CLINICAL STUDY PROTOCOL

alpha-star

Study Title:	A Phase 1b/2 Single and Multiple Dose Study to Assess the Safety, Tolerability, Clinical Activity, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of STAR-0215 in Participants with Hereditary Angioedema (The ALPHA-STAR Trial)
Study Number:	STAR-0215-201
Study Phase:	Phase 1b/2
Product Name:	STAR-0215
IND Number:	156585
EUCT Number:	2022-502953-32
Indication:	Hereditary Angioedema
Sponsor:	Astria Therapeutics, Inc. 75 State Street Suite 1400 Boston, Massachusetts, United States of America 02109
Sponsor Contact:	Telephone: +1-617-349-1971 Fax: +1-617-273-2637
Previous Versions:	v04 (21 September 2023) v03 (29 Aug 2023) v02 (11 April 2023) v01 (08 December 2022)
Version:	v05
Version Date:	10 October 2023

INVESTIGATOR'S AGREEMENT

I have read and understand the protocol and agree to conduct the study as outlined. I will conduct the study according to the procedures specified herein, and according to the principles of the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practices, and all applicable national and local regulations and requirements (including Clinical Trials Regulation [Regulation (EU) No 536/2014] and the United States Code of Federal Regulations Title 21). No changes will be made to the study protocol without prior written approval by the Sponsor and the Institutional Review Board (IRB)/independent ethics committee (IEC)/research ethics committee (REC). I understand that the information in this protocol is confidential and must not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MM/YYYY)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition
ACE	Angiotensin-converting enzyme
ADA	Anti-drug (STAR-0215) antibody
AE	Adverse event
[redacted]	[redacted]
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
BMI	Body mass index
C1-INH	C1-esterase inhibitor protein
cHMWK	Cleaved high-molecular-weight kininogen
C_{max}	Maximum drug concentration
CRF	Case report form
CSR	Clinical study report
CRO	Contract research organization
ECG	Electrocardiogram
EDC	Electronic data capture
Fc	Fragment crystallizable
FcRn	Neonatal fragment crystallizable receptor
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HMWK	High-molecular-weight kininogen, the natural substrate of human plasma kallikrein
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IgG1	Immunoglobulin G1

Abbreviation or Specialist Term	Definition
IRB	Institutional Review Board
IV	Intravenous(ly)
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
REC	Research ethics committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SOA	Schedule of assessments
SRC	Safety Review Committee
$t_{½}$	half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum drug concentration
ULN	Upper limit of normal
WBC	White blood cell
YTE	Tyrosine/threonine/glutamate

1. SYNOPSIS

Name of Sponsor/Company:
Astria Therapeutics, Inc.

Name of Investigational Product:
STAR-0215

Name of Active Ingredient:
STAR-0215 is a humanized immunoglobulin G1 (IgG1) kappa light chain monoclonal antibody with a YTE modified fragment crystallizable (Fc) domain

Protocol Number:
STAR-0215-201

Title of Study:
A Phase 1b/2 Single and Multiple Dose Study to Assess the Safety, Tolerability, Clinical Activity, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of STAR-0215 in Participants with Hereditary Angioedema (The ALPHA-STAR Trial)

Study center(s): Up to 25 sites in the United States and globally	**Phase of development:** 1b/2

Objectives and Endpoints:

Primary Objective	**Primary Endpoints**
• To assess the safety and tolerability of subcutaneous (SC) administration of single and multiple doses of STAR-0215 in participants with Type I or Type II hereditary angioedema (HAE)	• Incidence of adverse events (AEs) • Changes in vital signs, electrocardiogram (ECG) findings, physical examination findings, and clinical laboratory evaluations
Secondary Objectives	**Secondary Endpoints**
• To assess the efficacy of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Change from baseline in monthly HAE attack rate • Incidence of HAE attack severity (mild, moderate, and severe) • Duration of HAE attack (shorter than 12 hours, 12 to 24 hours, 24 to 48 hours, and longer than 48 hours) • The number of HAE attacks requiring on-demand therapy • Time to first HAE attack after first and last dosing
• To characterize the pharmacokinetics (PK) of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Concentration of STAR-0215 and the derived PK parameters

• To characterize the pharmacodynamics (PD) of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Change in plasma kallikrein activity
• To assess the immunogenicity of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Formation of anti-drug (STAR-0215) antibodies
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the impact of STAR-0215 on [redacted] of STAR-0215	• Changes from baseline in [redacted] related to [redacted] STAR-0215
• To conduct an exploratory assessment of the effect of STAR-0215 on [redacted] in participants with Type I or Type II HAE	• Changes from baseline in the [redacted]

Methodology and Study Design: STAR-0215-201 is a Phase 1b/2, multicenter, single and multiple dose study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity of STAR-0215 in participants with Type I or Type II HAE.

Properly consented participants will undergo screening assessments according to the inclusion and exclusion criteria and immediately enter the Run-In period. During the Run-In period, HAE attack information will be collected to determine if a participant meets the eligibility requirement of experiencing at least 2 HAE attacks during this time period and to establish a baseline prior to STAR-0215 administration. If a participant has an HAE attack during the Run-In period before Day 1 (first dose of STAR-0215), all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. The Run-In period may be extended after consultation with the Medical Monitor. In Cohorts 2 and 3, if a participant has an HAE attack immediately before the second dose (Day 84 and Day 28, respectively), signs and symptoms of the HAE attack should be improving per participant report prior to STAR-0215 administration; a washout period for on-demand treatment is not required before the second dose is administered.

In Cohort 1, each participant who has completed the Run-In period and is eligible for STAR-0215 administration will receive 1 dose of STAR-0215 on Day 1. When Cohort 1 has completed dosing, the Safety Review Committee (SRC) will review the cohort's cumulative safety data from the Screening/Run-In period through 21 days after dosing. Progression to Cohort 2 dosing will occur if there are no concerning safety signals.

In Cohort 2, each eligible participant will receive 2 doses of STAR-0215, the first on Day 1 and the second on Day 84. When 6 participants in Cohort 2 have received Dose 1, progression to dosing of Cohort 3 will begin.

In Cohort 3, each eligible participant will receive 2 doses of STAR-0215, the first on Day 1 and the second on Day 28.

Provided no safety concerns are noted from a cumulative review of safety data from this study and the ongoing first-in-human (FIH) study (STAR0215-101), [redacted] and [redacted] may be explored in [redacted].

STAR-0215 will be administered SC into the abdomen. There will be 4 participants in Cohort 1, 6 participants in Cohort 2, and 6 participants in Cohort 3. Based on the accumulated safety information and enrollment as continually monitored by the SRC [redacted] (Section 9.12), up to 6 additional participants may be added to Cohort 2 and/or Cohort 3 (maximum of 12 participants each in Cohorts 2 and 3) after the first 6 participants in Cohort 3 have been enrolled. The dose regimens and dose levels for each cohort are outlined in the table below. There is no placebo group in this study.

Cohort	Dose 1		Dose 2		# Participants
	STAR-0215 Dose Level (mg)	Dosing Day	STAR-0215 Dose Level (mg)	Dosing Day	
1	450	1	NA	NA	4
2	600	1	300	84	6; up to 12
3	600	1	600	28	6; up to 12

Abbreviations: NA = not applicable.

Study assessments will be performed in all cohorts through 6 months after the last dose of STAR-0215 (Day 168 in Cohort 1, Day 251 in Cohort 2, and Day 195 in Cohort 3). At this time, participants who are willing and eligible to consent can begin participation in the long-term open label extension study (STAR-0215-202). For any participants who do not enroll in the long-term open label extension study, monitoring will be performed through [redacted] months after the last dose of STAR-0215 in all cohorts (Day [redacted] in Cohort 1, Day [redacted] in Cohort 2, and Day [redacted] in Cohort 3) through regular contacts and scheduled site visit. Safety assessments (including AEs, vital signs, ECGs, physical examinations, clinical laboratory evaluations, and pregnancy testing), and efficacy, PK, PD, immunogenicity, biomarker, and [redacted] may be conducted at scheduled site visits.

Hereditary Angioedema Attack Management:

If a participant experiences HAE attacks during the study, they will be permitted standard-of-care on-demand treatment as prescribed by their physician.

Number of participants (planned):

Up to 28 participants with HAE are planned.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. At least 18 years of age at the time of Screening.
2. Willing and able to read, understand, and sign the institutional review board/independent ethics committee/research ethics committee approved informed consent form.
3. Documented diagnosis of HAE (Type I or II). All of the following must be met:
   a. Documented clinical history consistent with HAE (e.g. SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).

b. C1-esterase inhibitor protein (C1-INH) antigen or functional level less than 40% of the normal level. Participants with antigen or functional C1-INH level 40% to 50% of the normal level may be eligible if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Testing for C1-INH and C4 will be performed at Screening. Historical test results for C1-INH may be used to confirm eligibility if the screening C1-INH antigen test or functional level or C4 level laboratory values are inconclusive, after discussion with the medical monitor.

c. Age at reported onset of first angioedema symptoms 30 years of age or younger, or a family history consistent with HAE Type I or II.

4. Agree not to receive a dose of any vaccine within 7 days before or after STAR-0215 administration.
5. Participants of childbearing potential must have a negative serum pregnancy test at Screening, must be not pregnant or breastfeeding at Screening, and agree to use one of the protocol defined forms of highly effective contraception during the study and for a total of [redacted] months after the last dose of STAR-0215.

   Note: Participants who are not capable of becoming pregnant (e.g. defined as surgically sterile or post-menopausal), per the protocol, are not required to use any form of contraception during the study.
6. Participants capable of producing sperm who have partners of childbearing potential must agree to use one of the protocol defined forms of contraception during the study, unless the participant is azoospermic or their partner is surgically sterile (as defined in the protocol).
7. Agree not to donate or store sperm or engage in any other activity intended to produce sperm for the purpose of insemination during the study, unless such sperm were collected before the administration of the first dose.
8. Agree not to donate or store eggs or undergo assisted reproductive or fertility treatment during the study and for a total of [redacted] months after the last dose of STAR-0215.
9. Experienced at least 2 HAE attacks during the Run-In period, as confirmed by an investigator based on meeting the protocol-specified definition of an HAE attack.

Exclusion Criteria:

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
2. Any exposure to an investigational drug or device within 90 days or 5 half-lives (whichever is longer) prior to Screening.
3. Exposure to a monoclonal antibody or recombinant protein bearing a Fc domain (such as a soluble receptor-Fc fusion protein) within 5 half-lives prior to Screening.
4. Use of therapies prescribed for the prevention of HAE attacks prior to Screening:
   a. lanadelumab within 90 days
   b. berotralstat within 21 days
   c. all other prophylactic therapies, within 7 days
5. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as hormonal contraceptives or hormone replacement therapy) within 28 days prior to Screening. (Topical estrogens applied externally or intravaginally are allowed, provided the Investigator and Medical Monitor agree that the systemic absorption is minimal and unlikely to have health impacts to the participant.)

6. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 7 days prior to Screening.
7. History of chronic viral infection with positive test for HIV or hepatitis B surface antigen. History of hepatitis C virus (HCV) that has not been adequately cured.
8. Active liver disease (e.g. acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).
9. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) above 3 times the upper limit of normal (ULN), or aspartate aminotransferase (AST) above 3 times the ULN, or total bilirubin above 1.5 times the ULN (unless participant has known Gilbert's Syndrome and a total bilirubin > 3mg/dL).
10. History of drug or alcohol abuse in the 12 months before Screening.
11. Participant has ongoing cancer, except for the following: basal cell carcinoma of the skin. Ongoing cancer is defined as requiring therapy or intervention to treat or prevent recurrence/progression of disease.
12. Known sensitivity to the ingredients in STAR-0215.
13. Participant is employed by or is an immediate family member of the Sponsor or study site staff or who is committed to an institution by virtue of an order issued by the judicial or the administrative authorities.
14. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g. a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

Investigational product, dosage, and mode of administration:

STAR-0215 drug product is supplied as a [redacted]. It will be administered in a 300, 450, or 600 mg dose.

Duration of treatment:

Individual participants will receive 1 dose of STAR-0215 (Cohort 1; Day 1) or 2 doses of STAR-0215 (Cohort 2; Days 1 and 84 and Cohort 3; Days 1 and 28).

Duration of study:

The duration of study participation for each participant, including the Screening and Run-In period, is up to [redacted] or [redacted] days in Cohorts 1, 2, and 3, respectively. The study is composed of 3 periods as follows:

- Screening/Run-In: at least 56 days
- Treatment Period: Individual participants will receive STAR-0215 on Day 1 (Cohort 1), Day 1 and 84 (Cohort 2), or Day 1 and 28 (Cohort 3).
- Follow-up Period: approximately 6 months after the last dose of STAR-0215 (Day 168 for Cohort 1, Day 251 for Cohort 2, and Day 195 for Cohort 3). At this time, participants who are willing and eligible to consent can begin participation in the long-term open label extension study (STAR-0215-202).
- Follow-up Period: For participants who do not enroll in the long-term open label extension study, safety monitoring will be performed through [redacted] months after the last dose of STAR-0215 in all cohorts (Day [redacted] in Cohort 1, Day [redacted] in Cohort 2, and Day [redacted] in Cohort 3).

Reference therapy, dosage, and mode of administration:

A reference therapy is not included in this study.

Criteria for evaluation

Safety:

Safety will be assessed by AEs, vital sign assessments, ECG findings, physical examination findings, and clinical laboratory evaluations, including chemistry, hematology, coagulation, and urinalysis.

Efficacy:

Efficacy will be assessed by weekly collection of investigator-confirmed HAE attacks and accompanying HAE attack information.

Pharmacokinetic:

Blood samples will be collected to measure the concentration of STAR-0215 before and after STAR-0215 administration.

Pharmacodynamic:

Blood samples will be collected to assess plasma kallikrein inhibition associated with STAR-0215 administration.

Immunogenicity Analysis:

Blood samples will be collected to measure anti-drug (STAR-0215) antibodies.

Sample size considerations:

This is the first time STAR-0215 is being administered to participants with HAE. No formal sample size calculations have been performed.

Up to 28 participants will be dosed in this study. This is considered adequate to characterize the safety, tolerability, efficacy, PK, PD, and immunogenicity of STAR-0215.

Statistical methods:

Data will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) or frequency counts and percentages, as appropriate. Results will be presented by cohort. Details regarding the management of all data and statistical methodology, including an explanation of the analyses of exploratory endpoints and imputation of missing data, will be included in the statistical analysis plan (SAP), which will be finalized prior to database lock.

Interim Analyses

In preparation for future clinical development of STAR-0215 and subsequent study planning, [redacted] interim analyses of data in accumulating cohorts are planned (see table below). The [redacted] interim analysis will occur after the [redacted] in [redacted] reaches the [redacted] visit and will include all available data from [redacted]. The [redacted] interim analysis will occur after the [redacted] in [redacted] reaches [redacted] of STAR-0215 (the [redacted] visit) and will include all available data from [redacted]. Details of any additional interim analyses that may be conducted as warranted will be specified in the SAP. At each interim analysis the Sponsor will review the accumulated safety, efficacy, PK, PD, and immunogenicity data. If no safety concerns are noted following interim analyses, efficacy, PK, PD, and immunogenicity results may inform the decision to add additional participants to Cohorts 2 or 3 (up to a total of 12 in each) and/or [redacted] exploring [redacted] and [redacted]. All analyses will be predefined in the SAP as applicable.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] reaches the [redacted] visit	All available cumulative safety, PK, PD, immunogenicity, and efficacy data through the [redacted] visit in [redacted] and the [redacted] visit in [redacted]	• Potential addition of up to 6 participants to Cohort 2 (maximum of 12 participants total) • [redacted] to [redacted] • [redacted] study [redacted]
[redacted]	[redacted] reaches [redacted] after [redacted] (the [redacted] visit)	All available cumulative safety, PK, PD, immunogenicity, and efficacy data through the [redacted] visit in the [redacted] visit in [redacted], and the [redacted] visit in [redacted]	• Potential addition of up to 6 participants to Cohort 2 and/or Cohort 3 (maximum of 12 participants total in Cohorts 2 and 3) [redacted] to [redacted] • [redacted] study [redacted] • Inform Sponsor's decision-making regarding [redacted]

1.1. Schedules of Assessments

Table 1: Schedule of Assessments: Cohort 1

	Screen-ing	Run-In[1]	Treatment and Follow-up															
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ±1**	**14 ±2**	**28 ±2**	**56 ±3**	**84 ±3**	**112 ±5**	**140 ±5**	**168[15] ±7 or ET**	**[redacted][16] ±7**	**[redacted][16] ±7**	**[redacted][16] ±7**	**[redacted][16] ±7**	**[redacted][17] ±7 or ET**
			Pre	**Post**														
Study Assessments																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical History/ Demographics	X																	
FSH[2]	X																	
Virus Serology (HBsAg, HCV, and HIV)	X																	
C1-INH (level or function)	X																	
C4	X																	
Confirm Eligibility			X															
STAR-0215 Administration			X															
Pregnancy Test[3]	S		U					S	S	S			S					S
12-Lead ECG[4]	X		X			X	X	X	X	X			X					X
Hematology[5]	X		X			X	X	X	X	X	X	X	X					X
Chemistry[6]	X		X			X	X	X	X	X	X	X	X					X
Coagulation[7]	X		X			X	X	X	X	X	X	X	X					X
Urinalysis[8]	X		X			X	X	X	X	X	X	X	X					X

Table 1: Schedule of Assessments: Cohort 1

	Screen-ing	Run-In[1]	Treatment and Follow-up														
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ±1**	**14 ±2**	**28 ±2**	**56 ±3**	**84 ±3**	**112 ±5**	**140 ±5**	**168[15] ±7 or ET**	[redacted][16] ±7	[redacted][16] ±7	[redacted][16] ±7	[redacted][16] ±7	[redacted][17] ±7 or ET
			Pre	**Post**														
Vital Signs[9]	X		X	X[9]	X	X	X	X	X	X	X	X	X					X
Physical Examination (including Height/Weight/BMI)[10]	X		X	X[10]	X	X	X	X	X	X	X	X	X					X
HAE Attack Information	X	Weekly contacts[11]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (±1) 21, 35, 42, 49, 63, 70, 77, 91, 98, 105, 119, 126, 133, 147, 154, and 161											
Pharmacokinetic Blood Sample			X	X[12]	X	X	X	X	X	X	X	X	X					
Pharmacodynamic Blood Sample (plasma kallikrein)	X		X	X[12]	X	X	X	X	X	X	X	X	X					
Immunogenicity (anti-drug antibody)			X				X	X	X	X	X	X	X					
[redacted] (serum/plasma)	X		X			X		X	X	X			X					
Transcriptomics (RNA PAXgene®)	X		X			X		X	X	X			X					
Optional Pharmacogenetics/-omics (DNA PAXgene®)[13]			X					X		X			X					
[redacted]			X					X	X	X	X	X	X					
Prior and Concomitant Medications	X	Weekly	X	X	X	X	Scheduled site visits and weekly contacts on:							X	X	X	X	X

Table 1: Schedule of Assessments: Cohort 1

	Screening	Run-In[1]	Treatment and Follow-up														
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ±1**	**14 ±2**	**28 ±2**	**56 ±3**	**84 ±3**	**112 ±5**	**140 ±5**	**168[15] ±7 or ET**	[redacted][16] ±7	[redacted][16] ±7	[redacted][16] ±7	[redacted][16] ±7	[redacted][17] ±7 or ET
			Pre	**Post**														
		contacts[11]					Days (±1) 21, 35, 42, 49, 63, 70, 77, 91, 98, 105, 119, 126, 133, 147, 154, and 161											
Adverse Events[14]	X	Weekly contacts[11]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (±1) 21, 35, 42, 49, 63, 70, 77, 91, 98, 105, 119, 126, 133, 147, 154, and 161							X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; C1-INH = C1-esterase inhibitor protein; CBC = complete blood count; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HAE = hereditary angioedema; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PD = pharmacodynamic; PK = pharmacokinetic; Pre = pre-dose; Post = post-dose; [redacted]; S = serum; U = urine.

Note: If a participant presents to the study site with symptoms of an HAE attack during the study (Screening through the 6 month follow-up after the last dose of STAR-0215) and it does not coincide with a scheduled site visit, HAE attack information, prior and concomitant medications, AEs, targeted physical examination, vital signs, and blood samples for C1-INH, PK (excluding Run-In period), plasma kallikrein, serum and plasma biomarkers, and immunogenicity (excluding Run-In period) should be collected during that unscheduled visit.

1 If a participant has an HAE attack during the Run-In period before Day 1, all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. The Run-In period may be extended after consultation with the Medical Monitor.

2 FSH testing is only performed if needed to confirm a postmenopausal state (i.e. no menses for 12 months without an alternative medical cause) in participants not using hormonal contraception or hormone replacement therapy.

3 Pregnancy testing performed only for participants of childbearing potential.

4 All 12-lead ECG assessments must be performed before blood sample collection. Assessment is to be performed after the participant has been in a supine position for at least 5 minutes.

5 The hematology assessment will be a CBC with differential.

6 The chemistry assessment includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, uric acid, blood urea nitrogen, creatinine, calcium, sodium, potassium, chloride, carbon dioxide, phosphate, magnesium, cholesterol, triglycerides, and creatine phosphokinase.

7 The coagulation assessment includes international normalized ratio, activated partial thromboplastin time, and prothrombin time.

8 The urinalysis includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin, and microscopy (if urinalysis is abnormal).

9 Vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) will be taken prior to blood sample collection and after the participant has been in a supine position for at least 5 minutes. Vital signs will be taken pre-dose within 4 hours of dosing and 4 hours (±30 minutes) post-dose.

10 Height collected at Screening only. Complete physical examinations will be performed at Screening and the post-dose timepoint on Day 1. All other physical examinations will be a targeted evaluation of general appearance, skin, abdomen, and cardiovascular and respiratory systems. The Day 1 post-dose physical examination will be performed at 4 hours (±30 minutes).

11 During the Run-In period, the weekly contacts will be conducted on Days (±1) -49, -42, -35, -28, -21, -14, and -7. HAE attacks will be collected from the time of informed consent.
12 On Day 1, PK and PD blood samples will be collected pre-dose and 4 hours ±15 minutes post-dose.
13 Blood sample collection for pharmacogenetics/-omics testing is optional and requires additional participant consent.
14 All AEs will be recorded from the time of informed consent through the final study visit.
15 For participants who do enroll in the long-term open label extension study, this will serve as the final visit with end of study assessments.
16 Remote visits to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.
17 On-site visit to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.

Table 2: Schedule of Assessments: Cohort 2

	Scree-ning	Run-In[1]	Treatment and Follow-up																					
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ± 1**	**14 ±2**	**28 ±2**	**56 ±3**	**84±3[1]**		**85[2]**	**90[2] ±1**	**97[2] ±2**	**111[2] ±3**	**139[2] ±5**	**167[2] ±5**	**209[2] ±5**	**251[2,16] ±7 or ET**	**[17] ±7**	**[17] ±7**	**[17] ±7**	**[17] ±7**	**[18] ±7 or ET**
			Pre	**Post**						**Pre**	**Post**													
Study Assessments																								
Informed Consent	X																							
Inclusion/ Exclusion Criteria	X																							
Medical History/ Demographics	X																							
FSH[3]	X																							
Virus Serology (HbsAg, HCV, and HIV)	X																							
C1-INH (level or function)	X																							
C4	X																							
Confirm Eligibility			X																					
STAR-0215 Administration			X							X														
Pregnancy Test[4]	S		U					S	S	U					S	S	S		S					S
12-Lead ECG[5]	X		X			X	X	X	X	X			X	X	X	X	X		X					X
Hematology[6]	X		X			X	X	X	X	X			X	X	X	X	X	X	X					X
Chemistry[7]	X		X			X	X	X	X	X			X	X	X	X	X	X	X					X

Table 2: Schedule of Assessments: Cohort 2

	Scree-ning	Run-In[1]	Treatment and Follow-up																					
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ± 1**	**14 ±2**	**28 ±2**	**56 ±3**	**84±3[1]**		**85[2]**	**90[2] ±1**	**97[2] ±2**	**111[2] ±3**	**139[2] ±5**	**167[2] ±5**	**209[2] ±5**	**251[2,16] ±7 or ET**	**[17] ±7**	**[17] ±7**	**[17] ±7**	**[17] ±7**	**[18] ±7 or ET**
			Pre	**Post**						**Pre**	**Post**													
Coagulation[8]	X		X			X	X	X	X	X			X	X	X	X	X	X	X					X
Urinalysis[9]	X		X			X	X	X	X	X			X	X	X	X	X	X	X					X
Vital Signs[10]	X		X	X[10]	X	X	X	X	X	X	X[10]	X	X	X	X	X	X	X	X					X
Physical Examination (including Height/Weight/ BMI)[11]	X		X	X[11]	X	X	X	X	X	X	X[11]	X	X	X	X	X	X	X	X					X
HAE Attack Information	X	Weekly contacts [12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 35, 42, 49, 63, 70, 77, 104, 118, 125, 132, 146, 153, 160, 174, 181, 188, 195, 202, 216, 223, 230, 237, and 244																	
Pharmacokinetic Blood Sample			X	X[13]	X	X	X	X	X	X	X[13]	X	X	X	X	X	X	X	X					
Pharmacodynamic Blood Sample (plasma kallikrein)	X		X	X[13]	X	X	X	X	X	X	X[13]	X	X	X	X	X	X	X	X					
Immunogenicity (anti-drug antibody)			X				X	X	X	X					X		X		X					
[redacted] (serum/plasma)	X		X			X		X	X	X			X		X	X	X	X	X					
Transcriptomics (RNA PAXgene®)	X		X			X		X	X	X			X		X	X	X	X	X					

Table 2: Schedule of Assessments: Cohort 2

	Scree-ning	Run-In[1]	Treatment and Follow-up																		
Study Day Window (days)	-56	-56 to -1	1 Pre	1 Post	2	7 ± 1	14 ±2	28 ±2	56 ±3	84±3[1] Pre	84±3[1] Post	85[2]	90[2] ±1	97[2] ±2	111[2] ±3	139[2] ±5	167[2] ±5	209[2] ±5	251[2,16] ±7 or ET	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][18] ±7 or ET
Optional Pharmacogenetics /-omics (DNA PAXgene®)[14]			X					X		X					X		X		X					
[redacted]			X					X	X	X					X	X	X	X	X					
Prior and Concomitant Medications	X	Weekly contacts[12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 35, 42, 49, 63, 70, 77, 104, 118, 125, 132, 146, 153, 160, 174, 181, 188, 195, 202, 216, 223, 230, 237, and 244													X	X	X	X	X
Adverse Events[15]	X	Weekly contacts[12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 35, 42, 49, 63, 70, 77, 104, 118, 125, 132, 146, 153, 160, 174, 181, 188, 195, 202, 216, 223, 230, 237, and 244													X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; C1-INH = C1-esterase inhibitor protein; CBC = complete blood count; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HAE = hereditary angioedema; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PD = pharmacodynamic; PK = pharmacokinetic; Pre = pre-dose; Post = post-dose[redacted] S = serum; U = urine.

Note: If a participant presents to the study site with symptoms of an HAE attack during the study (Screening through the 6-month follow-up after the last dose of STAR-0215) and it does not coincide with a scheduled site visit, HAE attack information, prior and concomitant medications, AEs, targeted physical examination, vital signs, and blood samples for C1-INH, PK (excluding Run-In period), plasma kallikrein, serum and plasma biomarkers, and immunogenicity (excluding Run-In period) should be collected during that unscheduled visit.

1 If a participant has an HAE attack during the Run-In period before Day 1, all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. The Run-In period may be extended after consultation with the Medical Monitor. If a participant has an HAE attack immediately before the second dose (Day 84), signs and symptoms of the HAE attack should be improving per participant report prior to STAR-0215 administration; a washout period for on-demand treatment is not required before the second dose is administered.

2 The Day 85 visit must occur 24 hours after the Day 84 visit. The visits subsequent to the second dose of STAR-0215 must be scheduled from the actual day of the second dose, e.g. Day 90 is 6 (±1) days after dosing, Day 97 is 13 (±2) days after dosing, Day 111 is 27 (±3) days after dosing, etc.

3 FSH testing is only performed if needed to confirm a postmenopausal state (i.e. no menses for 12 months without an alternative medical cause) in participants not using hormonal contraception or hormone replacement therapy.

4 Pregnancy testing performed only for participants of childbearing potential.

5 All 12-lead ECG assessments must be performed prior to blood sample collection. Assessment is to be performed after the participant has been in a supine position for at least 5 minutes.
6 The hematology assessment will be a CBC with differential.
7 The chemistry assessment includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, uric acid, blood urea nitrogen, creatinine, calcium, sodium, potassium, chloride, carbon dioxide, phosphate, magnesium, cholesterol, triglycerides, and creatine phosphokinase.
8 The coagulation assessment includes international normalized ratio, activated partial thromboplastin time, and prothrombin time.
9 The urinalysis includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin, and microscopy (if urinalysis is abnormal).
10 Vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) will be taken prior to blood sample collection and after the participant has been in a supine position for at least 5 minutes. Vital signs will be taken pre-dose within 4 hours of dosing and 4 hours (±30 minutes) post-dose.
11 Height collected at Screening only. Complete physical examinations will be performed at Screening and the post-dose timepoints on days of STAR-0215 administration. All other physical examinations will be a targeted evaluation of general appearance, skin, abdomen, and cardiovascular and respiratory systems. The post-dose physical examination on the days of STAR-0215 administration will be performed at 4 hours (±30 minutes).
12 During the Run-In period, the weekly contacts will be conducted on Days (±1) -49, -42, -35, -28, -21, -14, and -7. HAE attacks will be collected from the time of informed consent.
13 On days of STAR-0215 administration, PK and PD blood samples will be collected pre-dose and 4 hours ±15 minutes post-dose.
14 Blood sample collection for pharmacogenetics/-omics testing is optional and requires additional participant consent.
15 All AEs will be recorded from the time of the informed consent through the final study visit.
16 For participants who do enroll in the long-term open label extension study, this will serve as the final visit with end of study assessments.
17 Remote visits to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.
18 On-site visit to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.

Table 3: Schedule of Assessments: Cohort 3

	Screen-ing	Run-In[1]	Treatment and Follow-up																			
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ± 1**	**14 ±2**	**28±2[1]**		**29[2]**	**34[2] ±1**	**41[2] ±2**	**55[2] ±3**	**83[2] ±5**	**111[2] ±5**	**153[2] ±5**	**195[2,16] ±7 or ET**	[17] **±7**	[17] **±7**	[17] **±7**	[17] **±7**	[18] **±7 or ET**
			Pre	**Post**				**Pre**	**Post**													
Study Assessments																						
Informed Consent	X																					
Inclusion/ Exclusion Criteria	X																					
Medical History/ Demographics	X																					
FSH[3]	X																					
Virus Serology (HBsAg, HCV, and HIV)	X																					
C1-INH (level or function)	X																					
C4	X																					
Confirm Eligibility			X																			
STAR-0215 Administration			X					X														
Pregnancy Test[4]	S		U					U					S	S	S		S					S
12-Lead ECG[5]	X		X			X	X	X			X	X	X	X	X		X					X
Hematology[6]	X		X			X	X	X			X	X	X	X	X	X	X					X
Chemistry[7]	X		X			X	X	X			X	X	X	X	X	X	X					X
Coagulation[8]	X		X			X	X	X			X	X	X	X	X	X	X					X
Urinalysis[9]	X		X			X	X	X			X	X	X	X	X	X	X					X
Vital Signs[10]	X		X	X[10]	X	X	X	X	X[10]	X	X	X	X	X	X	X	X					X

Table 3: Schedule of Assessments: Cohort 3

	Screen-ing	Run-In[1]	Treatment and Follow-up																		
Study Day Window (days)	**-56**	**-56 to -1**	**1**		**2**	**7 ± 1**	**14 ±2**	**28±2[1]**		**29[2]**	**34[2] ±1**	**41[2] ±2**	**55[2] ±3**	**83[2] ±5**	**111[2] ±5**	**153[2] ±5**	**195[2,16] ±7 or ET**	[17] **±7**	[17] **±7**	[17] **±7**	[17] **±7**	[18] **±7 or ET**
			Pre	**Post**				**Pre**	**Post**													
Physical Examination (including Height/Weight/ BMI)[11]	X		X	X[11]	X	X	X	X	X[11]	X	X	X	X	X	X	X	X					X
HAE Attack Information	X	Weekly contacts [12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 48, 62, 69, 76, 90, 97, 104, 118, 125, 132, 139, 146, 160, 167, 174, 181, 188																
Pharmacokinetic Blood Sample			X	X[13]	X	X	X	X	X[13]	X	X	X	X	X	X	X	X					
Pharmacodynamic Blood Sample (plasma kallikrein)	X		X	X[13]	X	X	X	X	X[13]	X	X	X	X	X	X	X	X					
Immunogenicity (anti-drug antibody)			X				X	X					X		X		X					
[redacted] (serum/plasma)	X		X			X		X			X		X	X	X	X	X					
Transcriptomics (RNA PAXgene®)	X		X			X		X			X		X	X	X	X	X					
Optional Pharmacogenetics /-omics (DNA PAXgene®)[14]			X					X					X		X		X					
[redacted]			X					X					X	X	X	X	X					

Table 3: Schedule of Assessments: Cohort 3

	Screening	Run-In[1]	Treatment and Follow-up																	
Study Day Window (days)	-56	-56 to -1	1		2	7 ± 1	14 ±2	28±2[1]		29[2]	34[2] ±1	41[2] ±2	55[2] ±3	83[2] ±5	111[2] ±5	153[2] ±5	195[2,16] ±7 or ET	[17] ±7	[17] ±7	[17] ±7	[17] ±7	[18] ±7 or ET
			Pre	Post				Pre	Post													
Prior and Concomitant Medications	X	Weekly contacts[12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 48, 62, 69, 76, 90, 97, 104, 118, 125, 132, 139, 146, 160, 167, 174, 181, 188											X	X	X	X	X
Adverse Events[15]	X	Weekly contacts[12]	X	X	X	X	Scheduled site visits and weekly contacts on: Days (± 1) 21, 48, 62, 69, 76, 90, 97, 104, 118, 125, 132, 139, 146, 160, 167, 174, 181, 188											X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; C1-INH = C1-esterase inhibitor protein; CBC = complete blood count; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HAE = hereditary angioedema; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PD = pharmacodynamic; PK = pharmacokinetic; Pre = pre-dose; Post = post-dose; [redacted] S = serum; U = urine.

Note: If a participant presents to the study site with symptoms of an HAE attack during the study (Screening through the 6-month follow-up after the last dose of STAR-0215) and it does not coincide with a scheduled site visit, HAE attack information, prior and concomitant medications, AEs, targeted physical examination, vital signs, and blood samples for C1-INH, PK (excluding Run-In period), plasma kallikrein, serum and plasma biomarkers, and immunogenicity (excluding Run-In period) should be collected during that unscheduled visit.

1 If a participant has an HAE attack during the Run-In period before Day 1, all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. The Run-In period may be extended after consultation with the Medical Monitor. If a participant has an HAE attack immediately before the second dose (Day 28), signs and symptoms of the HAE attack should be improving per participant report prior to STAR-0215 administration; a washout period for on-demand treatment is not required before the second dose is administered.

2 The Day 29 visit must occur 24 hours after the Day 28 visit. The visits subsequent to the second dose of STAR-0215 must be scheduled from the actual day of the second dose, e.g. Day 34 is 6 (±1) days after dosing, Day 41 is 13 (±2) days after dosing, Day 55 is 27 (±3) days after dosing, etc.

3 FSH testing is only performed if needed to confirm a postmenopausal state (i.e. no menses for 12 months without an alternative medical cause) in participants not using hormonal contraception or hormone replacement therapy.

4 Pregnancy testing performed only for participants of childbearing potential.

5 All 12-lead ECG assessments must be performed prior to blood sample collection. Assessment is to be performed after the participant has been in a supine position for at least 5 minutes.

6 The hematology assessment will be a CBC with differential.

7 The chemistry assessment includes total protein, albumin, glucose, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, uric acid, blood urea nitrogen, creatinine, calcium, sodium, potassium, chloride, carbon dioxide, phosphate, magnesium, cholesterol, triglycerides, and creatine phosphokinase.

8 The coagulation assessment includes international normalized ratio, activated partial thromboplastin time, and prothrombin time.

9 The urinalysis includes pH, glucose, ketones, blood, specific gravity, nitrite, protein, bilirubin, and microscopy (if urinalysis is abnormal).

10 Vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) will be taken prior to blood sample collection and after the participant has been in a supine position for at least 5 minutes. Vital signs will be taken pre-dose within 4 hours of dosing and 4 hours (±30 minutes) post-dose.

11 Height collected at Screening only. Complete physical examinations will be performed at Screening and the post-dose timepoints on days of STAR-0215 administration. All other physical examinations will be a targeted evaluation of general appearance, skin, abdomen, and cardiovascular and respiratory systems. The post-dose physical examination on the days of STAR-0215 administration will be performed at 4 hours (±30 minutes).
12 During the Run-In period, the weekly contacts will be conducted on Days (±1) -49, -42, -35, -28, -21, -14, and -7. HAE attacks will be collected from the time of informed consent.
13 On days of STAR-0215 administration, PK and PD blood samples will be collected pre-dose and 4 hours ±15 minutes post-dose.
14 Blood sample collection for pharmacogenetics/-omics testing is optional and requires additional participant consent.
15 All AEs will be recorded from the time of the informed consent through the final study visit.
16 For participants who do enroll in the long-term open label extension study, this will serve as the final visit with end of study assessments.
17 Remote visits to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.
18 On-site visit to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.

2. INTRODUCTION

2.1. Background

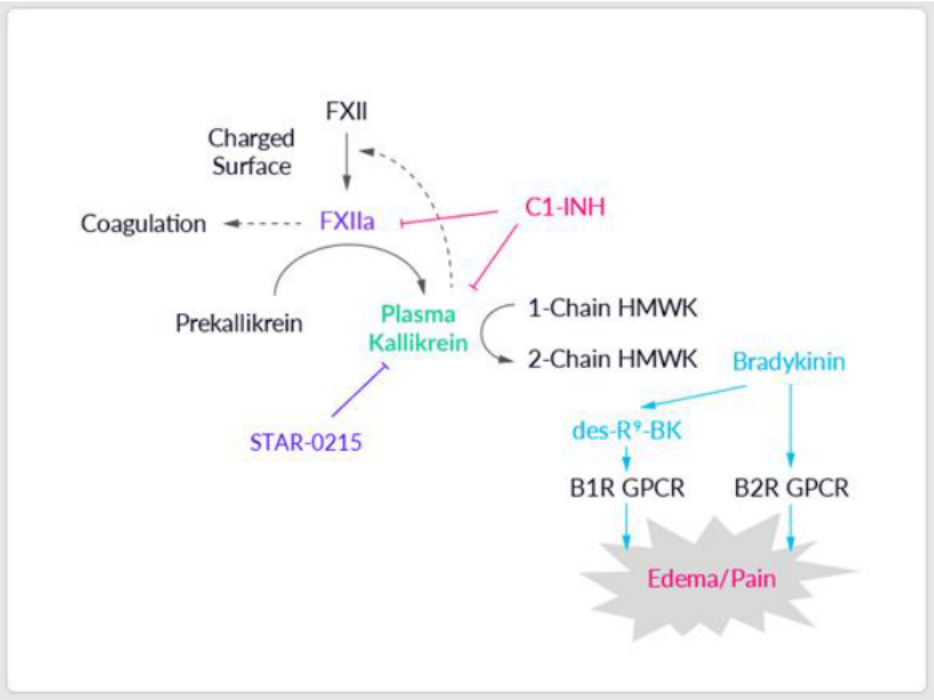
2.1.1. Hereditary Angioedema

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disease characterized by severe, recurrent, unpredictable, often painful, and sometimes life-threatening swelling in the face, limbs, abdomen, and airway (Zuraw 2008).

The majority of HAE cases (Type I and Type II) are caused by mutations in the SERPING1 gene that lead to a reduction in the amount (Type I, approximately 85% of patients) or function (Type II, approximately 15% of patients) of C1-esterase inhibitor protein (C1-INH) encoded by this gene (Zuraw 2008; Busse 2021). The process by which a deficiency in the amount or function of C1-INH leads to HAE is shown in Figure 1. Fully functional C1-INH inhibits the activity of 2 key enzymes in the contact activation system, Factor XIIa and plasma kallikrein: a deficiency in the amount or function of C1-INH results in the unregulated activity of these enzymes (Craig 2012). The uninhibited activity of the contact pathway in Type I and Type II HAE leads to an unchecked and widespread surge in the production of bradykinin by plasma kallikrein, resulting in excessive and pathologic edema and pain (Zeerleder 2016).

The estimated prevalence of Type I and Type II HAE ranges from 1 in 10,000 to 1 in 50,000 with less than an estimated 8,000 patients in the United States and less than an estimated 15,000 patients in Europe (Nzeako 2001; Lumry 2018; Busse 2021). Patients with HAE are typically diagnosed by the age of 20 with the average age of disease onset of approximately 11 years old (Christiansen 2016). Patients typically present with symptoms to the emergency department or to a primary care physician, but limited disease awareness, although improving, often precludes referrals to allergists, immunologists, and HAE specialists for diagnosis. Clinical suspicion of Type I and Type II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are markedly reduced at all times in blood from most patients. The most common comorbidities associated with HAE include cardiovascular disease, hypertension, hyperlipidemia, and autoimmune diseases, particularly systemic lupus erythematosus and thyroid disease (Sundler Bjorkman 2022). In addition, psychiatric symptoms, such as anxiety and depression, are not uncommon but are generally considered to be caused by the burden of the disease (Banerji 2020; Lumry 2020).

Figure 1: Biochemical and Cellular Processes Leading to Hereditary Angioedema



Source: Adapted from Kenniston 2014.
Abbreviations: FXII = Factor XII; FXIIa = activated Factor XII; C1-INH = C1-esterase inhibitor protein; HMWK = high-molecular-weight kininogen; des-R9-BK = des-Arg(9)-bradykinin; B1R GPCR = G-protein-coupled receptor bradykinin receptor 1; B2R GPCR = G-protein-coupled receptor bradykinin receptor 2.

2.1.2. Current Treatment Options for Hereditary Angioedema and Unmet Need

Current therapies can be divided into 2 general groupings: (1) historical and not mechanism based (these include attenuated androgens and antifibrinolytics) and (2) mechanism based (purified plasma derived C1-INH, plasma kallikrein inhibitor, and bradykinin B2-R blocker).

Currently, approved HAE drugs are indicated either for prophylaxis or for on-demand treatment of HAE attacks.

Depending on the geographical location, the following drugs may be available for prophylactic use in patients with HAE: substituted androgen danazol, plasma derived C1-INH products (Cinryze®, Haegarda®/SC Berinert®), plasma kallikrein monoclonal antibody (mAb) inhibitor (Takhzyro® [lanadelumab]), and plasma kallikrein small molecule inhibitor (Orladeyo® [berotralstat]).

Similarly, depending on the geographical location, the following drugs may be available for on-demand use in patients with HAE: plasma derived C1-INH (Berinert®), recombinant protein plasma kallikrein inhibitor (Kalbitor® [ecallantide]), bradykinin receptor antagonist (Firazyr® [icatibant]), and recombinant human C1-INH product (Ruconest®).

Despite the existence of approved therapies, many patients still face a major challenge to achieve a satisfactory treatment strategy to prevent HAE attacks. This is primarily due to patients' variable response to approved medications, which leads to unpredictable and incomplete attack prevention, and that dosing and administration regimens require burdensome and often frequent

procedures. Both patients and physicians report a need for less burdensome, easier to administer treatments (Bouillet 2022).

2.1.3. STAR-0215

STAR-0215 is a humanized immunoglobulin G1 (IgG1) kappa light chain mAb designed to be a highly potent and specific inhibitor of plasma kallikrein, thereby inhibiting the conversion of its substrate high molecular-weight kininogen (HMWK) to cleaved HMWK (cHMWK) and bradykinin. The fragment crystallizable (Fc) domain of STAR-0215 incorporates a 3 amino acid YTE modification designed to enhance pH-dependent neonatal Fc receptor (FcRn) binding and extend circulating half-life ($t_{½}$).

Inhibition of plasma kallikrein by STAR-0215 is expected to reduce the cleavage of HMWK and the formation of bradykinin, thereby preventing the characteristic angioedema in HAE (Figure 1).

With STAR-0215, the goal is to provide a safe and effective preventative treatment, with infrequent dosing, to decrease the burden of disease and the burden of treatment for people with HAE.

2.1.4. Nonclinical Experience

Nonclinical studies have been conducted to evaluate the pharmacology, safety pharmacology, pharmacokinetic (PK), toxicokinetic, and toxicology profiles of STAR-0215. Overall, no safety issues regarding STAR-0215 have been identified to date up to a dose of 100 mg/kg in animals. STAR-0215 presents a nonclinical safety profile with minimal risks and supports clinical development of STAR-0215.

For more details on the nonclinical evaluation of STAR-0215, refer to the latest edition of the Investigator's Brochure (IB).

2.1.4.1. Nonclinical Pharmacology

Primary and secondary pharmacology studies for STAR-0215 demonstrated that STAR-0215 specifically binds and inhibits the activity of its target, plasma kallikrein, without exhibiting off-target activity or enhanced potential for effector function. Target engagement in vivo was demonstrated following administration of STAR-0215 in normal cynomolgus monkeys as measured by the rapid and durable inhibition of ex vivo contact-activated cleavage of HMWK. These data demonstrate the durable inhibition of plasma activity from the subcutaneous (SC) administration of STAR-0215.

Results of in vivo safety pharmacology assessments demonstrated no notable effects on the central nervous system, cardiovascular system, or respiratory system.

2.1.4.2. Nonclinical Pharmacokinetics

The PK profile of STAR-0215 was characterized in a series of single- and repeat-dose studies performed in the rat and monkey. Overall, STAR-0215 was rapidly absorbed after SC administration, with time to maximum drug concentration (T_{max}) achieved within [redacted] hours (rats) and [redacted] hours (monkeys). The serum concentration of STAR-0215 increased with increasing dose level in a [redacted] manner. The extended circulating $t_{½}$ was observed in

monkeys at approximately [redacted] days and [redacted] days, following SC and intravenous (IV) administration, respectively. There were no apparent sex-related PK differences, and no apparent accumulation was observed after SC dosing (which was not evaluated in rats due to anti-drug antibody [ADA] response). ADAs were detected in both rats and monkeys after STAR-0215 administration, although the ADA prevalence in monkeys was lower overall than in rats. The Fc YTE modification successfully resulted in an extended terminal $t_{½}$ and long residence in the circulation.

There was no apparent difference in T_{max} between the dose levels tested. The finding is consistent with literature summarizing SC-dosed mAbs and the corresponding rate and extent of absorption. Literature reviews of mAbs administered SC indicate a T_{max} after SC administration ranges from 2 to 8 days (Viola 2018; Sanchez-Felix 2020) and concluded that T_{max} is highly sensitive to lymphatic flow rate and not sensitive to other physiological parameters (Sanchez-Felix 2020). Lymphatic flow rate is a physiological parameter that is independent from the therapeutic mAb or the specific modification in their Fc region. Therefore, the SC absorption is comparable to what has been observed for other mAbs.

2.1.4.3. Toxicology

Treatment with STAR-0215 was well tolerated and no overt toxicities were observed in Good Laboratory Practice–compliant safety studies performed in rodent (Sprague Dawley rat) and nonrodent (cynomolgus monkey) species. IV administration did not result in any infusion reactions and SC administration did not result in any local reactions at the injection site, other than minimal inflammatory mononuclear cell infiltration observed in rats. Within the liver, slight hypertrophy of the sinusoidal cells was observed only in the rat, in a small percentage of animals administered either IV or SC at the highest STAR-0215 dose of 100 mg/kg. These findings were minimal in severity, almost completely reversible, were without any associated transaminase elevations, and were considered to be non-adverse. Additionally, STAR-0215–related changes in white blood cell (WBC) counts were seen in male rats at ≥ 10 mg/kg SC (1.16- to 1.52-fold) and female rats at 100 mg/kg/dose IV (1.40-fold); given the low magnitude and lack of microscopic correlates, these hematology parameter changes in both male and female rats were considered non-adverse.

The only consistent finding in the animal studies (in rats and monkeys of both sexes) was a minimal and low amplitude prolongation of the activated partial thromboplastin time (aPTT) value. This finding was attributed to the pharmacological action of STAR-0215 and was considered non-adverse; it was present at all dose levels and was not dose related.

An additional toxicity study revealed that STAR-0215 has no hemolytic potential.

The high dose level of 100 mg/kg was well tolerated with no histopathology findings in rats and monkeys and was established as the no observed adverse effect level for both species.

2.1.5. Clinical Experience

The first-in-human (FIH) study of STAR-0215 is ongoing; STAR-0215-101 is a single-center, Phase 1a, randomized, double-blind, placebo controlled, single ascending dose study evaluating STAR-0215 administered SC in up to 48 healthy adult participants ages 18 to 60, inclusive. Eligible participants are randomized 3:1 to receive STAR-0215 or placebo in 5 cohorts of 8 participants with dose levels of 100, 300, 600, or 1200 mg by SC administration or 600 mg by

IV bolus administration, respectively. In STAR-0215-101, the Safety Review Committee (SRC) meets when a cohort has completed dosing and all study visits through 14 days after study drug administration. A new cohort is not dosed until the appropriate data have been reviewed by the SRC. The primary objective of the study is safety, which is being evaluated by adverse events (AEs), clinical laboratory results, 12-lead electrocardiograms (ECGs), and vital signs.

Please refer to the latest edition of the IB for further details.

2.2. Study Rationale

This is a Phase 1b/2 single and multiple dose study evaluating the safety, tolerability, efficacy, PK, pharmacodynamics (PD), and immunogenicity of SC administration of STAR-0215 in participants with HAE.

The therapeutic modality of STAR-0215 aims to induce a long-term prophylactic effect via infrequent administration to reach lasting blockade of the plasma kallikrein-kinin pathway. Inhibition of plasma kallikrein suppresses production of cHMWK and bradykinin, which prevents the triggering events of HAE.

STAR-0215 has been shown in nonclinical studies to be a highly potent and specific inhibitor of plasma kallikrein activity and, through its enhanced FcRn binding, has a long $t_{½}$ that, translated to humans, could potentially enable patients to dose less frequently.

This study is being conducted to progress the clinical development of STAR-0215 from healthy participants to an evaluation in participants with HAE.

2.3. Study Design Rationale

STAR-0215-201 is a multicenter, single- and multiple-dose study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity of STAR-0215 in participants with Type I or Type II HAE. STAR-0215 is a humanized IgG1 kappa light mAb, designed to be a highly potent and specific inhibitor of plasma kallikrein, with a YTE-modified Fc domain to enable a prolonged $t_{½}$ in circulation. The study design is a standard approach to the evaluation of the safety and tolerability of an investigational product.

As the first study of STAR-0215 in participants with HAE and the first evaluation of a multiple-dose regimen, Cohort 1 will be employed to evaluate a single dose in a smaller subset of the study's planned participants (n = 4) ahead of the majority of participants (up to 12 each) being treated in Cohort 2 and Cohort 3, evaluating multiple doses and dosing schemes. In the planned dosing scheme, available data from the first cohort through 21 days after dosing will be reviewed by the SRC before proceeding to multiple doses in Cohort 2 (Section 4.2). A 21-day safety review period is being employed in this study based on the SC absorption profile of STAR-0215(Section 2.1.4.2). There will be ongoing oversight by the SRC. Provided no safety concerns are noted from a cumulative review of safety data from this study and the ongoing FIH study (STAR-0215-101), [redacted] and [redacted] in [redacted] may be explored.

In Cohorts 2 and 3, the visits subsequent to the second dose of STAR-0215 administration are scheduled from the actual day of the second dose, as opposed to the day of the first dose. This scheduling provides precision and consistency in the timing of post-dose sample collection and

will enable the STAR-0215 pharmacokinetic profiles after the first and second dose to be compared.

No placebo group will be used in this study; each participant will serve as their own control. Data collected during the Run-In period will be used to establish each participant's baseline.

2.4. Dose Selection Rationale

The starting dose of STAR-0215 for participants with HAE in this study was based on PK/PD modeling. The information evaluated for dose selection for this study included: (1) estimated plasma kallikrein inhibition required for HAE attack suppression based on literature reports (Section 2.4.1) and (2) human PK models (empirical and minimal physiologically-based PK). Based on the totality of the PK/PD modeling, a single dose of 450 mg was estimated to provide adequate target coverage for HAE attack suppression in participants with HAE for a prolonged duration. Therefore, 450 mg was selected to be the starting dose in this Phase 1b/2 study. The planned dosing regimen for Cohort 2 is 600 mg followed by 300 mg 84 days later. Based on PK/PD modeling, this regimen, in which the initial dose is a loading dose, has the potential to rapidly boost C_{min} concentrations to levels believed to provide robust and durable inhibition of plasma kallikrein that may translate into immediate and sustained clinical reductions in HAE attacks. The planned dosing regimen for Cohort 3 is 600 mg followed by 600 mg 28 days later. This regimen includes an initial loading dose on D1 and a second dose on D28, expected to result in higher STAR-0215 concentrations during the follow-up period. Upon review of emerging data from the ongoing Phase 1a trial and Cohorts 1, 2, and 3 from this trial, [redacted] and [redacted] in [redacted] may be explored.

Single doses of up to and including 1200 mg are being evaluated in the ongoing Phase 1a study in healthy adult participants. Initial clinical PK data from the Phase 1a study support the administration of STAR-0215 in humans at a dose level of at least 1600 mg for SC administration and 1200 mg for IV administration. Please refer to the IB for updated information regarding safety and PK from the Phase 1a study.

2.4.1. Target Coverage Needed for HAE Attack Suppression Based on PK Modeling

From an exposure-response analysis of the clinical trials with the plasma kallikrein mAb inhibitor, lanadelumab, HAE attack suppression was found to be positively correlated to target inhibition. It was demonstrated that by maintaining a high level of target coverage ($\geq$ 67 nM), the HAE attack frequency in patients decreased to < 0.1 attack/month (Wang 2020). A single dose of 450 mg is estimated to achieve and maintain the adequate level of circulating plasma kallikrein inhibition to potentially suppress HAE attacks. After approximately 6 months from the last dose administered, it is estimated that STAR-0215 concentrations may decrease to levels that may no longer suppress HAE attacks. For participants who opt not to participate in the long-term open label extension trial STAR-0215-202 at Day 168 for Cohort 1, Day 251 for Cohort 2, and Day 195 for Cohort 3, certain permitted medications for HAE attack prevention may be administered (see Section 7.15).

2.5. Benefit-Risk Assessment

This is the first study in which STAR-0215 will be evaluated in participants with HAE. STAR-0215 was designed to reduce the number and severity of HAE attacks and for less

frequent dosing, due to its extended half-life, than currently available prophylactic treatments for HAE (described in Section 2.1.2).

As described in Section 2.1.4 and in further detail in the IB, the STAR-0215 nonclinical safety profile presents minimal risks and supports the clinical development of STAR-0215.

Based on the considerations summarized above, the benefit-risk assessment favors the administration of STAR-0215 in adults with HAE. Please refer to the latest edition of the IB for the overall benefit-risk assessment, potential risks (prolongation of aPTT, increased WBC, development of ADA, and hepatic sinusoidal hypertrophy), and the most accurate and current information regarding metabolism, PK, clinical activity, and safety of STAR-0215.

Many national health authorities have issued guidelines that aim to provide recommendations for the conduct of clinical studies of medical products during the COVID-19 pandemic. Because the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at a rapid pace. Special attention will be paid to protect study participants and site staff against infection with SARS-CoV-2. Risk assessment and monitoring of the COVID-19 pandemic will be conducted and are described in more detail in Section 10.4.

3. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
• To assess the safety and tolerability of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Incidence of adverse events • Changes in vital signs, ECG findings, physical examination findings, and clinical laboratory evaluations
Secondary Objectives	**Secondary Endpoints**
• To assess the efficacy of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Change from baseline in monthly HAE attack rate • Incidence of HAE attack severity (mild, moderate, and severe) • Duration of HAE attack (shorter than 12 hours, 12 to 24 hours, 24 to 48 hours, and longer than 48 hours) • The number of HAE attacks requiring on-demand therapy • Time to first HAE attack after first and last dosing
• To characterize the PK of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Concentration of STAR-0215 and the derived PK parameters[1]
• To characterize the PD of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Change in plasma kallikrein activity
• To assess the immunogenicity of SC administration of single and multiple doses of STAR-0215 in participants with Type I or Type II HAE	• Formation of anti-drug (STAR-0215) antibodies
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the impact of STAR-0215 on [redacted] of STAR-0215	• Changes from baseline in [redacted] of STAR-0215
• To conduct an exploratory assessment of the effect of STAR-0215 on [redacted] in participants with Type I or Type II HAE	• Changes from baseline in the [redacted]

Abbreviations: [redacted] ECG = electrocardiogram; HAE = hereditary angioedema; PD = pharmacodynamics; PK = pharmacokinetics[redacted]; SC = subcutaneous.
[1] Pharmacokinetic parameters are listed in Section 9.5.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

STAR-0215-201 is a Phase 1b/2, multicenter, single and multiple dose study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity of STAR-0215 in participants with Type I or Type II HAE.

Properly consented participants will undergo screening assessments according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) and immediately enter the Run-In period. During the Run-In period, HAE attack information will be collected to determine if a participant meets the eligibility requirement of experiencing at least 2 HAE attacks during this time period and to establish a baseline prior to STAR-0215 administration. If a participant has an HAE attack during the Run-In period before Day 1 (first dose of STAR-0215), all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. The Run-In period may be extended after consultation with the Medical Monitor. In Cohorts 2 and 3, if a participant has an HAE attack immediately before the second dose (Day 84 and Day 28, respectively), signs and symptoms of the HAE attack should be improving per participant report prior to STAR-0215 administration; a washout period for on-demand treatment is not required before the second dose is administered.

In Cohort 1, each participant who has completed the Run-In period and is eligible for STAR-0215 administration will receive 1 dose of STAR-0215 on Day 1. When Cohort 1 has completed dosing, the SRC will review the cohort's cumulative safety data from the Screening/Run-In period through 21 days after dosing. Progression to Cohort 2 dosing will occur if there are no concerning safety signals. Details of the SRC's review are provided in Section 4.2.

In Cohort 2, each eligible participant will receive 2 doses of STAR-0215, the first on Day 1 and the second on Day 84. When 6 participants in Cohort 2 have received Dose 1, progression to dosing of Cohort 3 will begin.

In Cohort 3, each eligible participant will receive 2 doses of STAR-0215, the first on Day 1 and the second on Day 28.

Provided no safety concerns are noted from a cumulative review of safety data from this study and the ongoing FIH study (STAR0215-101), [redacted] and [redacted], may be explored in [redacted] would be added through an amendment to the protocol.

STAR-0215 will be administered SC into the abdomen. There will be 4 participants in Cohort 1, 6 participants in Cohort 2, and 6 participants in Cohort 3. Based on the accumulated safety information and enrollment as continually monitored by the SRC [redacted] up to 6 additional participants may be added to Cohort 2 and/or Cohort 3 (maximum of 12 participants each in Cohorts 2 and 3) after the first 6 participants in Cohort 3 have been enrolled. The dose regimens and dose levels for each cohort are in Table 4. There is no placebo group in this study. An overview of the study design is provided in Figure 2.

As detailed in the Schedules of Assessments (SOAs; Section 1.1), study assessments will be performed in all cohorts through 6 months after the last dose of STAR-0215 (Day 168 in Cohort 1, Day 251 in Cohort 2, and Day 195 in Cohort 3). At this time, participants who are willing and

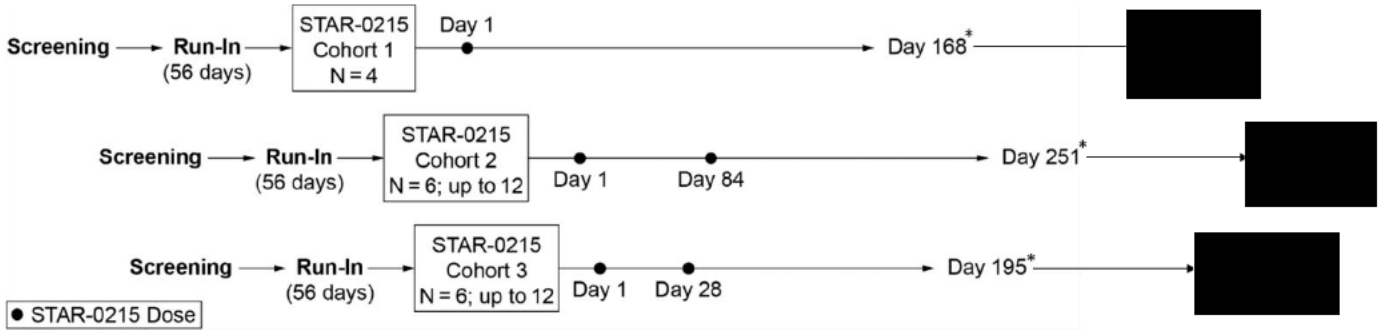
eligible to consent can begin participation in the long-term open label extension study (STAR-0215-202). For participants who do not enroll in the long-term open label extension study, safety monitoring will be performed through [redacted] months after the last dose of STAR-0215 in all cohorts (Day [redacted] in Cohort 1, Day [redacted] in Cohort 2, and Day [redacted] in Cohort 3) through regular contacts and scheduled site visit. Visits subsequent to STAR-0215 administration are scheduled with respect to the actual day of STAR-0215 dosing for consistency and precision in post-dose sample collection. Safety assessments (including AEs, vital signs, ECGs, physical examinations, clinical laboratory evaluations, and pregnancy testing), and efficacy, PK, PD, immunogenicity, biomarker, and [redacted] may be conducted at scheduled site visits.

Table 4: STAR-0215 Dose Regimens

Cohort	Dose 1		Dose 2		# Participants
	STAR-0215 Dose Level (mg)	Dosing Day	STAR-0215 Dose Level (mg)	Dosing Day	
1	450	1	NA	NA	4
2	600	1	300	84	6; up to 12
3	600	1	600	28	6; up to 12

Abbreviations: NA = not applicable.

Figure 2: Overview of Study Design



*Participants may opt to participate in the long-term open label extension trial STAR-0215-202

Notes: When Cohort 1 has completed dosing, the Safety Review Committee will review the cohort's cumulative safety data from the Screening/Run-In period through 21 days after dosing. Progression to Cohort 2 dosing will occur if there are no concerning safety signals. When 6 participants in Cohort 2 have received Dose 1, progression to dosing of Cohort 3 will begin.

4.2. Safety Review Committee

The SRC will be composed of a clinician with expertise in HAE, a medical monitor, and representatives from the Sponsor. The SRC will be responsible for making recommendations related to study progression.

The SRC will meet when Cohort 1 has completed dosing and all study visits through 21 days after dosing. The SRC will review the cohort's cumulative safety data, including AEs, results of vital sign assessments, clinical laboratory assessments, and ECG assessments. Cohort 2 will not be dosed until the appropriate data from Cohort 1 have been reviewed by the SRC. There will be ongoing oversight by the SRC, as there may be ad hoc meetings of the SRC upon the emergence of an unexpected safety signal at any time during the study. In the event of emergent safety concerns posing substantial risk to participants, the SRC will consult with the Protocol Stopping Rules (Section 4.7).

4.3. Number of Participants Planned

Up to 28 participants with HAE in 3 dosing cohorts are planned (4 in Cohort 1, 6 in Cohort 2, and 6 in Cohort 3). Based on the accumulated safety information and enrollment as continually monitored by the SRC [redacted] up to 6 additional participants may be added to Cohort 2 and/or Cohort 3 (maximum of 12 participants each in Cohorts 2 and 3) after the first 6 participants in Cohort 3 have been enrolled. Each participant is unique and will not be included in subsequent dosing cohorts. Participants who do not receive a complete dose or regimen of STAR-0215 or withdraw before 21 days after dosing may be replaced at the Sponsor's discretion.

4.4. Treatment Assignment

All eligible participants will receive STAR-0215. In Cohort 1, participants will receive a single dose of STAR-0215. In Cohorts 2 and 3, participants will receive 2 doses of STAR-0215. There is no placebo group in this study. Dose regimen and dose level information for each cohort is provided in Table 4.

4.5. Duration of Treatment and Duration of Study

Individual participants will receive 1 dose of STAR-0215 (Cohort 1; Day 1) or 2 doses (Cohort 2; Days 1 and 84, and Cohort 3; Days 1 and 28). The duration of study participation for each participant, including the Screening and Run-In period, is up to [redacted], or [redacted] days in Cohorts 1, 2, and 3, respectively. The study is composed of 3 periods, as follows:

- Screening/Run-In: at least 56 days
- Treatment Period: Individual participants will receive STAR-0215 on Day 1 (Cohort 1), Day 1 and 84 (Cohort 2), or Day 1 and 28 (Cohort 3).
- Follow-up Period: approximately 6 months after the last dose of STAR-0215 (Day 168 for Cohort 1, Day 251 for Cohort 2, and Day 195 for Cohort 3). At this time, participants who are willing and eligible to consent can begin participation in the long-term open label extension study (STAR-0215-202).
- Follow-up Period: For participants who do not participate in the long-term open label extension study, monitoring will be performed through [redacted] months after the last dose of STAR-0215 in all cohorts (Day [redacted] in Cohort 1, Day [redacted] in Cohort 2, and Day [redacted] in Cohort 3) through regular contacts and scheduled study visit.

4.6. End of Study Definition

The end of the study is defined as the date the last participant is examined for the purposes of final data collection for the overall study.

4.7. Stopping Rules

Table 5: Stopping Rules for Study STAR-0215-201

Adverse Event Criteria	Action
At least 2 participants in a dose cohort experience similar SAEs or At least 2 participants in a dose cohort experience similar Grade 2 treatment-related AEs	The SRC will make a recommendation as to continuation, including potentially modifying the starting dose of the subsequent cohort.
Any 1 participant in a dose cohort experiences a Grade 3 or greater treatment-related AE	Dosing for the participant and the remainder of the cohort will be halted until a review of the event by the SRC is completed and the SRC has made a recommendation.
Any occurrence of a treatment-related SAE	May result in suspension of any further dosing in the study by the Medical Monitor until the SRC has evaluated the event and determined the next appropriate course of action.

Abbreviations: AE = adverse event; SRC = Safety Review Committee; SAE = serious adverse event.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion Criteria

A participant must meet all the following criteria to be eligible for this study.

1. At least 18 years of age at the time of Screening.
2. Willing and able to read, understand, and sign the IRB/IEC/REC approved informed consent form (ICF).
3. Documented diagnosis of HAE (Type I or II). All of the following must be met:
   a. Documented clinical history consistent with HAE (e.g. SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   b. C1-INH antigen or functional level less than 40% of the normal level. Participants with antigen or functional C1-INH level 40% to 50% of the normal level may be eligible if they also have a C4 level below the normal range and a family history consistent with HAE Type I or II. Testing for C1-INH and C4 will be performed at Screening. Historical test results for C1-INH may be used to confirm eligibility if the screening C1-INH antigen test or functional level or C4 level laboratory values are inconclusive, after discussion with the medical monitor.
   c. Age at reported onset of first angioedema symptoms 30 years of age or younger, or a family history consistent with HAE Type I or II.
4. Agree not to receive a dose of any vaccine within 7 days before or after STAR-0215 administration.
5. Participants of childbearing potential must have a negative serum pregnancy test at Screening, must not be pregnant or breastfeeding at Screening, and agree to use one of the protocol defined forms of highly effective contraception (Appendix 1) during the study and for a total of [redacted] months after the last dose of STAR-0215.

   Note: Participants who are not capable of becoming pregnant (e.g. defined as surgically sterile or post-menopausal), per the protocol (Appendix 1), are not required to use any form of contraception during the study.
6. Participants capable of producing sperm who have partners of childbearing potential must agree to use one of the protocol defined forms of contraception (Appendix 1) during the study, unless the participant is azoospermic or their partner is surgically sterile as described in Appendix 1.
7. Agree not to donate or store sperm or engage in any other activity intended to produce sperm for the purpose of insemination during the study, unless such sperm were collected before the administration of the first dose.
8. Agree not to donate or store eggs or undergo assisted reproductive or fertility treatment during the study and for a total of [redacted] months after the last dose of STAR-0215.

9. Experienced at least 2 HAE attacks during the Run-In period, as confirmed by an investigator based on meeting the protocol-specified definition of an HAE attack (Section 7.12).

5.2. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from this study:

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria.
2. Any exposure to an investigational drug or device within 90 days or 5 half-lives (whichever is longer) prior to Screening.
3. Exposure to an mAb or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein) within 5 half-lives prior to Screening.
4. Use of therapies prescribed for the prevention of HAE attacks prior to Screening:
    a. lanadelumab within 90 days
    b. berotralstat within 21 days
    c. all other prophylactic therapies, within 7 days
5. Any exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as hormonal contraceptives or hormone replacement therapy [HRT]) within 28 days prior to Screening. (Topical estrogens applied externally or intravaginally are allowed, provided the Investigator and Medical Monitor agree that the systemic absorption is minimal and unlikely to have health impacts to the participant.)
6. Any exposure to androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within 7 days prior to Screening.
7. History of chronic viral infection with positive test for HIV or hepatitis B surface antigen (HBsAg). History of hepatitis C virus (HCV) that has not been adequately cured.
8. Active liver disease (e.g. acute or chronic hepatitis B or C, alcoholic or non-alcoholic steatohepatitis).
9. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) above 3 times the upper limit of normal (ULN), or aspartate aminotransferase (AST) above 3 times the ULN, or total bilirubin above 1.5 times the ULN (unless participant has known Gilbert's Syndrome and a total bilirubin < 3 mg/dL).
10. History of drug or alcohol abuse in the 12 months before Screening.
11. Participant has ongoing cancer, except for the following: basal cell carcinoma of the skin. Ongoing cancer is defined as requiring therapy or intervention to treat or prevent recurrence/progression of disease.
12. Known sensitivity to the ingredients in STAR-0215.

13. Participant is employed by or is an immediate family member of the Sponsor or study site staff or who is committed to an institution by virtue of an order issued by the judicial or the administrative authorities.
14. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g. a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of study results).

5.3. Discontinuation of Study Drug

A participant may choose to discontinue the study drug at any time for any reason. Reasons for discontinuation from study drug may include, but are not limited to, the following:

- Adverse event
- Pregnancy
- Investigator discretion
- Participant request

If a participant discontinues the study drug, the reason and date of discontinuation must be recorded. If STAR-0215 is discontinued, the participant should remain in the study to complete all follow-up visits and assessments as described in the SOAs (Section 1.1). Participants who become pregnant while participating in the study will be discontinued from STAR-0215 and followed for safety. Pregnancy reporting is described in Section 8.5.1.

5.4. Participant Withdrawal Criteria

A participant may choose to withdraw from the study for any reason, at any time, without penalty. A participant may be withdrawn from the study for the following reasons:

- Adverse event
- Protocol deviation/substantial noncompliance with the study requirements
- Investigator decision

A participant must be withdrawn from the study for any of the following reasons:

- A participant withdraws consent for the study
- Contact has been adequately attempted, but participant is considered lost to follow-up
- Sponsor decision to terminate the study
- Participant death

If a participant discontinues the study, the reason and date of discontinuation must be recorded.

If a participant withdraws from the study, regardless of reason, all reasonable effort should be made to have the participant return to the clinic to complete the end-of-treatment assessments as described in the SOAs (Section 1.1).

5.5. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

6. TREATMENT OF PARTICIPANTS

6.1. Study Drug Materials and Management

STAR-0215 drug product is supplied as a sterile, [redacted] (Table 6). STAR-0215 will be administered by study site staff.

Table 6: Study Drug Dosage and Mode of Administration

Intervention Name	**STAR-0215**
Intervention Description	[redacted]
Dose Formulation	[redacted]
Unit Dose Strength(s)	[redacted]
Dosage Level(s)	[redacted]
Route of Administration	[redacted]
Use	[redacted]
IMP or NIMP	[redacted]
Inactive ingredients	[redacted]
Sourcing	[redacted]
Packaging and Labeling	[redacted]

Abbreviations: IMP = investigational medicinal product.

6.2. Shipping, Storage, Preparation, and Accountability

The Sponsor will authorize the initial shipment of STAR-0215 to the study site and will notify the study site in advance of this shipment. STAR-0215 will be shipped in a [redacted] °C. Shipments will be arranged to ensure that they can be received promptly by the study site. The Investigator or designee must confirm appropriate conditions (e.g. temperature) have been maintained during transit for all STAR-0215 received, and any discrepancies have been reported and resolved before use of STAR-0215.

The Investigator acknowledges that STAR-0215 is investigational and as such must be handled strictly in accordance with the protocol and container label. Upon receipt, STAR-0215 must be [redacted] °C. STAR-0215 will be maintained in accordance with the labeled storage conditions with access limited to the pharmacist or designated site staff.

Only eligible participants may receive STAR-0215, and only the pharmacist or designated site staff may supply, prepare, or administer it.

[redacted]The appropriate dose will be prepared by the pharmacist or designated site staff, depending on the dose level. [redacted] for administration. STAR-0215 must be administered to the participant within the 4 hours after the [redacted] is breached. Complete instructions for the preparation of STAR-0215 are provided in the Pharmacy Manual.

The Investigator is responsible for STAR-0215 accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

All used, unused, or expired STAR-0215 will be returned to the Sponsor, the Sponsor's designee, or, if authorized by the Sponsor, disposed of at the study site per the site's standard operating procedures and documented.

Further guidance and information for the final disposition of unused STAR-0215 are provided in the Pharmacy Manual.

6.3. Prior and Concomitant Medications

All medications administered in the 30 days before the participant provided informed consent through the final study visit will be recorded. This includes non-prescription and prescription medications, vitamins, and herbal supplements. Any medications associated with the prophylaxis of HAE attacks administered in the 90 days before the participant provided informed consent will also be recorded.

6.3.1. Prohibited Medications

Use of the following treatments will not be permitted during the study:

- Long-term prophylaxis for HAE (use of C1-INH for long-term prophylaxis, kallikrein inhibitors, attenuated androgens, or anti-fibrinolytics). See Section 7.15 for additional details pertaining to the use of certain permitted prophylaxis medications for participants who do not participate in the long-term open label extension study
- ACE inhibitors
- Estrogen-containing medications with systemic absorption (such as hormonal contraceptives or HRT). Topical estrogens applied externally or intravaginally are allowed, provided the Investigator and Medical Monitor agree that the systemic absorption is minimal and unlikely to have health impacts to the participant.
- Androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone)
- Any investigational drug or device
- Any other mAb
- Vaccine doses within the 7 days before or after STAR-0215 administration

6.3.2. Permitted Medications

All medications not specified in Section 6.3.1 are permitted at the discretion of the Investigator. Vaccinations, including COVID-19 vaccines, are allowed per local guidelines and regulations; there is a timing restriction for vaccine doses with respect to STAR-0215 administration (Section 6.3.1), which is also specified in the inclusion criteria (Section 5.1).

If a participant experiences HAE attacks during the study, they will be permitted standard-of-care on-demand treatment as prescribed by their physician. The date and time of on-demand attack treatment as well as the name and dosage regimen of the treatment must be recorded.

6.4. Treatment Compliance

STAR-0215 will be administered by qualified site personnel responsible for STAR-0215 administration.

6.5. Overdose

An overdose is defined as a significant excess quantity from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of STAR-0215 is considered a dose that is at least 2-fold higher than the intended dose for the participant. Receipt of dose(s) at levels in excess of intended dose(s) will be captured as protocol deviation(s).

If an overdose of STAR-0215 were to occur **during the trial**, the participant should be observed closely for signs of toxicity and appropriate supportive treatment should be provided if clinically indicated, including measures of coagulation parameters such as aPTT.

6.6. Randomization

This study is not randomized.

6.7. Blinding

This is an open-label study.

6.8. Continued Access to Study Drug After the End of the Study

Enrollment into the long-term open-label extension study STAR-0215-202 is available to eligible participants of this study.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are outlined in the SOAs in Section 1.1. If necessary, to facilitate a participant's continued participation, alternative methods for study visits and safety assessments may be implemented, which may include remote or virtual study visits and assessments per site standard practice and local regulations.

7.1. Informed Consent

Informed consent will be obtained before any study procedures are performed.

7.2. Screening/Eligibility

All screening evaluations must be completed and documented by the Investigator within the specified Screening and Run-In period (refer to the SOAs in Section 1.1). The Investigator will confirm the participant's eligibility before STAR-0215 administration on Day 1.

Screen failures are defined as participants who provide informed consent to participate in the clinical study but who do not meet the eligibility criteria for participation in this study. Individuals who do not meet the criteria for participation in this study may be rescreened once, provided the reason for screen failure is considered transient and likely to change before rescreening and after consultation with the Medical Monitor. If a participant is rescreened within 28 days of the date of screen failure, the following screening assessments do not need to be repeated unless they were the cause of the screen failure: chemistry, hematology, and virus serology laboratory evaluations. Screening laboratory evaluations may be repeated at the discretion of the Investigator.

7.3. Diagnosis and History of Hereditary Angioedema

Diagnosis of HAE will be based on clinical history, age of onset of first angioedema symptoms, and blood tests of C1-INH antigen or functional level and C4 level. Testing for C1-INH and C4 will be performed according to the central laboratory's standard procedure.

Date of diagnosis, onset of symptoms, and type of HAE (I or II) will be collected. Historical HAE attack information, which includes the number of HAE attacks in the 12 months prior to Screening, will be collected at Screening.

7.4. Virus Serology

Blood tests for virus serology (HCV, HBsAg, and HIV) all must be confirmed negative, except if the participant is cured of the HCV infection and this is documented in the medical record. Testing will be performed according to the central laboratory's standard procedures.

7.5. Physical Examination

Per the SOAs (Section 1.1), a complete or targeted physical examination will be conducted by the Investigator or their qualified designee. Weight will also be collected. Height will be collected at Screening only. The complete physical examination will include general appearance; head, eyes, ears, nose, and throat; neck; abdomen; and respiratory, cardiovascular, neurologic,

musculoskeletal, and dermatologic systems. Targeted physical examinations will include the evaluation of general appearance, skin, abdomen, and cardiovascular and respiratory systems.

Study participants must be monitored after STAR-0215 dosing for signs and symptoms of hypersensitivity including: bronchospasm, angioedema, hypotension, loss of consciousness, generalized skin rash, nausea, vomiting, and abdominal cramps, among other symptoms. The Investigator will advise the participant to monitor themselves and seek medical attention if they experience any hypersensitivity after leaving the investigative site. All reports of hypersensitivity will be recorded as an adverse event.

7.6. Demographics/Medical History

Demographics (age, sex, race, and ethnicity) and medical history will be obtained from the participant. Medical history will capture the participant's current medical status (current disease processes), past medical status (past disease processes), history of surgery, and allergies.

7.7. Vital Signs

Vital signs will be measured by the Investigator or their qualified designee. Routine vital sign assessments will be taken after the participant has been in a supine position for at least 5 minutes and will include blood pressure, heart rate, respiratory rate, and body temperature. When relevant, vital signs will be collected before blood sample collection.

7.8. Electrocardiograms

A standard 12-lead ECG will be performed after the participant has been in a supine position for at least 5 minutes. ECGs will be performed before blood sample collection.

7.9. Clinical Laboratory Assessments

All clinical laboratory assays (hematology, chemistry, coagulation, and urinalysis) will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition may, at the discretion of the Investigator or Sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Clinical laboratory parameters are listed in Table 7.

Table 7: Clinical Laboratory Parameters

Hematology	Chemistry	Coagulation	Urinalysis
CBC with differential: Hemoglobin Hematocrit RBC count Platelet count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration WBC count with differential (lymphocytes, neutrophils, monocytes, eosinophils, and basophils)	Albumin Alkaline phosphatase ALT AST Bilirubin (total and direct) Blood urea nitrogen Calcium Carbon dioxide Chloride Cholesterol Creatine phosphokinase Creatinine Gamma-glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Triglycerides Total protein Uric acid	Activated partial thromboplastin time Prothrombin time International normalized ratio	Bilirubin Blood Glucose Ketones Nitrite pH Protein Specific gravity Microscopy (if urinalysis is abnormal)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; RBC = red blood cell; WBC = white blood cell.

7.10. Follicle-Stimulating Hormone Test

Testing for follicle-stimulating hormone (FSH) is only performed if needed to confirm a postmenopausal state (i.e. no menses for 12 months without an alternative medical cause) in participants not using hormonal contraception or HRT. Testing will be performed according to the central laboratory's standard procedures.

7.11. Pregnancy Testing

A serum human gonadotropin pregnancy test will be performed on participants of childbearing potential at Screening. Additional serum or urine pregnancy tests will be collected as outlined in the SOAs (Section 1.1). Testing will be performed according to the laboratory's standard procedures.

7.12. Hereditary Angioedema Attack Information

Hereditary angioedema attacks will be assessed throughout the study to evaluate the efficacy of STAR-0215. The HAE attack information collected during the Run-In period will be used to establish a participant's eligibility and baseline. Study staff will collect HAE attack information from participants weekly through 6 months following the last dose administered. Investigators will assess this collected information against the HAE attack definition (Section 7.12.1) to confirm occurrence of HAE attacks. The clinical information related to any HAE attacks that will be collected will include, but not be limited to, attack location, severity, time of onset, duration of attack, hospitalization status, and treatment with any acute on-demand therapy.

If a participant experiences HAE attacks during the study, they will be permitted standard-of-care on-demand treatment as prescribed by their physician (Section 6.3.2).

If a participant has an HAE attack before Day 1 (first dose of STAR-0215), all signs and symptoms of the HAE attack must be resolved before dosing. A washout period for on-demand treatment is not required. In Cohorts 2 and 3, if a participant has an HAE attack immediately before the second dose (Day 84 and Day 28, respectively), signs and symptoms of the HAE attack should be improving per participant report prior to STAR-0215 administration; a washout period for on-demand treatment is not required before the second dose is administered.

Guidance on the collection of HAE attack information with respect to AE collection is provided in Section 8.2.1.

7.12.1. HAE Attack Definition

Defining an event as an HAE attack will be based on an assessment of the signs and symptoms of an event against predefined criteria and Investigator clinical judgment.

To be considered an HAE attack, the Investigator must confirm that the event has signs or symptoms consistent with an HAE attack that meet at least 1 of the following criteria:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

Only meeting at least 1 of the criteria above is not sufficient to confirm an HAE attack. The Investigator will employ his/her clinical judgment to evaluate other features of the event before confirming an HAE attack occurred. Examples of features that may lead to an event not being confirmed as an HAE attack are symptoms that are not consistent with an HAE attack, the event's duration is longer than typical for an HAE attack, or the event has a plausible alternative etiology.

Prodromal symptoms or participant-reported use of on-demand HAE attack treatment alone are not sufficient to define an event as an HAE attack.

Each HAE attack must be unique. To be distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

The HAE attack resolution is defined as the participant no longer having symptoms of the HAE attack.

The HAE attack severity will be graded by the Investigator per the following definitions:

- Mild: Transient or mild discomfort
- Moderate: Mild to moderate limitation in activity, some assistance with daily activities needed
- Severe: Marked limitation in activity, assistance with daily activities required

7.13. Pharmacokinetic, Pharmacodynamic, Immunogenicity, and [redacted] Assessments

Blood samples for PK, PD, immunogenicity, and [redacted] will be collected according to the SOAs (Section 1.1). Remaining samples or remaining volumes of samples may undergo additional testing for future research if the participant provides additional consent for this testing (Section 12.6.2). Use of samples for future research and sample retention is described in more detail in Section 12.6.

7.13.1. Pharmacokinetic Assessments

Pharmacokinetic blood sample collection times and time of dosing will be monitored and recorded. Pharmacokinetic blood sample collection must not deviate from the nominal collection times set forth in the protocol by more than the windows specified in the SOAs (Section 1.1) on the day of STAR-0215 administration.

A full description of the PK blood collection, handling, storage, and shipping can be found in the Laboratory Manual.

The concentration of STAR-0215 will be measured using the most current validated bioanalytical method.

7.13.2. Pharmacodynamic Assessments (Plasma Kallikrein)

Pharmacodynamic blood samples will be obtained to evaluate plasma kallikrein inhibition due to STAR-0215 administration.

A full description of the PD blood collection, handling, storage, and shipping can be found in the Laboratory Manual.

The samples will be evaluated using an appropriate validated assay to measure plasma kallikrein activity.

7.13.3. Immunogenicity

Blood samples will be obtained to measure STAR-0215 ADAs.

A full description of the blood collection, handling, storage, and shipping can be found in the Laboratory Manual.

The detection and characterization of antibodies to STAR-0215 will be measured using the most current validated bioanalytical method.

7.13.4. [redacted]

Blood will be collected for assessment of [redacted] or STAR-0215 [redacted] or [redacted] of STAR-0215. It is possible that not all assays will be performed at each timepoint. Decisions to perform assays will be made based on considerations that include statistical and scientific planning, available technologies, and study outcomes.

7.13.4.1. Serum/Plasma Biomarkers

Mechanistic and disease biomarkers may be evaluated in serum and plasma. These evaluations may provide a better understanding of the disease mechanism of action or factors related to an HAE attack, as well as biomarkers that may change as a result of STAR-0215 administration or that affect the response to STAR-0215. Assessments may include, but are not limited to, plasma kallikrein and prekallikrein concentrations in circulation, alternative measures of plasma kallikrein activity, functional C1-INH levels over time, and other biomarkers in the contact activation, complement, coagulation, fibrinolysis pathways, or other related disease pathways.

7.13.4.2. Transcriptomics (RNA)

Whole blood samples will be collected in a PAXgene® blood RNA tube to isolate RNA for assessing expression levels of genes or pathways associated with HAE, such as the contact activation or complement pathway, or expression transcripts that may change in response to STAR-0215 administration. These assessments may be performed using technologies such as microarray and RNA-seq, or other sequencing technologies.

7.13.4.3. Pharmacogenetics/-omics (DNA; Optional)

With participant consent, whole blood will be collected in a PAXgene® blood DNA tube for pharmacogenetic/-omic assessments including genetic polymorphisms (baseline) and epigenetic modifications associated with HAE, or that impact a participant's response to STAR-0215 or result from STAR-0215 administration.

HAE cases (Type I and Type II) are caused by mutations in the SERPING1 gene that lead to a reduction in the amount or function of C1-INH encoded by this gene. Variants in the SERPING1 gene or other genes in the contact activation, kinin, coagulation or related pathways have been shown to influence the severity of HAE (Porebski 2021; Parsopoulou 2022). The assessment of epigenetics (such as DNA methylation) and genetic variation in genes related to HAE etiology or drug disposition may be beneficial in understanding participant response to STAR-0215 administration. Whole genome sequencing will not be performed. The results of these assessments may be reported in the clinical study report (CSR) or a separate scientific report.

7.14. [redacted]

[redacted] is a validated, angioedema-specific, patient-reported outcome measure that is self-administered and used to evaluate the impact of recurrent angioedema on patients' [redacted] It is a [redacted] Each item has 5 answer options (scored 1 to 5), with higher scores indicating a more adverse effect. Raw scores are transformed into a linear scale that ranges from 0 to 100, with a score of 100

indicating the worst possible impairment in [redacted]. The minimal clinically important difference is defined as a change of 6 points from baseline.

7.15. Follow-Up Assessments

For participants who are willing and eligible to consent to the long-term open label extension study (STAR-0215-202), study assessments will be performed through 6 months after the last dose of STAR-0215 in all cohorts (Day 168 in Cohort 1, Day 251 in Cohort 2, and Day 195 in Cohort 3). Upon enrollment in STAR-0215-202, participants will continue to receive STAR-0215 and be monitored according to the procedures defined in that protocol. For participants who do not enroll in the long-term open label extension study, monitoring will be performed through [redacted] months after the last dose of STAR-0215 in all cohorts (Day [redacted] in Cohort 1, Day [redacted] in Cohort 2, and Day [redacted] in Cohort 3). These participants will be followed for an additional [redacted] months which includes 4 remote contacts and one on-site visit.

Remote contacts will collect information on any AEs (including HAE attacks), concomitant medication and any pregnancy information for participants of childbearing potential.

Final on-site visits will include safety assessments including AEs (including HAE attacks), concomitant medication, vital signs, ECGs, physical examinations, and clinical laboratory evaluations. A serum human gonadotropin pregnancy test will be performed on participants of childbearing potential.

NOTE: Participants who do not enroll in the long-term open label extension study and continue in STAR-0215-201 will be permitted to use certain medications for prophylaxis of HAE attacks after the 6 month follow up after the last dose of STAR-0215 (Day 168 in Cohort 1, Day 251 in Cohort 2, and Day 195 in Cohort 3). These permitted medications include pdC1-INH, attenuated androgens, and anti-fibrinolytics. Oral or parenteral inhibitors of plasma kallikrein, including berotralstat and lanadelumab, are NOT allowed until [redacted] months after the last dose of STAR-0215.

8. ADVERSE AND SERIOUS ADVERSE EVENTS

8.1. Overview of Safety Monitoring

It is the responsibility of the principal investigator to oversee the safety of all participants at their study site and to report all AEs including serious adverse events (SAEs) that are observed or reported during the study, regardless of the relationship to study drug (as assessed by the Investigator) or clinical significance of these events.

8.2. Adverse Event Definitions

8.2.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Laboratory abnormalities are generally not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention. A clinically significant laboratory abnormality that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to study drug interruption or discontinuation, will be considered an AE.

If a participant experiences symptoms that support an HAE attack, those symptoms/attacks will not be reported as AEs. However, if those symptoms are not supportive of an HAE attack, they will be reported as AEs. Any HAE attack that meets the definition of an SAE (Section 8.2.2) will be captured as an SAE.

For participants who do not enroll in the long-term open label extension study, and experience HAE attacks after 6 months following the last dose of STAR-0215, those will be reported as AEs.

8.2.2. Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that meets at least 1 of the criteria listed:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

8.3. Relationship to Study Drug

The Investigator must make the determination of relationship to study drug for each AE. Association of AEs and SAEs to study drug will be made using the following definitions:

Unrelated: An AE that is not related to the use of the study drug.

Unlikely: An AE that is unlikely to be due to the use of the study drug. An alternative explanation, e.g. concomitant drug(s) or concomitant disease(s), is plausible. A relationship to the study drug is improbable but not impossible.

Possible: An AE that conceivably could be due to the use of the study drug. An alternative explanation, e.g. concomitant drug(s) or concomitant disease(s), is not conclusive. The relationship of the event in time follows a plausible temporal sequence from administration of the study drug so that a causal relationship cannot be excluded but could have been produced by the participant's clinical condition or other therapy.

Probable: An AE that might be due to the use of the study drug. An alternative explanation is less likely, e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is suggestive and follows a reasonable temporal association with study drug administration. The reaction cannot be reasonably explained by the known characteristics of the participant's clinical state or other modes of therapy administered to the participant.

Related: An AE that is almost certainly related to the use of the study drug. The AE cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s) or concomitant disease(s).

For purposes of assigning relatedness – "Unrelated" and "Unlikely" will be considered not related. "Possible," "Probable," and "Related" will be considered related.

8.4. Assessment of Severity

The severity of AEs will be graded with a scale appropriate for use with people with HAE, who are otherwise generally healthy individuals.

Tables are provided in Appendix 2 to guide investigator assessment of AE severity.

Any AEs that cannot be graded using the scales provided in Appendix 2 will be graded according to the Investigator's medical judgment using the definitions for the severity categories in Table 8.

Table 8: Guide for Grading Adverse Event Severity

Severity	Definition	Grade
Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	1
Moderate	Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living	2
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self care Activities of Daily Living	3
Life-threatening	Life-threatening consequences; urgent intervention indicated.	4
Fatal	Death related to an adverse event	5

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.2.2. An AE of severe intensity may or may not be considered serious.

8.5. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study by the investigational site staff.

All AEs (related and unrelated) will be recorded from signing of the ICF through the last study visit.

The AE term should be reported in standard medical terminology when possible. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event or diagnosis. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, relationship, action taken, seriousness, outcome (if applicable), and whether it caused the participant to discontinue the study.

AEs that are not resolved by the end of the study, or that were not resolved upon discontinuation of the participant's participation in the study, are to be followed until 1 of the following occurs:

- the event resolves
- the participant's condition stabilizes or is fully characterized
- the event returns to baseline value (if a baseline value is available)

8.5.1. Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during a clinical study using an investigational drug must be reported. This report is for tracking purposes only. Details of pregnancies in participants and partners of participants who are of childbearing potential will be recorded and followed to conclusion; the outcome of each must be reported. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. If a pregnancy is reported, the Investigator will report the pregnancy information to Parexel Pharmacovigilance within 24 hours of learning of the participant's or participant's partner's pregnancy (after obtaining the necessary signed informed consent from the participant's partner).

8.6. Reporting Adverse Events

All AEs, regardless of seriousness, severity, or relationship to study drug, will be recorded throughout the study.

All SAEs must be reported to the Sponsor or designee within 24 hours of the first awareness of the event. The Investigator must verify the accuracy of the information recorded for the SAE with the corresponding source documents.

Information about all SAEs (either initial or follow-up information) will be collected and recorded in English on the electronic SAE Report Form within the electronic data capture (EDC) system. The Investigator will assess the relationship to STAR-0215. If the event meets seriousness criteria and it is not possible to access the EDC system, a paper SAE Report Form will be sent to the contract research organization (CRO) via email or fax, or if the EDC, fax, or email are not available, the Investigator will call the CRO's SAE hotline within 24 hours of being made aware of the SAE (refer to the site manual for contact information). When the EDC system becomes available, the SAE information will be entered within 24 hours.

The Investigator will report follow-up information relating to an SAE to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness by updating the electronic case report form (CRF) with the new information or by submitting a paper SAE Report Form in the event that the EDC system is not available. When the EDC system becomes available, the SAE information will be entered within 24 hours. The participant will be observed and monitored carefully until the condition resolves or stabilizes.

The Investigator must complete, sign, and date the SAE pages/screens and verify the accuracy of the information recorded with the corresponding source documents. In the event that the EDC is offline, the paper SAE report will be sent to the contact number specified on the study-specific SAE form, to the attention of Parexel Pharmacovigilance.

Additional follow-up information, if required or available, should be recorded within 24 hours of receipt.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. The Investigator will receive prompt notification of any adverse experience related to STAR-0215 that is both serious and unexpected, or any finding that suggests a significant risk for participants. The Investigator will promptly inform their IRB/IEC/REC of the notification and

insert the notification in the Investigator's Regulatory Binder in accordance with country-specific submission requirements for notification to the competent authority.

8.7. Medical Safety Monitoring

8.7.1. Medical Monitor

The study Medical Monitor has medical authority to evaluate the safety aspects of the clinical study and may be a Sponsor representative or a representative of a CRO if this obligation is transferred. Investigators may contact the Medical Monitor with specific medical questions on the study protocol, participant eligibility, or for discussion of AEs. Contact information for the Medical Monitor will be provided separately.

9. STATISTICAL METHODS

9.1. Sample Size Determination

This is the first time STAR-0215 is being used in participants with HAE. No formal sample size calculations have been performed.

Up to 28 participants will be dosed in this study. This is considered adequate to characterize the safety, tolerability, efficacy, PK, PD, and immunogenicity of STAR-0215.

No placebo group will be used in this study; each participant will serve as their own control. Data collected during the Run-In period will be used to establish each participant's baseline.

9.2. Statistical and Analytical Plans

Data will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) or frequency counts and percentages, as appropriate. Results will be presented by cohort. Details regarding the management of all data and statistical methodology, including an explanation of the analyses of exploratory endpoints and imputation of missing data, will be included in the statistical analysis plan (SAP), which will be finalized prior to database lock.

9.3. Analysis Sets

For all analysis sets, participants will be analyzed according to the assigned dose cohort.

9.3.1. Safety Analysis Set

The Safety Analysis Set is defined as all participants who received any amount of STAR-0215. This analysis set will be the primary analysis set for all safety and immunogenicity (ADA) endpoints.

9.3.2. Efficacy Analysis Set

The Efficacy Analysis Set is defined as all participants who received any amount of STAR-0215 and have 1 post baseline assessment. This analysis set will be the primary analysis set for all efficacy endpoints. Additionally, this analysis set will have no major protocol deviations that could affect the evaluation of efficacy parameters.

9.3.3. Pharmacokinetic Analysis Set

The PK Analysis set is defined as all participants who receive STAR-0215 and have at least 1 concentration post-dose sample available to enable assessment of PK. Additionally, this analysis set will have no major protocol deviations that could affect the evaluation of PK parameters.

9.3.4. Pharmacodynamic Analysis Set

The PD Analysis set is defined as all participants who received at least 1 dose of STAR-0215 and had PD assessments at baseline and at least 1 post-baseline visit assessment. Additionally, this analysis set will have no major protocol deviations that could affect the evaluation of PD parameters.

9.4. Safety Analysis

9.4.1. Adverse Events Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher and will be graded as described in Section 8.4.

Summaries of AEs will be based on treatment emergent AEs (TEAEs), defined as AEs with an onset at the time of or following the start of treatment with study drug, or medical conditions present before the start of treatment that increase in severity or relationship at the time of or following the start of treatment.

Treatment emergent AEs will be summarized separately for each dose level and by the number of participants experiencing TEAEs corresponding to MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs) by highest grade.

Separate tabulations may also be produced for TEAEs assessed as related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs greater than or equal to Grade 3 in severity. Common AEs will be summarized by MedDRA PT from most to least common. Treatment emergent SAEs and treatment emergent SAEs related to study drug will also be tabulated.

9.4.2. Safety Laboratory Analysis

For continuous hematology and clinical chemistry laboratory parameters, descriptive statistics for by-visit values and changes from baseline will be presented by dose cohort. Abnormal laboratory values will be listed by participant.

Additional analyses of laboratory data may be outlined in the SAP.

9.4.3. Vital Signs Analysis

Vital signs (body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure) will be summarized by dose at each scheduled visit. Descriptive statistics for by-visit values and changes from baseline will be presented.

9.4.4. Weight Analysis

Weight and body mass index (BMI) will be summarized by dose at each scheduled visit. Descriptive statistics for by-visit values and changes from baseline will be presented. Height at baseline will be used to calculate BMI.

9.4.5. Electrocardiogram Analysis

Heart rate, PR, QRS, QT, and QTcF will be summarized by dose at each scheduled visit. Descriptive statistics for by-visit values and changes from baseline will be presented. A tabulation of the overall ECG interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) will also be presented.

9.4.6. Prior and Concomitant Medications Analysis

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced Version Global B3 March 2021or higher. Prior and concomitant medications will be grouped by Anatomical Therapeutic Classification (ATC) and PT.

Prior medications are those medications that were stopped before first STAR-0215 administration. Concomitant medications are medications that are ongoing before baseline or taken at least once after STAR-0215 administration. Medications stopping on the same day as first STAR-0215 administration will be considered concomitant medications.

9.5. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted on participants in the PK Analysis Set.

Pharmacokinetic parameters will be listed by participant and summarized by dose group using descriptive statistics.

STAR-0215 PK parameters will be computed, when data allow, using standard noncompartmental methods based on observed STAR-0215 concentrations and on actual sample collection times. The following noncompartmental PK parameters, when data allow, will be calculated and reported:

- Maximum drug concentration (C_{max})
- Time of C_{max} (T_{max})
- Area under the curve (AUC) after a defined duration or at steady state
- Circulating half-life ($t_{½}$)
- Apparent clearance (CL/F)
- Volume of distribution (V/F)

Individual blood concentrations of STAR-0215 will be plotted by actual time on both linear and semi-logarithmic scales. Mean blood concentrations will be plotted by nominal time and on both linear and semi-logarithmic scales. A preliminary assessment of dose proportionality will be made by examining plots of dose-normalized AUC and C_{max} values versus the STAR-0215 dose. When data allow, accumulation will be assessed.

Full details of the PK analysis and modeling approach will be provided in the SAP or a separate PK analysis plan as appropriate.

9.6. Efficacy Analysis

Unless otherwise specified, all analyses of HAE attack data will be presented similarly during the Run-In and treatment periods using the Efficacy Analysis Set. Data will be summarized for all investigator-confirmed HAE attacks.

The frequency and duration of HAE attacks will be presented with descriptive statistics overall and by participant. The following categories will be presented for attack duration: shorter than 12 hours, 12 to 24 hours, 24 to 48 hours, and longer than 48 hours.

Attack severity categorized as Mild, Moderate, or Severe will be presented overall and by participant.

The number and type of on-demand therapies used to treat HAE attacks will be summarized.

The proportion of HAE attack-free participants during the treatment period will be summarized.

The time normalized number of investigator-confirmed HAE attacks per month (attack rate) will be presented at 4-week intervals and at the end of the study. The mean monthly rate and 95% confidence interval will be presented.

To assess HAE attacks within a participant, the actual and percentage change from baseline (Run-In period) in monthly attack rate with respect to on-treatment attack rate will be calculated. The mean change and 95% confidence interval will be presented.

The proportion of participants with a clinical response to treatment will be presented in increments as greater than or equal to 40%, 50%, 60%, 70%, 80%, 90%, and 100% reduction of HAE attacks relative to baseline will be presented.

Time to first HAE attack after first and last dose of STAR-0215 will be presented using Kaplan-Meier estimates.

9.7. Pharmacodynamic Analysis

Pharmacodynamic analyses will be conducted on data from participants in the PD Analysis Set. Descriptive statistics will be presented for plasma kallikrein activity levels and change and percentage change from baseline levels will be presented at each visit.

9.8. Immunogenicity Analysis

ADA data will be presented for the Safety Analysis Set and will be based on status at baseline and throughout the study. The incidence and prevalence will be summarized by treatment group.

9.9. Biomarker Analysis

[redacted]analysis will be defined in the SAP or biomarker analysis plan as appropriate.

9.10. [redacted]

[redacted] will be assessed by means of the [redacted] Descriptive statistics for changes from baseline to each visit in the total score will be presented. A 95% confidence interval for the change will also be presented. Individual domain scores will be presented similarly.

9.11. Exploratory Analysis

Any pre-planned exploratory analysis of study endpoints will be described in the SAP.

9.12. Interim Analyses

In preparation for future clinical development of STAR-0215 and subsequent study planning, [redacted] interim analyses of data in accumulating cohorts are planned (Table 9). The [redacted] interim analysis will occur after the [redacted] in [redacted] reaches the [redacted] visit and will

include all available data from [redacted] The [redacted] interim analysis will occur after the [redacted] in [redacted] reaches [redacted] after the [redacted] of STAR-0215 (the [redacted] visit) and will include all available data from [redacted]. Details of any additional interim analyses that may be conducted as warranted will be specified in the SAP. At each interim analysis the Sponsor will review the accumulated safety, efficacy, PK, PD, and immunogenicity data. If no safety concerns are noted following interim analyses, efficacy, PK, PD, and immunogenicity results may inform the decision to add additional participants to Cohorts 2 or 3 (up to a total of 12 in each) and/or [redacted] exploring [redacted] and [redacted]. All analyses will be predefined in the SAP as applicable.

Table 9: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] in [redacted] reaches the [redacted] visit	All available cumulative safety, PK, PD, immunogenicity, and efficacy data through the [redacted] visit in [redacted] and the [redacted] visit in [redacted]	• Potential addition of up to 6 participants to Cohort 2 (maximum of 12 participants total) • [redacted] to [redacted] • [redacted] study [redacted]
[redacted]	[redacted] in [redacted] reaches [redacted] after [redacted] (the [redacted] visit)	All available cumulative safety, PK, PD, immunogenicity, and efficacy data through the [redacted] visit in [redacted], [redacted] visit in [redacted] and the [redacted] visit in [redacted]	• Potential addition of up to 6 participants to Cohort 2 and/or Cohort 3 (maximum of 12 participants total in Cohorts 2 and 3) • [redacted] to [redacted] • [redacted] study [redacted] • Inform Sponsor's decision-making regarding [redacted]

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

9.13. Handling of Missing Data

For participants who are withdrawn from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis. Data will be analyzed as observed. No imputation for missing data will be performed unless otherwise specified.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

As part of participating in an Astria-sponsored study, the study site will permit authorized representatives of the Sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. To facilitate source data verification and review, the Investigators and institutions must provide the Sponsor's representative direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/IEC/REC review.

10.1. Inspection of Records

The Sponsor and authorized representatives of the Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, STAR-0215 stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

10.2. Study Monitoring

Study monitors representing the Sponsor will visit the study sites throughout the study. Before the first participant is enrolled, a representative of the Sponsor will visit the investigational study site to determine the adequacy of the facilities and discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator. At the study initiation, a representative of the Sponsor will review the protocol and CRFs with the investigators and their staff.

During the study, both on-site and remote monitoring activities will be conducted by the Sponsor and authorized representatives of the Sponsor. The monitor will provide feedback to the Investigator and investigational staff on study conduct and compliance. Specifically, they will:

- provide information and support to the Investigator(s),
- ensure that the safety and rights of participants are being protected,
- confirm that facilities remain acceptable,
- confirm that the investigational team is adhering to the protocol and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP),
- ensure data are being accurately, completely, and verifiably recorded in the CRFs,
- conduct source data verification and review, and

- perform investigational product accountability checks.

Key study personnel must be available to assist during these activities. The monitor will be available between these scheduled activities if the Investigator(s) or other staff needs information or advice.

10.3. Audits and Inspections

Source data/documents must be available for inspections by a representative of the Sponsor or Health Authorities. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.4. Public Health Emergency/COVID-19 Mitigation Plan

Ongoing risk assessment and monitoring of the COVID-19 pandemic will be conducted by the Sponsor with input from the Investigator at both a site and country level. These ongoing assessments include changes to any of the following:

- Potential impact on recruitment
- Potential impact on study participants
- Potential impact on study site staff
- Potential impact on Sponsor/CRO staff conducting site monitoring and central review of data

Investigators should follow their institutional and locally accepted clinical and governmental recommendations to ensure the safety of study participants while at the site.

In order to mitigate the possible increased risk associated with study participation during the COVID-19 pandemic or other public health emergency, Investigators are encouraged to have frequent communication with participants (e.g. via additional phone or virtual visits) to ensure participant safety and address participant concerns.

Increased risk identified as part of pandemic monitoring may warrant protocol amendments to implement further safety measures for protection of participants and study staff.

In the event of any circumstances impacting the ability of enrolled participants to attend scheduled visits at the study site, such as travel restrictions imposed due to COVID-19, investigators must notify the Sponsor and make the necessary arrangements to ensure the safety of their enrolled participants. They should also evaluate whether their participants should continue in the clinical trial. Those participants who have not yet been dosed should be withdrawn from the study. Protocol deviations arising under such circumstances (e.g. missed or delayed visits, assessments not performed, etc.) will be clearly documented and the reasons will be collected.

10.5. Quality Control and Quality Assurance

This clinical study will be monitored according to the Sponsor’s current standard operating procedures or those of the designated CRO, as well as GCP/ICH Guidelines, and all applicable regulatory requirements.

Steps will be taken to ensure the accuracy and reliability of data before study start, including the implementation of a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Before study initiation, the Sponsor will identify potential risks associated with critical study processes and data and will implement plans for evaluating and controlling these risks.

During the study, the Investigator shall permit the Sponsor or its representatives to verify the progress of the study through on-site visits and remote monitoring activities. Qualified personnel will review CRF data for accuracy and completeness (remotely or on-site) utilizing the EDC system and against source documents as appropriate. Data discrepancies will be resolved with the Investigator or designees, as appropriate. The Investigator shall provide missing or corrected data and sign the data collection tools.

Data management and other qualified personnel will review CRF data for completeness, logical consistency, and safety; automated validation programs are used to help identify missing data, protocol violations, out of range data, and other data inconsistencies. Personal information will be treated as strictly confidential and will not be publicly available. The EDC system will maintain a full audit trail of electronic data changes. Access to all source documentation will be made available for monitoring and audit purposes.

11. DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP and regulatory and institutional requirements, for the protection of confidentiality of participants.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the Investigator. The study CRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported in the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested in the CRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the system. At the end of the study, the Investigator will receive participant data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

The Investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A Trial Master File will be established at the beginning of the study, maintained for the duration of the study, and retained according to appropriate regulations.

11.1. Retention of Records

The Sponsor and the Investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the study (EU CTR Article 58). All documentation relating to the study must be maintained for a period of at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications, or if not approved at least 2 years since formal discontinuation of clinical development of the investigational product and notification to relevant authorities, but in any case such documentation must be archived for a minimum of 25 years after the end of the study (EU CTR Article 58). The Sponsor will retain study documents for a longer length of time if required by relevant national or local health authorities. The medical files of participants shall be archived in accordance with national law.

No records may be disposed of by the Investigator/institution before having obtained written approval from the Sponsor. Written notification must be provided to the Sponsor before transferring any records to another party or moving them to another location. The Sponsor must be notified in writing of the name and address of the new custodian.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Ethics Review

This protocol, the ICFs, any information to be given to the study participant, and relevant supporting information must be submitted to an IRB/IEC/REC (national or regional) by the Investigator and must be reviewed and approved (or given a favorable opinion in writing) by an IRB/IEC/REC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/IEC/REC. The Investigator must obtain IRB/IEC/REC approval for the investigation. The Investigator must submit the IRB/IEC/REC written approval to the Sponsor before he or she can enroll any participant into the study.

Initial IRB/IEC/REC approval, and all materials approved by the IRB/IEC/REC for this study, including the participant consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

The Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC/REC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC/REC. Investigators are also responsible for promptly informing the IRB/IEC/REC of any protocol amendments. The protocol must be re-approved by the IRB/IEC/REC upon receipt of amendments and annually, as local regulations require.

In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC/REC. Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC/REC and archived in the site's study file.

The Investigator is also responsible for providing the IRB/IEC/REC with reports of AEs that are unexpected, serious, and having implications for the conduct of the study requiring a significant and safety-related change in the protocol (e.g. revising Inclusion/Exclusion criteria or including new monitoring requirements), informed consent, IB, or other aspects of the overall conduct of the clinical investigation. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC/REC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

This clinical study was designed, and shall be implemented and reported, in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including Clinical Trials Regulation [Regulation (EU) No 536/2014] and the United States Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

12.3. Financing and Insurance

Finance and insurance will be handled by the Sponsor. Insurance coverage will be maintained in accordance with the laws and regulations of the trial countries.

12.4. Written Informed Consent

The Sponsor's sample ICF will be provided to each site. A representative from the Sponsor must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternative consent forms proposed by the site (collectively, the "Consent Forms") before IRB/IEC/REC submission. The final IRB/IEC/REC approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The participant's signed and dated informed consent must be obtained before conducting any study-related activity. This will be done in accordance with the national and local regulatory requirements. The Investigator or authorized member of the investigational staff will provide the participant full and adequate oral and written information about the nature, purpose, possible risks or hazards, alternative treatment options, and potential benefits of the study. Participants will be told that they are free to refuse to participate and may withdraw their consent to participate at any time for any reason.

The participant should be provided sufficient time to read the ICF, consider the information provided, and the opportunity to ask questions. The informed consent obtained from the participant includes explicit consent for the processing of personal data where:

- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant 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/REC members, and by inspectors from regulatory authorities.

After their review and before entry into the study, consent is appropriately recorded by means of the participant's personally dated signature. If a participant is unable to read or write, an impartial witness must be present for the entire informed consent process, which includes reading and explaining all written information, and should personally sign and date the ICF after oral consent is obtained from the participant, if permitted by local law. The case history or clinical records for each participant shall document the informed consent process and that informed consent was obtained before participation in the study.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant.

The ICF should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. If the ICF is revised (through an amendment or an addendum) while a participant is participating in the study, the participant must re-consent with the most current version of the ICF or the addendum, in accordance with applicable laws and IRB/IEC/REC policy. All signed and dated

ICFs must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

12.5. Protection of Participant Data

The Sponsor, as Data Controller, will ensure that all processing activities involving personal data performed in the scope of this study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data, the Sponsor will implement and maintain the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors
- appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial
- effective pseudonymization of personal data in compliance with the European Data Protection Board's Recommendations 01/2020 (V2.0 adopted 18 June 2021)
- encryption of personal data, where appropriate
- ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services
- network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures, and response to such attacks
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident
- logging of security events/incidents in information systems
- procedures that cover reporting, analysis, monitoring, and resolution of security incidents
- ensuring that information systems, computers, and software involved in the performance of the services provided in the study are backed up
- a process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing
- procedures to detect within reasonable timely manner if a personal data breach has occurred
- procedures and practices for destruction of paper documents containing personal data

- business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption

All locations, personnel, and information systems that are used to perform services for the study will be covered.

Sponsor will ensure the technical and organizational security measures described above are regularly reviewed and updated to consider the technological developments.

The Sponsor may apply additional specific statutory requirements, where required by national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, the Sponsor, by means of internal measures and imposed contractual clauses to the selected vendors and partners (in their role of processors), will ensure the confidentiality of records and personal data of the participants.

With exception of the activities in the scope of the on-site monitoring, inspections, or audits, the name of the participant will neither be asked for, nor recorded by the Sponsor. An identification number will be allocated to each participant registered in the Study. This number will identify the participant and will be included in all CRFs and corresponding material and data associated with the participant.

Monitors acting on behalf of the Sponsor will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the study. Staff involved in the performance of this task will be bound by additional stricter confidentiality clauses imposed upon them, as compared with other staff members.

The Sponsor will ensure a functional process for reporting of any data breach occurring at Sponsor's or its vendor's and partner's (in their role of processor) facilities and premises. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data participants as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data participants will be reported to the relevant supervisory data protection authority within 72 hours of Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data participants will be informed by the Sponsor (via investigation site).

12.6. Biological Specimens and Storage

Biological samples collected during the study, and data resulting from sample testing, are protected by the use of the unique participant identification number. Samples collected during the study may also be used to reevaluate biological responses as assays are developed over time. If a participant withdraws from the study, all samples collected prior to study withdrawal may still be provided to and used by the Sponsor to maintain study integrity and fulfill study objectives. If study participation consent is withdrawn, the Sponsor is not required to destroy information or data already collected.

Sample analysis to support exploratory objectives may begin at any time during the sample storage period and may be reported in the CSR, or in a separate analysis summary.

Samples will be retained in a secure facility through marketing application approval for a maximum duration of up to 10 years with the exception of formal discontinuation of clinical development of STAR-0215 where retention through marketing application would not apply.

12.6.1. Genetics

Genetic (DNA) variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. The specifics of DNA evaluation are found in Section 7.13.4.3.

If a participant consents to the optional collection of blood for pharmacogenetic/-omic analysis, the Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. No participant personal identifying information is available to the Sponsor or organizations working with DNA. Accordingly, and as the analysis is exploratory, specific results will not be made available. Aggregate results of genetic analyses may be reported in the CSR or in a separate scientific report.

12.6.2. Future Research

Once study-specified objectives are completed, remaining samples and remaining volume of samples in storage may be used for future research if the participant provides additional consent for this testing.

It is not always possible to define or predict at study start what new research, information, or technology becomes available that enables a deeper understanding of factors related to the disease, disease pathway, or study therapeutic. Samples stored for future research may prove beneficial to, for example, understanding the disease mechanism of action or pathogenesis, risk factors, or how a participant responds to the study therapeutic. This research may be undertaken by the Sponsor, others such as researchers at universities, or clinicians.

Samples stored for future research retain the same participant ID used in the main study. Participants may withdraw consent for future use at any time during or after the study by contacting the study site Investigator. If future use consent is withdrawn, the Sponsor will destroy the sample once all study-related objectives have been completed; however, if the sample has already been used in future research, the results are not required to be destroyed.

12.7. Dissemination of Clinical Study Data

All information, including but not limited to information regarding STAR-0215 or the Sponsor's operations (e.g. patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information), supplied by the Sponsor (or designee) to the Investigator and not previously published, and any data generated as a result of the study, are privileged and confidential information. The Investigator agrees to maintain this information in confidence, use this information only to conduct the study, and not to use it for any other purpose without prior explicit written consent from the Sponsor.

It is understood that there is an obligation on the part of the Investigator to provide the Sponsor with the complete data obtained during the study. Such information will be used in the clinical development of the STAR-0215 and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

Policies concerning publication of data are described in Section 13.

12.8. Protocol Adherence

In compliance with ICH E6, Guidelines for GCP, the Investigator should not implement any deviation from or changes of the protocol without written agreement by the Sponsor and documented approval from the IRB/IEC/REC of a protocol amendment except where necessary to eliminate immediate hazards to study participants.

Investigators will use all diligence to avoid protocol deviations. Under no circumstances should the Investigator contact any representative of the Sponsor to request approval of a protocol deviation, as no authorized deviations are permitted. If the Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment for any change or addition to the protocol is agreed upon by the Sponsor and approved by the Sponsor, Health Authorities where required, and the IRB/IEC/REC, it cannot be implemented.

The protocol must be thoroughly read and the instructions must be followed; however, exceptions will be made in emergency situations when the protection, safety, and well-being of the participant requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator (or designee) must contact the Medical Monitor at the earliest possible time. This will allow for an early joint decision to be made as to whether the participant should continue in the study. The Investigator, the Sponsor (or designee), and the Medical Monitor will document the decision.

All protocol deviations will be documented in a database. All significant protocol deviations will be recorded and reported in the CSR.

12.9. Study Termination and Clinical Study Center Closure

Clinical study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Sponsor reserves the right to terminate the study or close the clinical study center at any time for any reason at the sole discretion of the Sponsor.

The Investigator may initiate study center closure at any time, provided there is reasonable cause, and enough notice is provided to the Sponsor in advance of the intended termination.

Reasons for study termination or the early closure of a clinical study center by the Sponsor or Investigator may include, but are not limited to, the following:

- Discovery of an unexpected serious or unacceptable risk to participants enrolled in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC/REC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further STAR-0215 development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRB/IEC/REC, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

13. PUBLICATION POLICY

All information regarding STAR-0215 supplied by the Sponsor to the Investigator or generated by the Investigator in accordance with the conduct of the study is privileged and confidential information of the Sponsor. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used by the Sponsor in connection with the development of STAR-0215 and may be disclosed by the Sponsor to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

The Investigator's right and obligations with respect to publishing or otherwise presenting information regarding the study are detailed in the Publication provisions of the Clinical Study Agreement among the Investigator, the clinical site, and the Sponsor. The Investigator shall comply with such provisions.

Publication by any study site of any data from this study must be carried out in accordance with the Clinical Trial Agreement and not without prior consent of Astria.

14. LIST OF REFERENCES

Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020;124(6):600-7.

Bouillet L, Fain O, Armengol G, et al. Long-term prophylaxis in hereditary angioedema management: Current practices in France and unmet needs. Allergy Asthma Proc. 2022;43(5):406-12.

Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-50 e3.

Christiansen SC, Davis DK, Castaldo AJ, et al. Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clin Pediatr (Phila). 2016;55(10):935-42.

Craig T, Aygoren-Pursun E, Bork K, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-99.

CTFG. Recommendations related to contraception and pregnancy testing in clinical trials. Clinical Trials Facilitation and Coordination Group; 2020.

Kenniston JA, Faucette RR, Martik D, et al. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. J Biol Chem. 2014;289(34):23596-608.

Lumry WR. Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front Med (Lausanne). 2018;5:22.

Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. Allergy Asthma Proc. 2020;41(Suppl 1):S08-S13.

Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med. 2001;161(20):2417-29.

Parsopoulou F, Loules G, Zamanakou M, et al. Searching for Genetic Biomarkers for Hereditary Angioedema Due to C1-Inhibitor Deficiency (C1-INH-HAE). Front Allergy. 2022;3:868185.

Porebski G, Kwitniewski M, Reshef A. Biomarkers in Hereditary Angioedema. Clin Rev Allergy Immunol. 2021;60(3):404-15.

Sanchez-Felix M, Burke M, Chen HH, et al. Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge. Adv Drug Deliv Rev. 2020;167:66-77.

Sundler Bjorkman L, Persson B, Aronsson D, et al. Comorbidities in hereditary angioedema-A population-based cohort study. Clin Transl Allergy. 2022;12(3):e12135.

Viola M, Sequeira J, Seica R, et al. Subcutaneous delivery of monoclonal antibodies: How do we get there? J Control Release. 2018;286:301-14.

Wang Y, Marier JF, Kassir N, et al. Pharmacokinetics, Pharmacodynamics, and Exposure-Response of Lanadelumab for Hereditary Angioedema. Clin Transl Sci. 2020;13(6):1208-16.

[redacted]

Zeerleder S, Levi M. Hereditary and acquired C1-inhibitor-dependent angioedema: from pathophysiology to treatment. Ann Med. 2016;48(4):256-67.

Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-36.

15. APPENDICES

APPENDIX 1. DEFINITION OF PARTICIPANT CAPABLE OF BECOMING PREGNANT AND CONTRACEPTIVE GUIDANCE

Definition of Participant of Childbearing Potential

A participant is considered fertile after menarche and until becoming postmenopausal unless permanently sterile. If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before administration of the first dose of STAR-0215, additional evaluation should be considered.

A participant is not considered capable of becoming pregnant if any of the following apply:

1. Premenarchal
2. Premenopausal with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy or ligation
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to a medical cause other than the above (e.g. mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study eligibility.

Documentation can come from the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal participant
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT; however, in the absence of 12 months of amenorrhea, confirmation with 1 FSH result of greater than 40 IU/L or mIU/mL is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study; otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Participants of childbearing potential and their partners capable of producing sperm, as well as participants capable of producing sperm and their partners of childbearing potential must use 1 of the forms of highly effective contraception listed below during the study, unless they are practicing true abstinence, only in line with the preferred and usual lifestyle of the participant, defined as refraining from heterosexual intercourse during the study.

Highly Effective Methods of Contraception (CTFG 2020)

- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion/ligation/removal
- Azoospermic participant or partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant capable of becoming pregnant and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

  Note: Documentation of azoospermia for a participant capable of producing sperm can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Sexual abstinence

Patients are exempt from contraception requirements if they are practicing complete abstinence, only in line with their preferred and usual lifestyle, defined as refraining from heterosexual intercourse during the study. Participants of childbearing potential must continue to use highly effective contraception for [redacted] months after the last dose.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

APPENDIX 2. ADVERSE EVENT SEVERITY GRADING SCALE TABLES

This appendix contains the adverse event severity grading scale tables to guide investigator assessment of adverse events (Source: Guidance for Industry, Toxicity Grade Scale for Healthy Adult and Adolescent Volunteers in Preventive Vaccine Clinical Trials (FDA 2007)). Refer to the guidance document for more information, available at fda.gov/media/73679/download.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness*	2.5 to 5 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling **	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

Abbreviations: ADL = activities of daily living; ER = emergency room.
Source: Based on the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (FDA 2007)
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

Source: FDA 2007
* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/ 24 hours	4 – 5 stools or 400 – 800 gms/ 24 hours	6 or more watery stools or > 800 gms/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Source:FDA 2007

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be reviewed by the site to confirm that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4) ****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4) ****
Bilirubin – when Liver Function Test is normal increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

Source:FDA 2007

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN **	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

Source:FDA 2007

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

Source: FDA 2007

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.