment Period 1 [TP1] [2 parts: 1 double-blind part and 1 open-label part] and open-label Treatment Period 2 [TP2]), and a Follow-up Period. After the Run-in Period, eligible subjects with C1-INH HAE were randomized to 1 of 4 treatment groups (placebo, or 75 mg, 200 mg, or 600 mg CSL312) in double-blind TP1. Subjects received a single IV loading dose of investigational product followed 1 week later by a single SC injection of investigational product once every 4 weeks for 12 weeks (for a total of 13 weeks). Additionally, further subjects were assigned to the open-label 400 mg CSL312 SC every 2 weeks treatment arm in TP1. In open-label TP2, subjects received a single SC injection of either 200 mg or 600 mg CSL312 every 4 weeks. Subjects receiving 600 mg CSL312 every 4 weeks in TP2 had their dose decreased to 200 mg CSL312 every 4 weeks effective with Protocol Amendment 2.

The study was conducted in 5 countries at 20 study sites; the first subject visit was on 29 October 2018. A total of 32 subjects with C1-INH type 1 or type 2 HAE were enrolled in the randomized double-blind treatment arms of TP1. Additionally, 6 subjects were assigned to the open-label 400 mg CSL312 SC every 2 weeks treatment arm in TP1. Of the 38 subjects who entered TP2, 36 subjects completed the study.

Among subjects with C1-INH HAE, in TP1, treatment with 200 mg or 600 mg CSL312 SC every 4 weeks resulted in a statistically significant reduction in the time-normalized number of HAE attacks per month when compared with placebo ($P < 0.001$ and $P < 0.001$, respectively). This represented a reduction in the mean time-normalized number of HAE attacks of 98.94% with 200 mg CSL312 and 91.68% with 600 mg CSL312, relative to placebo. In an exploratory analysis comparing the time-normalized number of HAE attacks in the 200 mg CSL312 treatment arm (mean [standard deviation (SD)]: 0.05 [0.127]) and the 600 mg CSL312 treatment arm (mean [SD]: 0.35 [0.407]), the difference was not statistically significant ($P = 0.082$). Of the 24 subjects randomized to blinded treatment with any dose of CSL312, 15 subjects were HAE attack-free during the efficacy evaluation period, including 7/8 (87.5%) subjects who were treated with 200 mg CSL312 and 3/7 (42.9%) subjects who were treated with 600 mg CSL312. No subjects who were treated with placebo were HAE attack-free during the same efficacy evaluation period. Of the 6 subjects in the 400 mg CSL312 every 2 weeks open-label treatment arm, 4/6 (66.7%) were HAE attack-free. All subjects receiving placebo had at least 1 HAE attack treated with on-demand HAE medication, compared with 3/9 (33.3%) subjects in the 75 mg CSL312 arm, 1/8 (12.5%) subjects in the 200 mg CSL312 arm, and 2/7 (28.6%) subjects in the 600 mg CSL312 arm. Subjects receiving CSL312 showed clinically meaningful improvements in the total score of the Angioedema Quality of Life questionnaire. Overall, the efficacy results for TP2 are consistent with TP1 and demonstrated a sustained treatment effect through TP2.

During TP1, blinded treatment with 75 mg, 200 mg, or 600 mg CSL312 SC every 4 weeks, as well as open-label treatment with 400 mg every 2 weeks, was safe and well tolerated. There were no safety signals or concerns, and no dose-dependent patterns in overall AE rates

were noted. The percentage of subjects experiencing at least 1 AE during treatment with any dose of CSL312 was similar to placebo. All AEs were nonserious and were assessed as mild or moderate intensity. There were no AESIs (anaphylaxis, thromboembolic events, or bleeding events), no AEs or SAEs leading to study discontinuation, and no deaths reported during TP1. Similar rates of AEs and no safety signals and concerns were observed in TP2.

Study CSL312_3001

Study CSL312_3001 is a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of 200 mg CSL312 administered SC once monthly (Q1M) as prophylaxis for 6 months to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with HAE. This study randomized 65 subjects since April 2021 and was recently completed. The study was conducted globally at 28 study sites.

Data from this study show that in subjects with C1-INH HAE, CSL312 was safe and effective in the prevention of HAE attacks during the 6-month Treatment Period. The primary efficacy results demonstrated that treatment with administration of SC CSL312 200 mg Q1M resulted in a statistically significant reduction in the time-normalized number of HAE attacks per month compared to placebo (first hierarchical test: $P < 0.001$, 2-sided Wilcoxon Test). Efficacy of CSL312 was consistently observed across different efficacy endpoints, and no safety signals or concerns were observed, consistent with previous studies.

Six adolescent subjects between the ages of 12 and 17 years were enrolled in the study (3 were male and 3 were female). Safety, PK, and efficacy were consistent with the adult population.

Study CSL312_3002

Study CSL312_3002 is a multicenter, open-label, phase 3b study designed to investigate the long-term safety and efficacy of SC administered CSL312 in the prophylactic treatment of HAE in subjects ≥ 12 years old. Subjects eligible to participate in this study are as follows:

- Subjects who participated in the phase 3 double-blind Study CSL312_3001
- Subjects who participated in Study CSL312_2001
- CSL312-naïve subjects with C1-INH HAE type 1 or 2

This study is being conducted globally in approximately 45 sites since March 2021.

Since May 2021, 161 subjects have enrolled in this study. The study included 11 adolescents between the ages of 12 and 17 years, and subjects rolled over from the phase 2 Study CSL312_2001 and phase 3 Study CSL312_3001. The overall clinical program of CSL312 in patients with HAE started in 2018, and no safety signals have been observed.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL312 is provided in the Investigator's Brochure.

2.2. Study Rationale

There is an evident unmet need in the patient population of children 2 to 11 years of age with HAE for a safe, efficacious, and convenient treatment, as there are very limited prophylactic

options approved. Currently approved prophylactic treatments for children under 12 years of age include C1-INH plasma-derived products such as Cinryze®, an IV plasma-derived medication which is injected twice a week, and Haegarda®, which lessens the burden associated with IV administration with SC injections, but dosing is twice a week, and it is only approved in the United States for patients 6 years of age and older. Two other less frequently used, approved prophylactic options include androgens and antifibrinolytics; however, they are not considered the best options for children due to significant side effects and / or poor efficacy [Maurer et al, 2022]. In general, the onset of HAE symptoms occurs in childhood or early in adolescence, and the pathophysiology of HAE is similar across all age groups (adults, adolescents, and children under 12 years of age). HAE attacks are unpredictable regardless of age, and in children, this has a direct impact on their ability to consistently attend school and participate in recreational activities, which negatively affects their quality of life [Caballero, 2013].

CSL312 is an inhibitor of FXIIa, which has been shown to increase in patients during acute HAE attacks. FXIIa inhibition is a viable target for preventing HAE attacks, and the efficacy and safety of CSL312 in adult patients with HAE have been demonstrated in a phase 2 study and confirmed in a phase 3 study in adult and adolescents with HAE. An ongoing open-label phase 3b study continues to support the efficacy and favorable safety of CSL312 in adolescents and adults.

CSL312 mechanism of action and the similarity of the HAE disease and clinical presentation across all age groups of patients support the study of CSL312 for the prophylactic treatment of HAE in children. Furthermore, the safety and tolerability of CSL312 demonstrated to date support the administration of CSL312 in this age group.

2.3. Benefit / Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CSL312 may be found in the Investigator's Brochure.

2.3.1. Benefit Assessment

Potential key benefits of CSL312 include prevention of HAE attacks, less frequent attacks, less severe attacks when attacks do occur, and less frequent use of on-demand medication for the treatment of acute attacks. Data from Study CSL312_2001, a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 dose-ranging study, provide support that treatment with CSL312 results in a clinically meaningful reduction in attack frequency while being safe and well tolerated. Recent data from Study CSL312_3001, a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study in adults and adolescents with HAE show no safety signals and statistically significant and clinically meaningful reduction in attack rates consistent with prior clinical studies. No relevant differences between the treatment-emergent adverse event (TEAE) profile of adolescent subjects and adult subjects have been observed. Similarly, in the ongoing long-term safety open-label phase 3b Study CSL312_3002, no safety signals have been observed to date. The HAE disease clinical presentation and pathophysiology are similar across all age groups, and the efficacy of CSL312 observed to date is expected to provide similar benefit to children between 2 and 11 years of age with HAE.

2.3.2. Risk Assessment

Table 1: Risks and Mitigation Strategies

Potential Risk	Rationale / Summary of Data	Mitigation Strategy
1. Severe hypersensitivity including anaphylaxis	Administration of therapeutic proteins, including monoclonal antibodies such as CSL312, is associated with the risk of hypersensitivity and anaphylactic reactions, some of which can be serious and life-threatening.	The first dose of CSL312 will be performed at the site under medical supervision with immediate access to emergency equipment and medication for the treatment of severe hypersensitivity including anaphylaxis. Subjects will be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Subjects will be required to remain at the site for monitoring for approximately 2 hours following the first dose administration. To date, no related severe hypersensitivity or anaphylactic type reactions have been observed after repeated administration of CSL312 in the completed or ongoing clinical trials.
2. Immunogenicity (antidrug antibodies)	All protein therapeutics are potentially immunogenic. Because CSL312 is a protein, it has the potential to cause the development of neutralizing and non-neutralizing ADAs.	The development of ADAs throughout the study will be monitored. To date, based on all available data, there is a low risk for the development of immunogenicity with CSL312.

ADA = antidrug antibody.

2.3.3. Benefit / Risk Conclusion

Given the potential benefit of CSL312 for patients with HAE, as well as the favorable safety data of CSL312 from Studies CSL312_1001, CSL312_2001, CSL312_3001, and interim data from the CSL312_3002 long-term safety study (Section 2.1.1.2) and considering the implementation of procedures in the current study to closely monitor subject safety, the associated benefit / risk assessment is considered acceptable for pediatric subjects who participate in Study CSL312_3003. Additional information on CSL312 can be found in the CSL312 Investigator's Brochure for HAE.

3. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objective	Endpoint	Summary Measure
Primary		
The primary objectives of the study are to evaluate the safety and PK of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.	TEAEs	Number of subjects, percentage of subjects, and number of events as well as the event rates per injection and per subject year
	PK parameters after SC administration of CSL312 at steady state: • C_{max} • C_{trough} • T_{max}	• Mean (SD) and geometric mean (geometric CV%) for all PK parameters except for T_{max} • Median (minimum, maximum) for T_{max}
Secondary		
The secondary objectives of this study are to evaluate efficacy, PD, and safety of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE.	• Time-normalized number of HAE attacks • Time-normalized number of HAE attacks treated with on-demand treatment • Time-normalized number of moderate and / or severe HAE attacks • Percentage reduction in the time-normalized number of HAE attacks	• The time-normalized number (per month and year) of HAE attacks, of HAE attacks treated with on-demand treatment, and of moderate and / or severe attacks on treatment, respectively • The percentage reduction and the number of subjects experiencing at least ≥ 50%, ≥ 70%, ≥ 90%, or equal to 100% (attack-free) reduction in the time-normalized number of HAE attacks on treatment compared to their time-normalized number of HAE attacks documented in medical records

Objective	Endpoint	Summary Measure
	• SAEs • Deaths • Related TEAEs • TEAEs leading to study discontinuation • TEAEs in each severity category • Anti-CSL312 antibodies • Laboratory findings reported as AEs • AESIs (severe hypersensitivity including anaphylaxis)	The number and percentage of subjects experiencing the specified safety events on treatment as well as the event rates per injection and per subject year
	FXIIa-mediated kallikrein activity at scheduled time points	Descriptive summaries by nominal time point and the percentage of baseline value
Exploratory		
The exploratory objective of the study is to further evaluate the PD effects of CSL312.	FXII concentration at scheduled time points	Descriptive summaries by nominal time points

AE = adverse event; AESI = adverse event of special interest; CV% = percent coefficient of variation; C_{max} = maximum plasma concentration; C_{trough} = trough plasma concentration; C1-INH = C1-esterase inhibitor; FXIIa = activated factor XII; HAE = hereditary angioedema; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; TEAE = treatment-emergent adverse event; T_{max} = time to reach maximum plasma concentration.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, open-label, phase 3b pediatric study designed to investigate the safety, PK / PD, and efficacy of SC administered CSL312 in the prophylactic treatment of HAE in children 2 to 11 years of age. An overview of the study is depicted in Figure 1.

Study Type	Prospective / interventional
Study Period	The following subjects will be eligible to participate in this study if they meet all eligibility criteria: • CSL312-naïve pediatric subjects with C1-INH HAE type 1 or 2 This phase 3b study is designed to evaluate the safety, PK / PD, and efficacy of CSL312 when administered SC at a dose of 100 mg Q1M (subjects 6 to 11 years of age) or every 2 months (Q2M; subjects 2 to 5 years of age) for at least 12 months. The study will consist of a Screening Period, an open-label Treatment Period, and Follow-up Period. Subjects that meet all eligibility criteria during Screening will then enter the Treatment Period. At the completion of study participation, subjects will undergo a follow-up consisting of either a study site visit or a phone call 3 months later. Subjects who complete the study have the option to continue treatment with CSL312 or another prophylactic treatment without a scheduled follow-up. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study. Refer to the Follow-up Period for details.
Blinding Type	The study will be conducted in an open-label manner.
Study Configuration	Parallel-arm
Method of Assignment to Treatment	Eligible subjects will be assigned to open-label CSL312 with a dosing regimen dependent on their age at the time of consent as follows: • 2 to 5 years of age: 100 mg Q2M • 6 to 11 years of age: 100 mg Q1M
Planned Number of Subjects	The target sample size is approximately 20 subjects to ensure that at least 15 subjects complete 12 months of treatment.

Planned Study Duration	Approximately 3 years
Planned Countries and Estimated Number of Sites	Approximately 5 countries and 15 study sites

4.2. Scientific Rationale for Study Design

This phase 3b, multicenter, open-label pediatric study is primarily designed for the assessment of safety and PK of 100 mg of CSL312 Q1M or Q2M SC dosing regimen, depending on age, for the prophylactic treatment of HAE attacks in pediatric subjects aged 2 to 11 years of age with C1-INH HAE type 1 or 2. PD and efficacy as secondary assessments will also be part of the objectives.

The study will include a Screening Period (up to 1 month) to assess subject eligibility and determination of subjects' baseline HAE attack rate based on medical records information, a Treatment Period (at least 12 months) for evaluation of the safety and PK in addition to PD and efficacy of the 100 mg CSL312 dose, and a Follow-up Period (Follow-up Visit takes place 3 months after the last dose of CSL312). Subjects who complete the study have the option to continue to receive access to CSL312 for a limited duration if they meet the criteria for the post-study access program. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program. For these subjects, the Follow-up Period in this study will not be applicable. Subjects who do not choose the post-study access program or another prophylactic treatment will complete the Follow-up Visit as mandated in this study.

The study will include children with HAE with an attack rate of at least 2 attacks in the last 6 months, as reflected in their medical records. The HAE disease in children is similar to adults / adolescents in clinical presentation and pathophysiology; however, the disease in pre-pubertal children is typically milder with less frequent and severe symptoms [Aygören-Pürsün and Andarawewa, 2019]. Therefore, the attack rate criteria for the patient population of children 2 to 11 years old with HAE is lower than the attack rate required in previous adult and adolescent studies to align with the respective disease activity expected in this age group and to accurately capture the patient population.

Children < 2 years of age are not included in this study, as the prevalence of HAE in this age group is extremely rare and the diagnosis is difficult, as children 0 to 2 years of age may have no symptoms, and the functional activity of C1-INH may not be accurately measured. The antigenic C1 and functional C1 inhibitor levels reach normal levels around 6 months to 1 year of age [Nielsen et al, 1994].

The mean age of onset of HAE symptoms in children reported in the literature varies between 4.4 and 11 years [Farkas, 2010; Bork et al, 2006; Bygum et al, 2017; Martinez-Saguer et al, 2009]. HAE as a rare disease has a low prevalence, and in children, the prevalence is even lower due to the time lag to diagnosis, which ranges between 11.2 and 21 mean years from first symptoms [Farkas, 2010; Frank et al, 2016; Bygum et al, 2017]. About 50% of the patients with experience symptoms by the age of 6, although the severity of the symptoms tends to be milder than those in adults or adolescents, as the severity of the HAE disease tends to increase with age and correlates with the start of puberty into adulthood.

Nevertheless, the earlier in childhood the onset of symptoms occurs, the more severe disease progression is expected [Farkas, 2010; Bygum et al, 2017; Bork et al, 2006; Aygören-Pürsün and Andarawewa, 2019; MacGinnitie, 2014], thus the need for a treatment that allows for prevention as early in childhood as possible. Therefore, the age range of the target population for this study is 2 to 11 years of age.

As the HAE disease in the age range of this patient population is very rare and the disease tends to be milder, the pool of treatable HAE children between the ages of 2 and 11 years is small. The target sample size for this study is approximately 20 subjects to ensure that at least 15 subjects complete 12 months of treatment, which is considered to be sufficient to inform the PK and safety of CSL312 in this patient population.

The dose and dosing regimen is detailed in Section 4.3 of this protocol.

4.3. Dose Rationale

The 100 mg dose administered SC either Q1M or Q2M is proposed for pediatric subjects aged 6 to 11 years and 2 to 5 years, respectively.

The dose and dosing regimen was selected to achieve similar steady-state exposures observed in adults based on data of PK, efficacy, and safety of CSL312 from previous clinical studies in the adult and adolescent population with HAE. Results from previous clinical studies in healthy volunteers and subjects with HAE showed that a single administration of CSL312 at doses of up to 10 mg/kg both IV and SC (Study CSL312_1001) and repeated SC administration of CSL312 at doses of up to 600 mg (Study CSL312_2001) were safe and well tolerated. Further, in the phase 3 studies, following a dose of 200 mg Q1M, CSL312 was found to be safe and well tolerated in adults and adolescent subjects with HAE.

A population PK model was developed to characterize the PK of CSL312 based on pooled data from previous clinical studies. PK simulations following 100 mg Q1M and 100 mg Q2M in these age groups suggest overall comparable steady-state exposures to adults following 200 mg Q1M dosing, which is the phase 3 dose in adults and adolescents.

4.4. Start of Study Definition

The study start date is the date on which the clinical study will be open for recruitment of subjects. The first act of recruitment is the date of the first Screening Visit of the first potential subject at a study site and will be considered the study start date.

4.5. End of Study Definition

The End of Study is defined as the date of the last visit of the last subject in the study.

A subject is considered to have completed the study if they have completed 12 months of treatment and the End of Treatment Visit (Section 1.3).

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study closeout visit has been performed.

5. STUDY POPULATION

Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for enrollment into this study. Prospective approval of protocol deviations to recruitment, and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

To be enrolled into the study, subjects must meet all the following inclusion criteria:

1. The subject's parent(s) or legally authorized representative(s) is capable of providing written informed consent for study participation before undergoing any study-specific assessments or procedures; subjects will provide assent for study participation according to local regulations.
2. Male or female.
3. Aged 2 to 11 years, inclusive, with body weight ≥ 10th percentile based on age (according to the Centers for Disease Control growth charts [CDC, 2017]), at the time of providing written informed consent / assent.
4. Diagnosed with clinically confirmed C1-INH HAE:
   a. Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
   b. C1-INH antigen and / or functional activity ≤ 50% of normal as documented in the subject's medical records, and
   c. C4 antigen concentration below the lower limit of the reference range as documented in the subject's medical records.
5. Experienced ≥ 2 HAE attacks during the 6 months before Screening, as documented in the subject's medical records.

   NOTE 1: For subjects taking any prophylactic HAE therapy during the 6 months before Screening, ≥ 2 HAE attacks may be documented over 6 months before commencing the prophylactic therapy.

   NOTE 2: If clinical confirmation of C1-INH HAE in the medical records is from 5 years or more ago (for subjects 6 to 11 years of age) or not available (for subjects 2 to 5 years of age), a blood sample to confirm the HAE disease will be collected at Screening.
6. Investigator believes that the subject (or the subject's legally authorized representative[s]) understands the nature, scope, and possible consequences of the study.

5.2. Exclusion Criteria

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

1. Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticaria, or HAE type 3.

2. Any preplanned major surgeries or procedures during the clinical study.
3. Use of C1-INH products, androgens, antifibrinolytics, approved or future approved medications, or other small-molecule medications for routine prophylaxis against HAE attacks within a minimum of 2 weeks before the Treatment Period.
4. Participation in another interventional clinical study during the 30 days before the Treatment Period or within 5 half-lives of the final dose of the investigational product administered during the previous interventional study, whichever is longer.
5. Known or suspected hypersensitivity to monoclonal antibody therapy, or hypersensitivity to the investigational product or to any excipients of the investigational product.
6. Has laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology or chemistry assessments performed during Screening.

   NOTE: Subjects with alanine aminotransferase or aspartate aminotransferase 2 × upper limit of normal may be eligible for participation if the results are not clinically significant. The determination that the abnormalities are not clinically significant for the subject must be recorded in the subject's source documents and initialed by the investigator.
7. Subject has any condition that, in the judgment of the investigator or CSL Behring (herein, "the sponsor"), may compromise their safety or compliance, impede successful conduct of the study, interfere with interpretation of the results, or would otherwise render the subject unsuitable for participation in the study, eg, significant illnesses or major comorbidities, such as a preexisting condition of coagulopathy or thrombotic disorders.

   Criterion revised at Amendment 1.
8. Currently receiving a therapy not permitted during the study, as defined in Section 6.11 (Table 4).
9. Involved in the planning and / or conduct of the study (applies to the sponsor, study site, and third-party vendors, and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.).
10. Are pregnant or breastfeeding.

5.3. Lifestyle Considerations

Refer to Section 10.3.2 for contraception guidance.

5.4. Screen Failure

A screen failure is defined as a subject who consents to participate in the clinical study but does not meet eligibility criteria. If a subject is not eligible for the study (ie, screen failure), minimal information should be recorded in the electronic Case Report Form (ie, demography, screen failure details, eligibility criteria, and any SAEs) to meet the Consolidated Standards

of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Subjects who do not meet the criteria for participation in this study (screen failure) may be screen failed or rescreened after 60 days. Rescreening is permitted as follows:

- A subject may be rescreened after approval from the sponsor.
- A subject may be rescreened a maximum of 1 time.
- If a subject is rescreened, all Screening assessments must be repeated during the second Screening Period.

If a subject is rescreened, a new informed consent form (ICF) does not need to be signed (Section 10.1.4).

Rescreened subjects should retain their originally assigned subject number through every screening / rescreening event.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Investigational Product

Investigational product should only be dispensed or administered to subjects currently enrolled in the study.

Investigational product must be used only as directed in the Clinical Study Protocol (CSP).

Table 3: Investigational Product - Pharmaceutical Properties, Formulation, and Administration Characteristics

Intervention	Study Product • Sponsor code: CSL312 • Sponsor product identifier: Factor XIIa inhibitor monoclonal antibody • INN: Garadacimab
Type [a]	Combination Product
Formulation	Solution for injection
Unit Dose Strength	100 mg
Diluent	Not applicable
Dose and Regimen	100 mg Q1M 100 mg Q2M
Total Volume	1.0 mL [b]
Route of Administration	Subcutaneous
Anatomical Location	Abdomen, upper arm, thigh
Supply	Provided centrally by the Sponsor
Storage	The recommended storage temperature is + 2° to + 8°C
Packaging and Labeling	CSL312 at a concentration of 100 mg/mL will be supplied in a 2.25 mL ready-to-use staked-in-needle pre-fillable glass syringe with a rigid needle shield and syringe plunger. The prefilled syringe is assembled with a plunger rod and embedded in a NSD and an extended finger flange, which are not in contact with the liquid.

INN = International Nonproprietary Name; NSD = needle safety device; Q1M = once monthly; Q2M = every 2 months.

[a] The term "combination product" includes 2 separate products, biologic / device (ie, CSL312 [100 mg]/NSD) that are produced as a single entity.

[b] The total volume represents the nominal volume.

6.2. Other Study Interventions

Not applicable.

6.3. Management of Investigational Product(s)

- The investigational product will be packaged and labeled according to current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines, and applicable legal requirements. Specific details regarding packaging of the investigational product(s) are provided in the Site Pharmacy Manual.
- The investigational product will be shipped by the sponsor or delegate according to ICH GCP and applicable regulatory requirements.
- The investigator or delegate will confirm receipt of all shipments of investigational product in the Interactive Response Technology (IRT) system.
- Records for the delivery of investigational product to the study site, the inventory at the study site, assignment to each subject, and the destruction or return of investigational product to the sponsor (or delegate) must be maintained by the investigator (or delegate) using the IRT system.
- All supplies of investigational product must be accounted for throughout the study.
- The investigator (or delegate) must provide reasons for any discrepancies in drug accountability in the IRT system.

Investigational product may be shipped from the study site to the subject's home in accordance with country-specific requirements:

- Investigational product may be shipped to the subject's home at the discretion of the investigator, following the completion of parent / caregiver training in investigational product administration at Visit Day 1 (further training may be provided at any subsequent visits as needed).
- The investigational product will be shipped per a schedule that coincides with study visits, or on demand as needed due to insufficient investigational product quantity. To ensure proper subject data confidentiality, a suitable courier service will be selected by study site with the sponsor's approval.

During administration of CSL312, any device malfunctions should be reported as a suspected Product Technical Complaint. Refer to the Site Investigational Product Manual for additional information.

Further details regarding management of the investigational product are provided in the Site Investigational Medicinal Product Manual.

6.4. Assignment of Subjects to Treatment Groups and Blinding

After providing written informed consent, the subject will be issued with a study-level unique subject identification number via an IRT system. The subject identification number will be used to identify the subject for the duration of the study including rescreening. Subject identification numbers are not to be reassigned or reused for another subject in the study.

6.4.1. Randomization

Not applicable; this study is not randomized.

6.4.2. Blinding

This is an open-label study, and all study personnel and study subjects will be unblinded.

6.4.2.1. Blinding Method

Not applicable.

6.5. Selection of Doses in the Study

The 100 mg dose administered SC either Q1M or Q2M is proposed for pediatric subjects aged 6 to 11 years and 2 to 5 years, respectively. The rationale for dose selection for the study is described in Section 4.3.

6.6. Selection and Timing of Dose for Each Subject

The investigational product will be administered to the subjects at the study site or administered by a trained caregiver at home (at the discretion of the investigator) at the time points specified in Section 1.3.

6.7. Dose Modification

Not applicable.

6.8. Investigational Product Compliance

The investigational product will be administered to the subjects at the site directly from the investigator (or delegate), under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents. The dose of investigational product and the subject's identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the investigational product.

At the discretion of the investigator, the investigational product may be administered by a trained caregiver at home (including on-site visit days) after completing training and after the first dose is administered at the study site under medical supervision. Compliance with investigational product will be assessed at each visit. For investigational product that is administered at the site, treatment compliance will be assessed by using the administration details documented in the source documents and relevant form. For investigational product that is administered at the subject's home, compliance will be assessed by review of completed subject dosing form and direct questioning during the following site visit, documented in the source documents. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of investigational product dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for investigational product delays and / or dose reductions, will also be recorded.

6.9. Access to Investigational Product After the End of the Study

Subjects who complete the study (ie, at least 12 months of treatment and the End of Treatment Visit) have the option to continue to receive access to CSL312 (if they meet the criteria for the post-study access program) or another prophylactic treatment. Any post-study access to CSL312 will be subject to the terms and conditions of the post-study access program or another prophylactic treatment. For the End of Study definition, please see Section 4.5.

6.10. Overdose

Overdose is defined as the administration of any dose of CSL312 that is higher than the intended dose and regimen. The highest studied single dose was 10 mg/kg IV and SC and multiple doses at 600 mg SC without clinically relevant side effects. The effects of potential overdose with CSL312 have not been studied. In case of overdose, the subject should be closely monitored, and supportive treatment should be administered as needed.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical monitor immediately.
- Evaluate the subject to determine, in consultation with the medical monitor, whether the investigational product should be interrupted or discontinued, or whether the dose should be reduced, if applicable.
- Closely monitor the subject for any AE, SAE, or clinical laboratory abnormalities.
- Document the quantity of the excess dose of investigational product and the duration of the overdose.
- Any overdose that occurs in association with an adverse sign or symptom must be entered into the Case Report Form (CRF) as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 10.2.6.2).
- Details (ie, volume and location of injection) of an overdose of CSL312 must be recorded in the study treatment administration CRF. Details of an overdose of any concomitant therapy must be recorded in the Concomitant Medication CRF.

See Section 10.2.6.5 for reporting AEs associated with overdose.

6.11. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and / or herbal supplements) or other specific categories of interest that the subject is receiving at the time of enrollment or receives during the subject's study participation must be recorded along with the following:

- Indication
- Dates of administration including start and end dates, if applicable
- Dosage information including dose and frequency

The sponsor's medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

Table 4: Permitted Prior and Concomitant Therapies

Prior and Concomitant Therapy / Procedure	Time Period
Vaccines	Allowed at any point prior to or during the study, per standard of care
Prescribed medication(s) required for the management of acute or chronic medical conditions	As prescribed
Therapies to treat any AEs the subject experiences during the study	As prescribed
On-demand HAE therapies [a]	Any time during the study for the treatment of HAE attacks
Medications (eg, IV C1-INH) for the prevention of HAE attacks	Prior to any medical procedure is PERMITTED at any time during the study.

AE = adverse event; C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous.
[a] If registered in the study country, therapies are permitted at any time during the study for the treatment of HAE attacks, if used according to the product label.
Note: In the event of future approval of medications for the treatment of HAE not listed above, sponsor approval will be required.

Table 5: Prohibited Prior and Concomitant Therapies

Prior Therapy	Time Period
Administration of any other investigational agent within 5 half-lives of the final dose of the investigational agent (from another interventional clinical study) or 30 days, whichever is longer, before administration of CSL312	Before first dose of CSL312
Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products, antifibrinolytics, androgens, approved or future approved medication	PROHIBITED within a minimum of 2 weeks before Treatment Period through End of Treatment. Prophylaxis treatment is allowed during the Follow-up Period.

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema.
Note 1: Subjects are not to be enrolled into the study if they receive any prohibited therapy that cannot be discontinued.
Note 2: If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study participation.

6.12. Drugs Used in the Clinical Trial

This section is not applicable as there are no study sites planned in Japan.

7. SUBJECT WITHDRAWAL AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT

7.1. Discontinuation of Investigational Product

Subjects may discontinue investigational product at any time at their own request, or at the discretion of the investigator or the sponsor for safety, behavioral, or administrative reasons.

Subjects who discontinue investigational product will remain in the study to complete follow-up activities or allow data collection as detailed in the Schedule of Activities (Section 1.3). Subjects discontinuing investigational product who decline further study procedures / visit participation will be withdrawn from the study (see Section 7.2).

Primary oversight during the conduct of the study will be the responsibility of the investigator. The investigator is responsible for evaluating the appropriateness of subjects to be enrolled in the study and for communicating any issues that may compromise subject safety with the sponsor to ensure appropriate action can be taken to protect subjects. Safety surveillance, medical safety assessment, and risk management will be conducted by the sponsor's Global Safety Committees as per Safety Processes at the sponsor. Additionally, an Independent Data Monitoring Committee (IDMC) will be established to monitor the efficacy and safety data generated during the study (Section 10.1.8.1). The IDMC will review accumulating data from the ongoing study. Based on these reviews, the IDMC will advise on the further conduct of the study.

7.1.1. Temporary Interruption

Not applicable.

7.1.2. Halting Criteria for Investigational Product

7.1.2.1. Individual Subject Halting Criteria

If a subject meets any of the following criteria during participation in the study, then further administration of CSL312 to that subject will be halted (ie, temporarily paused) until an assessment of that subject's safety is completed:

1. Symptoms of severe hypersensitivity including anaphylaxis considered by the investigator and / or the sponsor to be related to CSL312 administration
2. Any event or laboratory abnormality considered by the investigator and / or the sponsor to pose an unacceptable risk to the subject in the study

7.1.2.2. Study Halting Criteria

If any of the following criteria are met, then all further administration of investigational product and further enrollment of new subjects will be halted (ie, temporarily paused) until an assessment of the overall safety of continuing the study is completed:

1. One or more subject(s) develops an SAE that results in death and is considered by the investigator and / or the sponsor to be related to the administration of CSL312.
2. One subject develops any event that is deemed to pose an unacceptable risk to other subjects in the study, and these events are considered by the investigator and / or the sponsor to be related to the administration of CSL312.

If any halting criteria are met and the study is halted per IDMC recommendation, the sponsor's Global Safety Committees will conduct a safety assessment to establish if the study should be resumed or if the temporary halt should continue. The study can be resumed on the recommendation of the sponsor's Global Safety Committees, in agreement with the IDMC, if the safety assessment concludes that no further study modifications, protocol amendments, or risk mitigation measures are necessary, and it is safe to resume the study. Regulatory authorities and the Institutional Review Boards (IRBs) will be notified of the temporary halt and subsequent resumption of the study. A substantial protocol amendment will be submitted to the Regulators and the IRBs for approval if the safety assessment concludes that modifications to the protocol (including addition of new risk mitigation measures) are required to resume the study.

If the risk assessment concludes that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the sponsor's Global Safety Committees will be involved in recommending a study stop. Regulators and the IRBs will be notified of a study stop.

7.1.3. Rechallenge

Not applicable.

7.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, compliance, or administrative reasons (eg, AE, protocol deviation, subject noncompliance, or study termination).

The investigator may advise a subject to withdraw from the study if the subject's safety or wellbeing is compromised by further participation in the study. The interests of the subject must always prevail over the interests of the study.

At the time of subject withdrawal, if possible, the End of Treatment Visit assessments should be completed and documented (see Schedule of Activities in Section 1.3). If the subject is withdrawn from the study after receiving CSL312, every effort must be made to ensure that the relevant safety assessments are completed. The investigator may ask the subject to complete additional study assessments.

If a subject withdraws from the study, the sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

7.3. Lost to Follow-up

If a subject repeatedly fails to attend scheduled study visits (ie, site, telephone, or virtual), the site must make 3 attempts to contact the subject, counsel the subject on the importance of maintaining the assigned study visit schedule and ascertain whether or not the subject wishes to (and determine whether they should) continue in the study. All attempts to contact the subject should be documented in the subject's medical record.

A subject will be considered lost to follow-up if he or she repeatedly fails to attend scheduled visits and cannot be contacted by the study site after 3 attempts. When a subject is lost to follow-up, he or she will be considered to have withdrawn from the study.

7.4. Replacement Policy

Not applicable.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study assessments and procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Protocol waivers or exemptions are not allowed.
- The investigator should discuss any immediate safety concerns with the sponsor's medical monitor immediately upon occurrence or when the investigator becomes aware of the safety concern to determine if the subject should continue or discontinue investigational product.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 61 mL (2 to 5 years old) or 65 mL (6 to 11 years old).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Refer to Study Assessment and Procedure Considerations (Section 10.4) for a description of the assessments and visits, which may be performed in a remote / off-site setting.

8.1. Screening / Baseline Assessments

Written informed consent must be provided before any study-specific assessments or procedures are performed. Assessments will be performed at the Screening Visit as specified in the Schedule of Activities (Section 1.3). Refer to Table 6 for additional details.

8.2. Efficacy Assessments

Efficacy assessments will be performed at the time points specified in the Schedule of Activities (Section 1.3).

HAE attacks that are confirmed by investigator or designee will be used for the efficacy analysis and will be recorded on the CRF. All HAE symptoms reported by the subject will be displayed in a by-subject listing. The investigator will review the symptom(s) reported by the subjects. The investigator should confirm if the symptom(s) represent an HAE attack and, if not an HAE attack, then document the symptom(s) as an AE in the CRF. A prodromal symptom by itself or use of on-demand medication alone should not be considered as an attack. Appendix 2 contains assessment criteria for investigator confirmation of HAE attacks. At each study visit (after Visit Day 1), the investigator or designee will review the subject's electronic Diary (eDiary) entries. The investigator will consider all available medical information and may ask clarifying questions to assist in their confirmation of HAE attacks. The following information will be documented in the subject's eDiary:

- Date and time of HAE symptom onset

- Date and time of HAE symptom resolution (ie, subject no longer experiencing symptoms of the attack)
- Location of HAE symptom(s)
- Confirmation of interference of symptom(s) with the subject's daily activities
- If on-demand medication was used to treat HAE symptoms:
  - Name of medication
  - Date and time of administration
- Confirmation of medical assistance received for the HAE symptoms

The investigator will confirm the following details with the subject related to the symptoms:

- Location of HAE symptom(s)
- Start / end date / time of symptom(s)
- Dose(s) of on-demand medication(s) used
- Route(s) of administration of on-demand medication(s) used
- Self-administered or by parent / legal guardian or trained caregiver on-demand medication(s)? (yes / no)
- Administration of on-demand medication(s) at a study site, home, or emergency room
- Type of medical assistance or intervention provided by a healthcare professional during HAE symptoms, including hospitalization or emergency department visits
- Severity of the attack (based on degree of interference in daily activities and whether or not the use of on-demand medication and / or medical assistance was needed)

Note: All on-demand medications used between the onset and resolution of HAE symptoms need to be recorded.

8.3. Safety Assessments

Safety assessments will be performed at the time points specified in the Schedule of Activities (Section 1.3). The clinical procedures to be conducted during this study related to the evaluation of population demographics and safety are provided in Table 6.

Table 6: Study Procedures: Demographics and Safety Assessments

Assessment	Description
Demographics	Year of birth / age / sex / race and ethnicity
Medical History	Relevant medical history within the last 6 months with respect to the overall health of the subject Medical history of HAE history: type 1, type 2, age at diagnosis of HAE, medical records to support diagnosis (Section 5.1), HAE attack frequency, history of laryngeal attacks, prior prophylaxis therapy, and past on-demand treatment medication within 6 months prior to Screening

Assessment	Description		
	Prior (within 6 months before Screening) / concomitant medications and therapies		
Physical Examination	A full physical examination as per the study site's standard procedure. An abbreviated physical examination is limited to follow up of AEs or further evaluation of physical examination findings. For physical examinations, any changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the CRF as AEs.		
Adverse Events	Evaluation of all AEs (eg, causality / relatedness, severity, seriousness) Adverse events of special interest: Severe hypersensitivity including anaphylaxis		
Vital Signs	• Blood pressure (systolic and diastolic)	• Pulse rate	
	• Respiratory rate	• Temperature	
	• Height (Screening Visit, Month 6 Visit, and End of Treatment Visit only)	• Weight	
Pregnancy Testing	• A urine test for β-hCG, as indicated for adolescent females who had their first menstruation (ie, childbearing potential). • A serum pregnancy test may be performed if urine result is inconclusive or if a urine test is unavailable.		
Clinical Safety Laboratory Assessments [1]			
Hematology [a]	• Hemoglobin	• Hematocrit	
	• Erythrocytes (red blood cell count)	• Leukocytes (white blood cell count)	
	• Red blood cell indices: mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration		
	• Differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils		
Biochemistry [a]	• Sodium	• Potassium	• Chloride
	• Bicarbonate	• Albumin	• Alkaline phosphatase
	• Direct bilirubin	• Bilirubin, total	• Aspartate aminotransferase
	• Protein, total	• Calcium	• Alanine aminotransferase
	• Creatinine	• Phosphate	• Blood urea nitrogen
	• Glucose		

Assessment	Description
Coagulation [a, b]	aPTT / D-dimer / PT / INR
Other Screening Tests [c]	C1-INH functional activity and antigen concentration, and C4 antigen concentration
Immunogenicity [a]	Serum analyzed for the presence of binding antibodies (inhibitory and non-inhibitory) specific to FXIIa inhibitor monoclonal antibody (anti-CSL312)

AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; C1-INH = C1 esterase inhibitor; CRF = Case Report Form; FXIIa = activated factor XII; HAE = hereditary angioedema; PT / INR = prothrombin time / international normalized ratio.

[a] Analysis will be conducted at a central laboratory. Additional details will be provided in the Laboratory Manual.

[b] D-dimer will be measured as a part of the coagulation panel for assessment of safety.

[c] C1-INH functional activity and antigen concentration, and C4 antigen concentration laboratory sample to be collected if medical records laboratory results on these parameters used to confirm the HAE 1 or 2 disease are more than 5 years old.

Note 1: **Clinical Safety Laboratory Assessments:** Additional details will be provided in the Laboratory Manual.

8.3.1. Vital Signs

Vital signs will be collected as indicated in Table 6.

8.3.2. Clinical Safety Laboratory Assessments

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Refer to Table 7 for the assessment of severity of AEs associated with laboratory results.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within after the last dose of investigational product should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or sponsor's medical monitor.
    - If clinically significant values do not return to normal / baseline within a time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Section 1.3).
    - If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the subject's source documents.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Events

AEs and SAEs are defined in Section 10.2.1.

AESIs in this investigational product are as follows:

- Severe hypersensitivity including anaphylaxis (see Section 10.2.1.3).

The investigator and any qualified delegates are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

The methods of reporting, recording, evaluating, and assessing causality of AEs, SAEs, and other significant AEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.5. Pharmacokinetics

- Blood samples will be collected on the same day as CSL312 administration for assessment of CSL312 concentrations at time points specified in the Schedule of Activities (Section 1.3).
- Details related to the collection, preparation, and transfer of PK samples will be provided in the Laboratory Manual.

8.6. Pharmacodynamics and Biomarkers

Biomarkers will not be evaluated in this study.

- Blood samples will be collected on the same day as CSL312 administration for assessment of FXIIa-mediated kallikrein activity and FXII concentration at time points specified in the Schedule of Activities (Section 1.3).
- Details related to the collection, preparation, and transfer of PD samples will be provided in the Laboratory Manual.

8.7. Pharmacogenomics / Genomics

Pharmacogenomics / genomics will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity will be assessed as a safety endpoint (Section 8.3).

Blood samples will be collected on the same day as CSL312 administration for immunogenicity assessment at time points specified in the Schedule of Activities (Section 1.3). Details related to the collection, preparation, and transfer of immunogenicity samples will be provided in the Laboratory Manual.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

Not applicable; this study will enroll a prespecified number of subjects as agreed with health authorities.

9.3. Analysis Sets

9.3.1. Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent / assent.

9.3.2. Enrolled Analysis Set

The Enrolled Analysis Set consists of all subjects in the Screened Analysis Set who were enrolled (see Synopsis [Section 1.1] for definition of "enrolled") into the study.

9.3.3. Safety Analysis Set

The Safety Analysis Set consists of all subjects in the Enrolled Analysis Set who received at least 1 dose of investigational product. The Safety Analysis Set will be analyzed using the treatment that the subject actually received.

9.3.4. Per-protocol Analysis Set

The Per-protocol (PP) Analysis Set consists of all subjects in the Enrolled Analysis Set with no major protocol deviation potentially affecting the primary endpoint(s). Protocol deviations resulting in exclusion from the PP Analysis Set will be documented in the data review meeting report before database lock. The PP Analysis Set will be analyzed using the treatment to which the subject was assigned regardless of the treatment that the subject actually received.

9.3.5. Pharmacokinetic Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set for whom there is at least 1 quantifiable PK concentration of CSL312 after administration.

9.3.6. Pharmacodynamic Analysis Set

The PD Analysis Set consists of all subjects in the Safety Analysis Set for whom at least 1 PD measurement was obtained.

9.4. Statistical Analyses and Methods

The Statistical Analysis Plan (SAP) will include a more detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints and analyses.

9.4.1. General Considerations

All analyses will be done for 100 mg Q2M, 100 mg Q1M, and all (if not stated otherwise).

The primary objective of the study is to evaluate the safety and PK of SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE, and thus, the primary endpoint of the study is a safety and PK endpoint and not an efficacy endpoint. Please see Section 9.4.3 and Section 9.4.4 for a description of the primary safety and PK endpoints, respectively, and corresponding analyses.

9.4.2. Efficacy Analyses

The efficacy endpoints will not be calculated if the subject's observation time for the Treatment Period is less than 30 days, ie, the subject discontinued within 30 days after the Day 1 Visit or the date of the first investigational product administration, if available.

The efficacy endpoints will also be assessed over time for 6-month (ie, 182-day) time windows, with the first window starting at Visit Day 1.

9.4.2.1. Analysis of Primary Efficacy Endpoint(s)

There is no primary efficacy analysis.

9.4.2.2. Analysis of Secondary Endpoint(s)

The secondary efficacy endpoints are as follows:

- Time-normalized number of HAE attacks
- Time-normalized number of HAE attacks treated with on-demand treatment
- Time-normalized number of moderate and / or severe HAE attacks
- Percentage reduction in the time-normalized number of HAE attacks

9.4.2.2.1. Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed using the Enrolled Analysis Set. The endpoint "time-normalized number of HAE attacks" will also be analyzed using the PP Analysis Set.

Subjects / caregivers will enter HAE symptoms into their eDiary, along with the start and end dates and time, the interference of HAE symptom(s) with daily activities, and location(s) of the HAE symptom(s). Investigator-reported HAE attacks will be based upon review of subject diaries, relevant interval medical history, and physician judgment. The investigator may ask clarifying questions to assist in his / her assessment of whether an HAE attack occurred. If an attack occurred, then the investigator will record an attack in the CRF, with

the start / end date, the attack location(s), and the severity of the attack based on the most severe symptoms.

For all analyses considering HAE attacks, only the HAE attacks confirmed and reported by the investigator using the CRF 'HAE Attacks' form will be used.

HAE attacks with a start date and time after the first investigational product administration through the End of Treatment Visit will be counted for the Treatment Period and will be included in the analyses of efficacy.

HAE attacks will be listed, including start date / time, end date / time, time between start of the attack and end of the most recent preceding attack or Visit Day 1 (if no preceding attack), anatomical locations, severity, most recent actual CSL312 dose, potential trigger, duration in days, period in which the HAE attack occurred, and how many on-demand medications were taken per HAE attack.

The following derived endpoints based on HAE attacks will be presented in a listing:

- Time-normalized number of HAE attacks (per month and per year)
- Time-normalized number of HAE attacks treated with on-demand treatment (per month and per year)
- Time-normalized number of moderate and / or severe HAE attacks (per month and per year)
- Duration of the Treatment Period
- Total number of HAE attacks
- Reduction in attack rate (Treatment Period vs historical data)
- Time to first attack (in days)
- Maximum attack-free time (in days)

Additional derived endpoints may be presented, and details will be provided in the SAP.

The number of HAE attacks experienced by each subject, as well as the timing of (recurrent) HAE attacks, will be assessed. Different time-to-event analyses will be performed (eg, time to first HAE attack and maximum attack-free time). The maximum attack-free time is defined as the maximum time a subject was attack-free between all subsequent HAE attacks, calculated as start date / time of the following HAE attack - end date / time of the preceding HAE attack. Subjects with no HAE attack, no second HAE attack, no third HAE attack, etc, will be censored at the End of Treatment Visit. The maximum attack-free time for subjects with no attacks is equal to their length of treatment.

9.4.2.2.1.1. Time-normalized Number of Hereditary Angioedema Attacks

The time-normalized number (per month) of HAE attacks is calculated per subject as follows:

$$\frac{\text{The number of HAE attacks}}{\text{Length of subject treatment in days}} * 30.4375$$

where the length of subject treatment is calculated as the duration of the Treatment Period.

To transform the length of subject treatment, which are calculated in days into years, the number of days is divided by 365.25. Thus, time-normalized number of HAE attacks per year is calculated per subject as follows:

$$\frac{\text{The number of HAE attacks}}{\text{Length of subject treatment in days}} * 365.25$$

The time-normalized number of HAE attacks will also be calculated for the historical data.

The time-normalized number of HAE attacks per month and per year will be summarized descriptively including median (primary interest) and mean (secondary interest) with corresponding 95% confidence intervals (CIs). The CIs for the mean will be based on the t-distribution, whereas distribution-free CIs will be used for the median.

Besides the time-normalized number of HAE attack, the total number of HAE attacks (ie, not time-normalized) will also be summarized.

9.4.2.2.1.2. Time-normalized Number of Hereditary Angioedema Attacks Treated with On-demand Treatment

An HAE attack treated with on-demand treatment is identified using the CRF 'HAE Attacks' form, where whether on-demand treatment was administered is a field to be filled out.

The time-normalized number of HAE attacks per month treated with on-demand treatment is calculated as follows:

$$\frac{\text{Number of HAE attacks treated with on} - \text{demand treatment during treatment period}}{\text{Length of subject treatment in days}} * 30.4375$$

This will be summarized descriptively. To report in years, the number of days will be multiplied by 365.25 instead of 30.4375.

This summary table will also include the number and percentage of subjects who took a specific medication at least once and the total number of times a specific on-demand medication was used across all subjects. For each on-demand medication, the number of uses of the on-demand medication per HAE attack will be summarized descriptively, and Anatomical Therapeutic Chemical classification and preferred term (PT) will be displayed in a listing.

Both the categorical overview and the time-normalized number of HAE attacks will also be provided for moderate / severe HAE attacks (Section 9.4.2.2.1.3).

9.4.2.2.1.3. Time-normalized Number of Moderate and / or Severe Hereditary Angioedema Attacks

For the analysis of the time-normalized number of moderate and / or severe HAE attacks, an analog calculation and analyses as described in Section 9.4.2.2.1.1 will be done using all HAE attacks classified as moderate or severe.

9.4.2.2.1.4. Percentage Reduction in the Time-normalized Number of Hereditary Angioedema Attacks

The percentage reduction in the time-normalized number of HAE attacks is calculated within a subject as follows:

$$100 * \left(1 - \frac{\text{Time-normalized number of HAE attacks per month during treatment period}}{\text{Time-normalized number of HAE attacks per month from historical data}}\right)$$

This will be summarized descriptively.

The number and percentage of responders and nonresponders will be presented with corresponding 95% CIs. A subject is classified as a responder if the percentage reduction in the time-normalized number of HAE attacks under treatment compared to the time-normalized number of HAE attacks documented in the medical records is ≥ 50%. In addition, the number and percentage of subjects with percentage reductions of ≥ 70% and ≥ 90% will be presented with corresponding 95% CIs.

Furthermore, the number and percentage of subjects with a percentage reduction of 100%, ie, who do not experience an HAE attack and so are attack-free, will be presented and summarized with corresponding 95% CIs.

The 95%-Wilson CIs for percentages will be calculated based on Wilson's asymptotic confidence limits.

9.4.2.2.1.5. Supplementary Analysis of Secondary Endpoints

Subjects' profiles will be generated for each subject. The x-axis will show the HAE historical data and the Treatment Period. The different subject identification numbers will be plotted on the y-axis. For each subject, a horizontal bar will show the duration of his / her study participation; dots at the respective position of the x-axis will symbolize a mild (white dot), moderate (gray dot), and severe (black dot) HAE attack; an arrow above the bar at a certain position of the x-axis will show the time point when the subject took on-demand medication, and an asterisk will show the time of CSL312 administration. In addition, the subject's reason for study discontinuation (if applicable) will be given. Subjects' profiles will be sorted by dosing regimen, showing subjects receiving 100 mg Q2M followed by subjects receiving 100 mg Q1M.

The time-normalized number of HAE attacks and the time-normalized number of HAE attacks treated with on-demand treatment will also be assessed from Visit Day 1 until Visit Day 31 of the Treatment Period. This summary will be provided by dosing regimen. The analyses will also be repeated for moderate and severe attacks. The number and percentage of subjects not experiencing any attacks in the first month will also be displayed.

In addition, all secondary efficacy endpoints will also be assessed over time for 6-month (ie, 182 days) time windows, with the first window starting on Visit Day 1.

9.4.3. Safety Analyses

All safety analyses will be based on the Safety Analysis Set as defined in Section 9.3.3.

TEAEs are AEs that start on or after the date and time of the first administration of study treatment. TEAEs occurring until the Follow-up Visit (or the End of Treatment Visit for

subjects continuing into the post-study access program or another prophylactic treatment) will be summarized. All AEs regardless of when they were reported will be listed.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). There will be periodic updates of the MedDRA version. The latest licensed version will be used, and version updates will be implemented upon availability. AEs will be primarily classified by MedDRA PT. Analyses will be performed by system organ class (SOC) and PT. Aggregated incidences at SOC level and any TEAE will also be provided.

Coronavirus disease 2019 (COVID-19)-associated AEs will be included in TEAE tables identified by standard MedDRA coding.

Subjects with multiple occurrences of the same TEAE will be counted once in the total of those experiencing this PT. Similarly, a subject with 1 or more PT in a SOC will be counted once in the total of those experiencing PTs in that SOC. Percentages for subject incidence rates will be based on the Safety Analysis Set.

Analyses of other safety assessments (ie, vital signs, clinical laboratory safety markers, etc) will be described in the SAP.

9.4.3.1. Primary Safety Estimand

The primary safety interest is to assess whether TEAEs occurred at least once during SC administration of CSL312 in the prophylactic treatment of pediatric subjects with C1-INH HAE during treatment from the first investigational product administration at Day 1 Visit through the End of Treatment Visit or the latest available visit or event (whichever is later) for subjects without the End of Treatment Visit while subjects are allowed to treat HAE attacks with on-demand medications.

The primary safety estimand, in line with the primary safety interest of the study, follows the treatment policy strategy and is described as follows:

- Treatment condition: Q1M or Q2M treatment with 100 mg CSL312
- Population: The target patient population, defined by eligibility criteria and who received at least 1 dose of investigational product (Safety Analysis Set)
- Variable: TEAEs
- Intercurrent events: The occurrence of an intercurrent event is ignorable. All observed values will be used, regardless of occurrence of any of the following intercurrent events:
    - Administration of on-demand medication in addition to prophylactic treatment with CSL312
    - Prohibited concomitant medications due or not due to COVID-19 or COVID-19 vaccination
    - Treatment adherence or early treatment discontinuation due or not due to COVID-19
- Population-level summary: TEAE rate per subject year

9.4.3.2. Analysis of Primary Safety Endpoint

Following the estimand described in Section 9.4.3.1, the TEAEs for pediatric subjects with C1-INH HAE will be summarized by event rate per subject year using the Safety Analysis Set. All summary tables described will be by 100 mg Q2M, 100 mg Q1M, and overall.

TEAE rates per subject year will be calculated as follows:

$$\text{TEAE rate per subject year} = \frac{\text{Number of TEAE}}{\text{Subject years}}$$

where subject years will be the sum of the time in years that subjects were exposed to study treatment at that dosing regimen during the respective safety evaluation period. For the calculation of time exposed to a specific dosing regimen, each study day will be counted under the corresponding dosing regimen.

In addition, TEAEs will be summarized by the number of subjects and percentage of subjects experiencing at least 1 TEAE, the number of events, as well as the event rate per injection.

TEAE rates per injection will be calculated as follows:

$$\text{TEAE rate per injection} = \frac{\text{Number of TEAE}}{\text{Number of injections}}$$

where number of injections will be the sum of the injections that subjects received during the respective safety evaluation period at a specific dosing regimen the TEAE is assigned to.

An overview summary of TEAEs as well as a table by SOC and PT will be provided.

To evaluate the COVID-19 impact on the primary endpoint, the overview summary of TEAEs and the summary table by SOC and PT will be repeated as a sensitivity analysis excluding all of the COVID-19 related TEAEs (per the corresponding Standardized MedDRA Query).

All AEs will be presented in a by-subject listing.

9.4.4. Pharmacokinetics Analyses

The PK parameters after SC administration of CSL312 at steady state are primary endpoints in this study. The PK analysis will be performed using the PK Analysis Set.

9.4.4.1. Analysis of Primary Pharmacokinetic Endpoint

Plasma concentrations of CSL312 will be listed by individual subjects and will be summarized by nominal time points and by dosing regimen (ie, 100 mg Q2M, 100 mg Q1M) using the PK Analysis Set. Plasma concentrations will be summarized with descriptive statistics: n, mean, SD, percent coefficient of variation (CV%), median, minimum, maximum, first and third quartiles for continuous variables, and geometric mean and its respective 90% CI.

PK parameters will be derived using noncompartmental PK analyses and will be summarized descriptively by dosing regimen (ie, 100 mg Q2M, 100 mg Q1M). PK parameters will include maximum plasma concentration (C_{max}), trough plasma concentration (C_{trough}), and time to reach maximum plasma concentration (T_{max}). The following descriptive statistics will be presented for all PK parameters, except for T_{max}: n, mean, SD, CV%, median, geometric

mean, geometric CV%, minimum, and maximum. For T_{max}, n, median, minimum, and maximum will be provided.

Additional information on the analyses of PK parameters will be provided in the SAP.

9.4.5. Pharmacodynamic Analyses

PD data will be summarized using the PD Analysis Set. FXIIa-mediated kallikrein activity and FXII concentration will be listed by individual subjects and will be summarized by nominal time point and dosing regimen (ie, 100 mg Q2M, 100 mg Q1M). The PD data will be summarized with descriptive statistics: n, number and percentage of values below the limit of quantification, mean, SD, CV%, median, minimum, maximum, first and third quartiles for continuous variables, geometric mean and its respective 90% CI, and geometric CV%.

Additional information on the analyses of PD will be provided in the SAP.

9.4.6. Multiple Comparisons and Multiplicity

Type I error rate adjustment is not applicable, as there is no confirmatory test planned in this study. No statistical tests are planned.

9.4.7. Missing Data and Imputation

Missing efficacy data will not be imputed, as there is no formal statistical analysis being done. All subjects who drop out within the first 30 days of the Treatment Period will be regarded as missing for all efficacy analysis.

There will be no imputation of partial or complete missing dates.

Where AE start dates and / or times are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates and / or times or the AE end date and / or time indicate that the AE started before the first administration of study treatment.

If for a TEAE the relationship to study treatment is missing, the worst case will be assumed for summarizing analysis (ie, the relationship to study treatment will be assumed to be "Yes"). If the AE or SAE with missing relationship started before the first injection of study treatment, it will be considered as "not related" (realistic case). No other imputations for missing AE information will be done.

9.5. Interim Analysis

No formal interim analyses or sample size re-estimation are planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Research Agreement between the sponsor and the institution(s) representing the investigational study site(s). Financial support to the investigational site(s) will be detailed in the Clinical Trial Research Agreement. The Clinical Trial Research Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and sponsor and will form the contractual basis under which the clinical study will be conducted. Clinical Trial Research Agreements may be executed by electronic signature (current provider DocuSign) in compliance with 21 Code of Federal Regulations (CFR) Part 11 and simple or advanced electronic signature according to European Union (EU) Regulation No 910/2014 - eIDAS.

10.1.2. Regulatory and Ethics Considerations

This study will be conducted in accordance with the CSP and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable ICH GCP guidelines
- Applicable laws and regulations such as EU Clinical Trials Regulation 536/2014

The CSP, CSP amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements, study manual, and patient / caregiver facing materials) must be submitted to an IRB / Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB / IEC before the study is initiated.

Any CSP amendments will require IRB / IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

CSPs and CSP amendments will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB / IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB / IEC.
- Notifying the IRB / IEC of SAEs or other significant safety findings as required by IRB / IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB / IEC, European Clinical Trials Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.3. Financial Disclosure

Details regarding financial disclosure are provided in the Clinical Trial Research Agreement and ICF for the study.

10.1.4. Informed Consent Process

- The investigator or delegate will explain the nature of the study to the subject or their legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, and the IRB / IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or their legally authorized representative.
- A subject who is rescreened is not required to sign another ICF.

10.1.5. Data Protection

Measures used to protect individual subject data include the following:

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the sponsor in accordance with all applicable data protection laws. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the ICF.
- The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.1.6. Dissemination of Clinical Study Information and Data

- The sponsor will provide the relevant CSP information in public database(s) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.
- Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original CSP registration record.

- This CSP will be made public following study completion with results posting in any applicable public registry (eg, ClinicalTrials.gov). Company confidential information within the CSP and personal protected data may be redacted as defined by regulatory authorities.

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded either through the IRT system or on printed or electronic CRFs unless transmitted to the sponsor or delegate electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or delegate is responsible for the data management of this study including quality checks of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the timeline outlined in the Clinical Trial Research Agreement.
- Quality tolerance limits, where appropriate, will be predefined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and / or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the quality tolerance limits and remedial actions taken may be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk-Based Quality Management), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan and Quality Risk Management Plan.

10.1.8. Committees Structure

10.1.8.1. Independent Data Monitoring Committee

An IDMC will be established to monitor the safe conduct of the study. An IDMC charter outlines the roles and responsibilities of the committee and guides its operations. The IDMC will consist of independent clinical specialists in HAE, who also have experience in clinical trials. The IDMC responsibilities include the following:

- Review the safety data at planned intervals and identify if significant safety concerns arise during the study.
- Based on these reviews, provide recommendations regarding study conduct matters that affect safety.
- No success or futility thresholds will be set for the IDMC reviews.

- The sponsor will continue the study unless a safety issue is confirmed that warrants study termination.

The composition, activities, analyses, responsibilities, and timing of meetings of the IDMC will be described in the IDMC charter.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- The definition of what constitutes source data can be found in the Clinical Trial Research Agreement.
- Data reported through the IRT system or entered into the CRF that are transcribed from source documents must be consistent with the source documents. If there are data discrepancies, the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.
- The investigator must maintain accurate documentation (source data) to support the information entered into the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Premature Site Closure and Study Termination

The sponsor or delegate reserves the right to close the study site prematurely or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

Reasons for premature site closure include, but are not limited to, the following:

- Failure of the investigator to comply with the CSP, the requirements of the IRB / IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Enrollment target achieved earlier than expected.
- The reason for study termination may include, but is not limited to, discontinuation of investigational product development for any reason.
- If the study is terminated or suspended, the sponsor will promptly notify the investigators, the IRBs / IECs, the regulatory authorities, and any contract research organization(s) used in the study and provide the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator will promptly inform the subject and should ensure that they are properly transitioned out of the study.

10.1.11. Publication Policy

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Research Agreement for the study.

10.2. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definitions

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The observation period for AEs is defined in Section 10.2.4.

AEs may include the following:

- Exacerbation (ie, an increase in the frequency or severity) of a preexisting condition. Preexisting conditions should be recorded on the Medical History CRF and only reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent and before investigational product administration.
- Intercurrent illnesses with an onset after administration of investigational product.

AEs do not include the following:

- Events identified at Screening that meet exclusion criteria
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
  - Planned hospitalizations related to preexisting conditions that have not worsened
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery)
  - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy)
- Overdose of investigational product or any concomitant therapy that does not result in any adverse signs or symptoms

For laboratory and other safety parameters (eg, vital signs), any instances of absolute values or changes at any visit after study start that are considered by the investigator as clinically

significant must be recorded on the AE CRF. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters may be recorded on the AE CRF if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at Screening, unless a further increase / decrease can be considered an exacerbation of a preexisting condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

10.2.1.2. Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** – The sponsor considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is considered by the investigator to potentially jeopardize the subject or to require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

AEs that do not fall into the above categories are defined as nonserious AEs.

10.2.1.3. Adverse Event of Special Interest

The following AEs will be monitored as AESIs to enable an adequate risk-benefit evaluation of CSL312:

- Severe hypersensitivity including anaphylaxis (refer to Table 7 for AE severity classification)

AESIs will be identified by the investigator according to the Medical Monitoring Plan. Only AESIs identified by the investigator will be reported in listings and tables.

The reporting requirements for AESIs are detailed in Section 10.2.6.3.

10.2.2. Assessment of Severity

The severity of each AE (ie, nonserious and serious) is to be assessed by the investigator as follows:

Table 7: Definitions of Adverse Event Severity

Severity [a]	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	A type of AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

AE = adverse event; CRF = Case Report Form.
[a] The assessment of severity of AEs associated with laboratory results will be supplemented by referring to the Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table included in the electronic CRF completion guideline.
Source: CDISC SDTM CT file from 2023-09-29 (for any updates, the most current version will be used).

10.2.3. Assessment of Causality

The causal relationship of an AE to investigational product, the medical device (constituent), or the combination of device and investigational product **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to investigational product, the medical device (constituent), or the combination of device and investigational product. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to investigational product, the medical device (constituent), or the combination of device and investigational product until clarified with the site.

The degree of certainty with which an AE is attributed to investigational product or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of the following:

- Known pharmacology of investigational product
- Clinically and / or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products or reported in the literature for similar products as being product-related (eg, headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with investigational product, or drug withdrawal)

10.2.4. Observation Period for Adverse Events

The observation period for the reporting of AEs (and SAEs) for an individual subject will start at the time of giving written informed consent for participation in the current study and finish upon the subject's final visit.

If the investigator becomes aware of an SAE that has started after the observation period has ended, and there is at least a possible causal relationship with the investigational product or medical device constituent, the event must be reported to the sponsor following the same timelines and procedures described for SAEs occurring during the study (Section 10.2.6.2).

10.2.5. Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, nonserious AEs that have not resolved or stabilized will be followed until the subject completes the study. SAEs will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

10.2.6. Adverse Event Reporting

10.2.6.1. Adverse Events

At each study visit, the investigator (or delegate) will determine whether any AEs have occurred. All AEs are to be recorded on the CRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and / or symptoms. The investigator must follow the course of an AE until the event resolves or stabilizes. If an AE is ongoing after the End of Study Visit, the AE will continue to be followed until resolution or stabilization, or until the subject is lost to follow-up.

If, during the study, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded on the Medical History CRF.

10.2.6.2. Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the CRF.

All SAEs that occur during the study, whether or not causally related to CSL312, must be entered into the CRF immediately (within 24 hours of the investigator becoming aware of the event).

AEs occurring between the subject's written informed consent and the first exposure to CSL312 and that meet at least 1 of the criteria for seriousness, must be entered into the CRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the End of Study Visit that is considered to be causally related to CSL312 must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to the sponsor.** Such events are not entered into the CRF.

The minimum requirements for the reporting of SAEs are as follows:

- Subject identification number
- Suspected medicinal product and / or procedure
- Event term
- Identity of reporting source (ie, subject, caregiver, treating physician, investigator)

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant IRB / IEC within the time frame specified by the IRB / IEC.
- If the subject is an active subject in the study:
  - Enter follow-up information in the CRF until the SAE has resolved or, in the case of permanent impairment, until stabilized.
  - Ensure that the causality assessment for all SAEs is entered into the CRF.
- If the subject is no longer participating in the study, report the follow-up information to the sponsor.

In cases of death, the investigator should supply the sponsor and the IRB / IEC (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

10.2.6.3. Adverse Events of Special Interest

AESIs should be reported using the expedited reporting procedures, as described for SAEs (see Section 10.2.6.2).

10.2.6.4. Other Significant Events

Not applicable.

10.2.6.5. Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the CRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 10.2.6.2).

The details (ie, volume, location of injection) of an overdose of CSL312 (defined in Section 6.10) must be recorded into the appropriate CRF. Details of an overdose of any concomitant therapy must be recorded on the Concomitant Medication CRF.

10.2.6.6. Pregnancy and Breastfeeding

A female subject who becomes pregnant while participating in the study, or up to and including 3 months after the last dose of CSL312, must notify the investigator within 24 hours of a positive pregnancy result.

If a female subject becomes pregnant, she must discontinue treatment with CSL312, but may continue other study procedures at the discretion of the investigator. If the female subject is in the active Treatment Period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 7).

The investigator must notify the sponsor within 5 days of becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject exposed to CSL312 should be followed to term to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination or the status of the mother and child after delivery, should be reported by the investigator to the sponsor using a Pregnancy Reporting / Outcome Form.

All abnormal pregnancies and neonatal outcomes (eg, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly) will meet the criteria for SAE classification. The investigator should follow the procedure for reporting these events as SAEs (see Section 10.2.6.2).

10.2.7. IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification. The sponsor will provide investigators with all details of all SAEs reported to health authorities.

10.3. Contraceptive Guidance

10.3.1. Definitions

Females of Childbearing Potential

Female subjects in this study should be either of the following:

- Premenarchal and either Tanner stage 1 or less than age 9 years.
- Adolescent females who had their first menstruation (ie, childbearing potential) with a negative urine beta-human chorionic gonadotropin pregnancy test result prior to the first dose of investigational product on Visit Day 1. Adolescent females who had their first menstruation (ie, childbearing potential) must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.
- Sexually active adolescent females who had their first menstruation (ie, childbearing potential) should use a medically acceptable form of contraception. Adolescent females who had their first menstruation (ie, childbearing potential) must be advised to use acceptable contraceptives throughout the study period and for 90 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to

the package insert. Any adolescent female who had her first menstruation (ie, childbearing potential) who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 90 days following the last dose of investigational product.

10.3.2. Contraception Guidance

10.3.2.1. Female Contraception Guidance

Acceptable methods of contraception include the following:

- Intrauterine devices (all types) or intrauterine hormone-releasing systems, plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Progestin-only contraceptives associated with inhibition of ovulation (oral, patch, injectable, implant, or vaginal ring), stabilized for at least 30 days prior to the Screening Visit, plus condoms. Note: If the subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Note: Estrogen-containing medications with systemic absorption are not allowed in the study.

10.3.2.2. Male Contraception Guidance

Since the study population includes male children < 12 years of age only, male contraception is not required in this study.

10.4. Study Assessment and Procedure Considerations

10.4.1. Optional, On-demand Alternative Visit Modalities

The following alternative visit modalities and assessments may be implemented with sponsor approval as per the Schedule of Activities (Section 1.3) in a remote / off-site setting utilizing the following methods (if allowed according to local regulations):

- Telemedicine visit, a virtual visit performed via videoconference or telephone by a trained and qualified site personnel.
- A mobile health provider who is trained and qualified to perform specific assessments or procedures (ie, safety assessments including the collection of clinical laboratory safety assessments).

In the event of a state of emergency or public health threat resulting in travel restrictions that prevent a subject from returning to the study site for the required study assessments or procedures, or if the subject is unable to attend site visits due to extenuating circumstances, the following alternative visit modalities may be implemented with sponsor approval as per the Schedule of Activities (Section 1.3): telephone or video conference calls at home for safety follow-up, including assessment of AEs and concomitant therapies, and hematology, biochemistry, and pregnancy blood sampling at a local laboratory, where possible.

Telemedicine or virtual study visits may be performed by qualified, designated study site personnel.

Home health visits may be performed by a qualified medical provider approved by the sponsor.

A local laboratory may be used to collect and analyze protocol-required assessments.

Electronic clinical outcomes assessment (eCOA) solutions may also be offered directly to the subject to ensure that subjects can enter data remotely. In case alternative visit modalities are used in the study, data will continue to be protected and stored securely without disruption.

10.4.2. Use of Electronic Clinical Outcomes Assessment Solution

An eCOA solution will be used by the subjects and / or sites via a handheld eDiary or app.

The eCOA solution is provided as a means to capture electronic source data in a controlled and consistent way, and to provide access for investigators to these source data. The system also allows the subjects' health status to be remotely monitored during the study. The data residing in the eCOA system provider's database are considered the source and are under the control of the investigator at all times.

The investigator (or delegate) will have access to all eCOA data entered at site and / or all data reported within the subjects' eDiaries via a secure, role-based web portal provided by an external eCOA system provider. The eCOA system provider will transfer a copy of the source data across to the sponsor's Clinical Data Warehouse at a predefined frequency via a secure data channel for systematic review by the sponsor's clinical team.

The eCOA provider engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is not in any way intended as a substitute for normal medical care of the subjects. The vendor provides the service of hosting of the eCOA data on behalf of the study investigator(s), until such a time as the investigator is in receipt of a certified archive copy of all Diary data relating to subjects at that site and has confirmed that it is readable.

10.4.3. Genomics: Use and Analysis of DNA

Not applicable.

10.5. Country-specific Requirements

Not applicable.

11. REFERENCES

Aygören-Pürsün E, Andarawewa S. Hereditary angioedema with C1-inhibitor deficiency (HAE-C1-INH) in childhood and adolescence. Poster session presented at: 11th C1 Inhibitor Deficiency and Angioedema Workshop; 2019 May 23-26; Budapest, Hungary.

Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet. 2000;356(9225):213-7.

Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006;119(3):267-74.

Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esterase inhibitory deficiency. J Emerg Med. 2016;50(4):567-80.

Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. Front Med (Lausanne). 2017;4:212.

Caballero T. Angio-oedema due to hereditary C1 inhibitor deficiency in children. Allergol Immunopathol (Madr). 2013;41(1):45-53.

Cancian M, Perego F, Senter R, Arcoleo F, De Pasquale T, Zoli A, et al. Pediatric angioedema: essential features and preliminary results from the Hereditary Angioedema Global Registry in Italy. Pediatr Allergy Immunol. 2020;31 Suppl 24:22-4.

CDC. Clinical growth charts [Internet]. Centers for Disease Control and Prevention, National Center for Health Statistics. 2017 June 16 [cited 2022 August 30]. Available from: https://www.cdc.gov/growthcharts/clinical_charts.htm.

Cicardi M, Zanichelli A. Replacement therapy with C1 esterase inhibitors for hereditary angioedema. Drugs Today (Barc). 2010;46(11):867-74.

Csuka D, Veszeli N, Imreh É, Zotter Z, Skopál J, Prohászka Z, et al. Comprehensive study into the activation of the plasma enzyme systems during attacks of hereditary angioedema due to C1-inhibitor deficiency. Orphanet J Rare Dis. 2015;10:132.

Cugno M, Cicardi M, Coppola R, Agostoni A. Activation of factor XII and cleavage of high molecular weight kininogen during acute attacks in hereditary and acquired C1-inhibitor deficiencies. Immunopharmacology. 1996;33(1-3):361-4.

Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol. 2010;6(1):18.

Frank MM, Zuraw B, Banerji A, Bernstein JA, Craig T, Busse P, et al. Management of children with hereditary angioedema due to C1 inhibitor deficiency. Pediatrics. 2016;138(5):e20160575.

MacGinnitie AJ. Pediatric hereditary angioedema. Pediatr Allergy Immunol. 2014;25(5):420-7.

Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Klingebiel T, Kreuz W. Clinical surveillance program of pediatric hereditary angioedema (HAE) patients undergoing home treatment. J Allergy Clin Immunol. 2009;123(2):S116.

Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. Allergy. 2022;77(7):1961-90.

Nasr IH, Manson AL, Al Wahshi HA, Longhurst HJ. Optimizing hereditary angioedema management through tailored treatment approaches. Expert Rev Clin Immunol. 2016;12(1):19-31.

Nielsen EW, Johansen HT, Holt J, Mollnes TE. C1 inhibitor and diagnosis of hereditary angioedema in newborns. Pediatr Res. 1994;35(2):184-7.

Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet. 1998;351(9117):1693-7.

Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. J Allergy Clin Immunol. 1999;104(6):1321-2.

Renné T, Schmaier AH, Nickel KF, Blombäck M, Maas C. In vivo roles of factor XII. Blood. 2012;120(22):4296-303.

Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. Science. 1965;148:957-8.

Zanichelli A, Farkas H, Bouillet L, Bara N, Germenis AE, Psarros F, et al. The Global Registry for Hereditary Angioedema due to C1-Inhibitor Deficiency. Clin Rev Allergy Immunol. 2021;61(1):77-83.

Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-22.

APPENDIX 1. PRINCIPAL INVESTIGATOR SIGNATURE

SIGNATURE OF PRINCIPAL INVESTIGATOR

Study Title: A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age

Study Number: CSL312_3003 **Site Number:**

I have read the Clinical Study Protocol (CSP) Amendment 2 titled "A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age."

By signing this CSP, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the CSP, the standards of Good Clinical Practice (as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements.

Changes to the CSP will only be implemented after written approval is received from the sponsor and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the CSP.

_____ _____

(Signature) Date (DD Month YYYY)

_____

(Printed name)

_____

(Title)

APPENDIX 2. HEREDITARY ANGIOEDEMA ATTACK ASSESSMENT AND REPORTING INSTRUCTIONS

Hereditary Angioedema Attack Assessment and Reporting Instructions for Study CSL312_3003

Version: Version 1.0

Version Date: 20 September 2022

1 Purpose

The purpose of this document is to provide instructions on the reporting of hereditary angioedema (HAE) symptoms by the subject and the assessment of HAE attacks and subsequent follow-up by the investigator. This document will also present a definition of an HAE attack and a set of standardized requirements to aid the investigator in determining and recording an HAE attack based on the subject's reported symptoms.

Note: In the event that the subject is too young or otherwise unable to complete the tasks outlined herein, the parent or caregiver is responsible for recording all relevant information regarding HAE symptoms and the use of on-demand medication to treat those symptoms.

2 Hereditary Angioedema Symptom Reporting and HAE Attack Assessment

All symptoms potentially related to an HAE attack and information on the use of on-demand medication to treat those symptoms during the Treatment and Follow-up Periods will be entered by the subject in an electronic Diary (eDiary). The investigator or delegate will review the data in the eDiary and collect additional information that may be missing from the eDiary, and other relevant information needed for the assessment of the subject-reported symptoms.

2.1 Subject Training

At Visit Day 1, subjects eligible for entering the Treatment Period will be trained by the site's personnel on identifying symptoms of a potential HAE attack, the use of the eDiary to report a symptom(s), and the information they will need to report about their symptoms. The subject (with parent / legal guardian if applicable for minors) will confirm his / her understanding of what is required to report symptoms potentially related to an attack. Sites will assess the subject's compliance with the reporting requirements during the study and may retrain the subject if necessary.

2.2 Subject-reported Symptoms

At the onset of a symptom(s) of a potential HAE attack, subjects will be instructed to enter information about the symptom(s) in the eDiary. Subjects (with parent / or legal guardian if applicable for minors) will also be encouraged to notify and report details to the study site within 72 hours of the start of the first symptom(s) of a potential HAE attack. When a subject initiates the reporting of symptoms of a potential HAE attack in the eDiary, he / she will be reminded to contact the site within 72 hours of the onset of symptoms. In tandem, the site will receive an email alert from the eDiary portal indicating that a subject is experiencing symptoms of a potential HAE attack.

If on-demand medication is needed, subjects do not have to hold off / delay the start of the medication to treat the symptoms of the potential HAE attack till after contacting the site.

Note: If additional symptoms are experienced within 24 hours, the symptoms should be entered in the eDiary as "updates." In order to report onset (start) of a new symptom(s), the new symptom(s) must occur at least 24 hours after the resolution of the previously reported symptom(s). HAE symptom resolution is defined as the subject no longer having symptoms of the potential attack.

The following information needs to be reported in the eDiary:

- Date and time of onset of first symptom of potential HAE attack
- Date and time of HAE symptom(s) resolution (defined as the subject no longer having symptoms of an attack)
- Location (s) of HAE symptom(s)
- Confirmation of degree of interference of HAE symptom(s) with the subject's daily activities
- If on-demand HAE medication (s) was used to treat HAE symptoms:
  - Name of medication
  - Date and time of administration
- Confirmation of medical assistance received for the HAE symptoms

The investigator will confirm additional details with the subject related to the HAE symptoms:

- Location of HAE symptom(s)
- Start / end date / time of symptom(s)
- Dose(s) of on-demand medication(s) used
- Route(s) of administration of on-demand medication(s) used
- Self-administered or by parent / legal guardian or trained caregiver on-demand medication(s)? (yes / no)
- Administration of on-demand medication(s) at a study site, home, or emergency room
- Type of medical assistance or intervention provided by a healthcare professional during HAE symptoms, including hospitalization or emergency department visits
- Severity of the attack (based on degree of interference in daily activities, and whether or not the use of on-demand medication and / or medical assistance was needed)

Note: All on-demand medications used between the onset and resolution of HAE symptoms need to be recorded.

2.3 Hereditary Angioedema Symptoms Indicative of an HAE Attack

An HAE attack must be associated with at least 1 symptom / location or any of combined multiple symptoms / locations, as listed on Table 8 below. These symptoms may develop concurrently or consecutively, typically within 24 hours. The list of symptoms below is not exhaustive, and it is meant to assist the investigator / delegate in identifying HAE attack-related symptoms and their indicative locations.

Table 8: Hereditary Angioedema Symptom / Location Associated with a Hereditary Angioedema Attack

	Peripheral Attack Symptoms (Cutaneous)	**Abdominal Attack Symptoms**	**Laryngeal Attack Symptoms**
Locations	• Head • Face (external): lips, nose, cheeks, or eyes • Neck • Arms / hands • Chest, shoulder, or back • External abdominal area • External genitourinary areas (buttocks) • Legs / feet • Others	• Internal abdomen (including, but not limited to, the intestine, the bladder, and / or testicles or uterus) • Internal genitourinary (including, but not limited to, the penis and / or scrotum, or the labia and / or vulva)	Face internal or upper airway / throat: • Tongue / palate / inside mouth • Nasal cavity • Throat / voice box • Uvula • Larynx
Symptoms	• Pain / discomfort • Skin swelling • Itching / irritation • Tight skin • Burning • Redness / rash	• Pain / cramping / discomfort • Vomiting / nausea • Abdominal swelling / bloating / tightness / hard stomach • Diarrhea • Gassy • Low blood pressure • Pass out / feel dizzy	• Difficulty breathing (dyspnea), speaking, or swallowing • Voice change • Stridor / wheezing • Throat tightening • Turning blue

2.4 Attack Assessment / Confirmation by the Investigator

The investigator or delegate at each site will review the HAE symptoms reported by the subject in the eDiary and confirm an HAE attack(s) if applicable. It is recommended that the sites limit the number of experienced individuals responsible for assessing subject-reported symptoms to 1 or 2 individuals, where 1 of them should be the investigator. The assessors must be experienced with HAE and familiar with the study subject's disease history.

Each time the investigator / delegate contacts the subject or at a site visit, he / she will review the subject's eDiary entries. Additionally, the subject will be reminded to have his / her eDiary entries up-to-date and to check that symptoms indicative of an HAE attack are documented as instructed. The investigator / delegate may ask additional probing questions about the HAE symptoms experienced by the subject to assist his / her assessment of the symptoms and rule out if there are any possible alternative etiologies of the symptoms, eg, whether only prodromal symptoms were experienced and / or if anything is different from previous experiences.

Each individual HAE attack must be associated with at least 1 symptom or location but may be associated with multiple symptoms. These symptoms may develop concurrently or consecutively within 24 hours. If the investigator confirms an HAE attack, this should be reported in the Case Report Form (CRF) as a single HAE attack, including the symptom(s) associated with the attack. If there has been a completely symptom-free 24-hour minimum separation between the resolution of the prior attack and the onset of next attack, this new set of symptoms would constitute a new event and should be reported as a separate single attack if the investigator confirms the HAE attack.

The investigator will determine if the symptoms reported by the subject did not represent an HAE attack, eg, if the symptoms are not typical of an attack or if there is a more likely alternative cause for the symptoms, or if the symptoms did not resolve following the administration of the on-demand medication. Examples are throat irritation due to an upper respiratory illness or abdominal discomfort due to gastrointestinal upset.

In an effort to maintain consistency across data collection and analysis within this HAE prophylaxis development program, the following recommendations should be followed:

- The presence of prodromal symptoms by themselves are not considered as HAE attacks.
- Subject-reported use of on-demand medication to treat the prodromal symptoms by itself will not be confirmation that an HAE attack occurred.
- Any use of on-demand medication associated with prodromal symptoms only will be reported as concomitant medication in the CRF and not as an HAE on-demand medication.

HAE symptoms that are confirmed as HAE attacks by the investigator or delegate will be recorded in the CRF (see Section 2.4.1) as such and will be used for the efficacy analysis. All HAE symptoms reported by the subject will be displayed in a by-subject listing. Note that the assessment and outcome need to also be recorded in the subject's medical records.

Symptoms Reported as Adverse Events

The investigator or designee will evaluate the symptom data entered in the eDiary by the subject using the standardized set of requirements to determine if the symptoms reported constitute an HAE attack or not. If the investigator confirms the symptoms as an HAE attack, then the HAE attack will be reported in the CRF. If the assessment of the symptoms is not confirmed as an HAE attack, then the etiology of the symptoms must be reported and recorded as an adverse event.

2.4.1 Documenting Investigator-confirmed Attacks

Accurate and complete documentation of investigator-confirmed HAE attacks is important for the study as it will be used for the study primary endpoint analysis. All HAE attack information should be substantiated by supporting documentation and medical records.

The site should record the following information on each attack in the CRF:

- Start date and time of an attack
- End date and time of an attack
- Location(s) of HAE symptoms
- HAE symptom description
- HAE attack severity evaluation (refer to Section 2.4.1.3)
- Use of on-demand treatment (if yes, enter the following information in HAE treatment form):
  - Name of on-demand medication
  - Dose(s) of on-demand medication(s) used
  - Route(s) of administration of on-demand medication(s) used
  - Start date and time of administration(s) of on-demand medication(s) used
  - Select the identification number of the HAE attack the on-demand treatment was given for (to be selected from a list) in the CRF
  - Administration of on-demand medication(s) at a study site, home, emergency room

2.4.1.1 Attack Duration

The duration of an HAE attack will be reported by the investigator / delegate considering all available medical information, including the onset of first symptom and resolution of last of symptom of each attack entered in the eDiary. Unless there has been a completely symptom-free 24-hour minimum separation between the onset and resolution of all symptoms, a single HAE attack will be documented on the basis of the earliest start and the latest end date of symptoms in the anatomic locations listed.

2.4.1.2 Attack Location

HAE attacks can occur in any anatomical location or multiple locations of the body, and these locations are highly variable. An HAE attack may manifest itself in multiple anatomic locations. For example, swelling of the hand and abdomen may occur as symptoms of a single attack if they are temporally associated (ie, occurring at the same time or occurring within overlapping periods within 24 hours). Unless there has been a completely symptom-free 24-hour minimum separation between the onset of new symptom and resolution of prior symptoms in any / all location(s), a single HAE attack will be documented with all relevant locations listed in the CRF.

2.4.1.3 Attack Severity

The severity of each HAE attack (ie, mild, moderate, or severe) will be assessed by the investigator or designee based on the subject's description of the attack. The severity over the time that the attack develops, progresses, and resolves can range from mild to severe. The overall attack severity will reflect the maximum intensity of the attack, as assessed by the investigator.

All attacks regardless of the severity should be associated with perceivable swelling and / or discomfort. Further qualifiers for attack severity are described below. Note that these may vary between subjects and attacks.

- Mild
  - The use of HAE on-demand medication to treat the attack may not be necessary.
  - Other concomitant medication (eg, analgesics) may be used to treat attack symptoms.
- Moderate
  - The HAE attack causes daily activities to be difficult.
  - Some assistance may be needed to complete daily activities.
  - The use of HAE on-demand medication to treat the attack is probable.
- Severe
  - The HAE attack causes marked limitation of daily activities.
  - Medical assistance and intervention may be required, including at clinic emergency room visit or hospitalization.
  - HAE on-demand medication is used to treat the attack.