Protocol Astria STAR-0215-201

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)

Protocol Number: **(Version Date)**	STAR-0215-201 v05 (10 October 2023)
Name of Test Drug:	STAR-0215
Phase:	1b/2
Methodology:	Single and Multiple Dose (Open-Label) Study
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Document Date:	09Aug2024
Document Version:	v3.0

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SIGNATURE PAGE

Protocol 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)
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Document Date/Version:	V3.0/ 09Aug2024

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Sign **Signature:** [redacted]

Date **Email:**

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:

[redacted]
Astria Therapeutics

Signature: [redacted]

Email:

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MODIFICATION HISTORY

Current Version	Date	Amended by	Summary of Changes from previous version	Reason
1.0	11Jan2024		Original document	
2.0	05Apr2024	[redacted]	• Additional swimmer/Banerjee plot • Additional intervals (3 and 6 months from Baseline) for HAE rate and incidence • Repeating some analysis for participants who have completed intervals • HAE attack rate for sub-categories of HAEs (severity or rescue medication) • PK analysis repeated for treatment-emergent ADA status • Adding definitions for treatment-emergent, treatment induced, and treatment boosted ADA status	Some additional HAE attack and PK analysis was performed with IA1, formally documenting this analysis in the SAP. Adding sub-categories of HAEs based on 'administrative analysis'. ADA definition was already present in the shells.
3.0	09Aug2024	[redacted]	IA3 is added.	Client decision to perform analysis once the initial 16 participants completed.

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ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
[redacted]	[redacted]
AE	Adverse events
AM	Arithmetic Mean
AUC	Area under the concentration versus time curve
AUC_{0-24}	Area under the concentration versus time curve from time 0 to the end of the dosing interval 24 hours later, calculated using linear trapezoid rule
BQL	below the limit of quantification
Cavg	Average Concentration
C_{max}	Maximum plasma concentration
C_{min}	Trough plasma concentration, taken 24 hours after dose and prior to subsequent dose
CI	Confidence Intervals
CSR	Clinical study report
CV	Coefficient of Variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GM	Geometric Mean
HAE	Hereditary Angioedema
ICH	International Council on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical analysis plan
SOC	System Organ Class
SRC	Safety Review Committee
TEAEs	treatment emergent AEs
T_{max}	Time to maximum plasma concentration
$t_{½}$	Circulating half-life
WHO	World Health Organization

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1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). Details regarding the management of all data and statistical methodology, including an explanation of the analyses of exploratory endpoints and imputation of missing data, are included in the SAP, which will be finalized prior to the protocol specified [redacted]. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

1.2 Objectives

Table 1: STAR-0215 Objectives & 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 clinical activity 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

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• 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] 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]

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2 STUDY DESIGN

2.1 Introduction

STAR-0215-201 is a multicenter, single- and multiple-dose study to assess the safety, tolerability, clinical activity, 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 delayed clearance and prolonged time in circulation. The study design is a standard approach to the evaluation of the safety and tolerability of an investigational product.

Properly consented participants will undergo screening assessments according to the inclusion and exclusion criteria (Protocol 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 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. (Protocol 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. [redacted]

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 (STAR-0215-101), [redacted] and [redacted] may be explored in [redacted]

STAR-0215 will be administered SC into the abdomen. There are planned to 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] (Protocol 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) [redacted]

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[redacted] The dose regimens and dose levels for each cohort are in Table 2. There is no placebo group in this study. An overview of the study design is provided in Table 3.

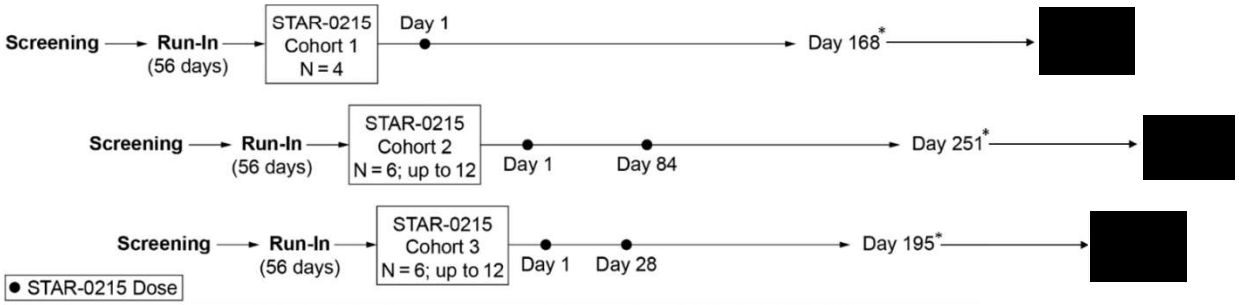
As detailed in the Schedules of Assessments, study assessments will be performed in all cohorts through 6 months after the last dose of STAR-0215 (Day 168 in Cohort 1, Day 251 in Cohort 2, and Day 195 in Cohort 3). At this time, participants who are willing and eligible to consent can begin participation 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 2: 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.

Table 3: 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

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occur if there are no concerning safety signals. [redacted]

2.2 Treatment Assignment

This study is not randomized.

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 2.

2.3 Safety Review Committee and Stopping Rules

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.

Table 4: 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.

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Adverse Event Criteria	Action
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.

2.4 Blinding

This is an open-label study.

2.5 [redacted]

In preparation for future clinical development of STAR-0215 and subsequent study planning, [redacted] of data in accumulating cohorts are planned (Table 5). The [redacted] was planned to occur after the [redacted] in [redacted] reaches the [redacted] visit. However, enrollment into the study was faster than anticipated and the [redacted] in [redacted] have the [redacted] visit [redacted] participants have data up to 90 days post first dose therefore it was decided that the [redacted] will include the [redacted] visit for these [redacted] and all other available data from [redacted] In addition, for the same reasons, the [redacted] will occur after the [redacted] in [redacted] reaches [redacted] of STAR-0215 (the [redacted] visit) and will include all available data from [redacted]. At each [redacted] the Sponsor will review the accumulated safety, efficacy, PK, PD, and immunogenicity data. If no safety concerns are noted following [redacted], 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].

A [redacted] will occur when the first 16 participants dosed complete the study. Separate analyses of the 'Initial 16 Participants' and cumulative data for all participants dosed at the time of data cut-off will be performed on the accumulated safety, efficacy, PK, PD, and immunogenicity data.

The IA will summarize safety, efficacy, PK, PD and immunogenicity (ADA) by cohort; as described in section 6 and per Table 5. Listings and figures will also be provided.

Additional ad hoc or unplanned administrative analyses may be performed to monitor safety, PK, PD, ADA and/or efficacy.

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Table 5: [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] • [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] 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] • [redacted] • Inform Sponsor's decision-making regarding [redacted]
[redacted]	[redacted] dosed completes study	All available cumulative safety, PK, PD, immunogenicity, and efficacy data for all participants enrolled	Inform Sponsor's decision-making regarding [redacted]

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

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3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Incidence of adverse events (AEs)
- Change from Baseline in vital signs, electrocardiogram (ECG) findings, physical examination findings, and clinical laboratory evaluations

3.2 Secondary Endpoints - Efficacy

- Change from baseline in monthly HAE attack rate, overall and per month.
    - 50%, 70%, and 90% overall reduction of HAE attacks
    - Investigator assessed HAE Attack definition is given in Protocol section 7.12.1:

      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, Abdominal angioedema, or Laryngeal angioedema.

      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.
- Proportion of participants who are HAE attack free
- Incidence of at least one HAE attack by maximum severity (mild, moderate, and severe), including participants without any attacks.
- 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, censored to End of Study visit.
- HAE attack free days, from treatment start until End of Study.

3.3 Secondary Endpoints - Pharmacokinetic, Pharmacodynamics (PD) and immunogenicity

- Concentration of STAR-0215 and the derived PK parameters
    - Maximum drug concentration (Cmax)

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- Time of Cmax (Tmax)
- Area under the curve (AUC) after a defined duration or at steady state
- Circulating half-life (t½)
- Apparent clearance (CL/F)
- Volume of distribution (V/F)

- Change in plasma kallikrein activity (PD)
- Formation of anti-drug (STAR-0215) antibodies

3.4 Exploratory Endpoints

- Changes from baseline in the [redacted]

  For the evaluation of the questionnaire, the total score is/will be measured based on [redacted], and the domains are/will be evaluated separately. The [redacted]. The [redacted] corresponded with the average of items found in one domain. The [redacted]

- Changes from baseline in [redacted] of STAR-0215

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4 ANALYSIS SETS

4.1 Analysis Set Definitions

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

4.1.1 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, biomarker and immunogenicity (ADA) endpoints.

4.1.2 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 of HAE attack (conducted at each treatment period visit). This analysis set will be the primary analysis set for all clinical activity endpoints. Additionally, this analysis set will have no important protocol deviations that could affect the evaluation of clinical activity parameters.

4.1.3 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 important protocol deviations that could affect the evaluation of PK parameters.

4.1.4 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 important protocol deviations that could affect the evaluation of PD parameters.

4.2 Protocol Deviations

Protocol Deviations will be classified as Important or Non-Important. Important Protocol Deviations may lead to removal of participants' data from efficacy, PK or PD analysis. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator and the study statistician. Determination of whether important deviations have an impact on any of efficacy,

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PK or PD assessments, will be determined prior to any formal analysis. A report of Protocol Deviations (excel or csv format) will include important /non-important distinctions, category, description, population impact (each of efficacy, PK or PD), in addition to dates and other relevant variables.

The number (%) of participants with at least one protocol deviation and the number (%) of participants with at least one important protocol deviation will be summarized. For the important protocol deviations, the number (%) of participants in each deviation category will be presented.

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5 DATA HANDLING

5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 25.1 or later. Concomitant medications will be coded using World Health Organization (WHO) Drug version Sept 2022 or later.

5.2 Data Conventions

- **Period definition:**
  - **Screening/Run-In Period:** Starts at the Screening visit until the day before first treatment, approximately Study Day -56 to -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.
  - **Treatment & Follow-up Period:** The period from date of first dose to End of Study Date.
  - **End of Study Date:** The latest of date of Early Termination visit or as designated by "End of Study" CRF page.
  - **Treatment Period (for HAE assessments)** is defined in Section 9.1; for this period the last scheduled visit for each cohort is Day 168 visit for cohort 1, Day 251 visit for cohort 2, and Day 195 visit for cohort 3. The last assessment date or last dose date can be used for participants that have not reached the end of their cohort's treatment period.
  - **First Dose Period (for HAE assessments)** is defined as the first dose until participant's second dose (cohorts 2 & 3) or end of treatment period.
  - **Study day:** Relative to the date of first treatment of STAR-0215: assessment date – first treatment date (+1 if assessment is after first treatment).
- **Conversion factors:**
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
  - 1 week = 7 days
- **Additional rules**
  - (Absolute) Change from baseline = Value at the time point – Baseline value.
  - Relative change from baseline = [(Value at the time point – Baseline value) / Baseline value] x 100.

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- % inhibition (of pharmacodynamic assessments) = 1 – [postdose rate / predose rate]) x 100.
- Duration on Study = (End of Study Date – Date of First STAR-0215 treatment) +1.
- Duration of Treatment Period = (Last Treatment period assessment date – Date of First STAR-0215 treatment) +1.

5.3 Methods of Pooling Data

Not applicable.

5.4 Withdrawals, Dropouts, Loss to Follow-up

For participants who withdraw from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis.

5.5 Visit Windows

Visit Windowing will not be applied. Summary tables or graphs will display scheduled visits and time points only; Unscheduled visits results will be listed, but not included in tables or graphs.

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6 STATISTICAL METHODS

6.1 Sample Size Justification

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, clinical activity, 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.

6.2 General Statistical Methods

6.2.1 General Methods

All outputs will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, PK, PD, Immunogenicity and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, Q1, Q3, minimum and maximum values will be presented. The PK summaries will additionally include the percent coefficient of variation (CV%), geometric mean, and geometric CV%. Descriptive statistics for categorical variables will consist of frequency counts and percentages.

Results will be presented by cohort.

No formal statistical hypothesis testing will be performed. Summary statistics will be presented, as well as 95% confidence intervals (CI) on selected parameters, as described in the sections below.

6.2.2 Definition of Baseline

For the analysis of HAE attacks, the Run-In Period will be considered as Baseline for rate, incidence or duration of HAE attacks.

For all other endpoints baseline is defined as the last non-missing assessment prior to the first dose of STAR-0215.

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6.2.3 Adjustments for Covariates

No statistical analysis assessment of possible covariate effects is planned.

6.2.4 Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

6.2.5 Subgroups

Subgroups analyses are not planned.

6.2.6 Missing, Unused, and Spurious Data

Data will be analyzed as observed. No imputation for missing data will be performed unless otherwise specified.

For binary endpoints participants who discontinue treatment will be considered as non-responders.

No other imputation of missing endpoints will be used.

For partial or missing AE start dates the following imputation will be applied:

1. If year is not missing and is after the year of first dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first dose:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.
    c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.
3. If year is missing then impute the year as the year of the first dose date:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, then impute the day as the day of the first dose date.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first dose date then impute the start date as the first dose date.
5. For any cases involving the rules above, if the AE end date is before the AE start date, then do not impute the AE start date and assume that the AE is treatment emergent for the

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purpose of the analysis. Further, if the AE stop date occurs prior to the first dose date, do not impute the AE start date, and assume that the AE is not treatment emergent.

No imputations will be applied to AE stop dates.

6.3 Study Population

6.3.1 Subject Disposition

Subject disposition will be presented, including the number screened, the number dosed, and the number that have completed, discontinued, or are ongoing in the study and reasons for discontinuation. The number of participants in each analysis set will also be presented.

The summaries will be presented by cohort and overall. The denominator for all percentages will be the total number of participants in each cohort.

The following by-subject listings will be presented.

- Study completion information, including the reason for premature study withdrawal.
- Inclusion/exclusion criteria
- Inclusion in study Analysis Sets; Reasons for exclusion from the Efficacy, PK, or PD analysis sets
- Protocol deviations

6.3.2 Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized for the Safety and Efficacy analysis sets using descriptive statistics.

Medical history will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). No formal statistical comparisons will be performed.

Baseline disease characteristics will include the type of HAE (Type 1 or 2), Age of onset of first angioedema symptoms (Years), and the Number of hereditary angioedema attacks in the previous 12 months.

Demographic and Baseline data will be provided in data listings.

6.3.3 STAR-0215 Administration

STAR-0215 Administration details will be listed by cohort.

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6.4 Efficacy Evaluation

All analyses of HAE attack data will be presented using the Efficacy Analysis Set. Both Run-In and Post-Treatment period will be displayed where applicable.

All HAE attacks that occurred on study will be listed for both Run-In and Treatment periods.

A summary of Run-In period HAE attack assessments will include Location of HAE attacks (Abdominal, Laryngeal, Peripheral); the baseline (Run-In period) values of: HAE attack rate, HAE attacks by worst severity (none/attack-free, mild, moderate, and severe), duration of each participants longest HAE attack, number and proportion of HAE attacks requiring on-demand therapy, and HAE Attack Free Days. This summary will be repeated for the first dose period.

6.4.1 Change from Baseline in Monthly HAE attack rate

HAE attack rate will be expressed as the number of unique investigator-confirmed HAE attacks per month. Only unique (non-overlapping) HAE attacks will be counted; attacks are considered overlapping when a start date falls within 24 hours of an earlier attack's end date. The HAE attack rate will be calculated as:

(number of HAE attacks / duration of evaluation period in days) * 30.4375; where the duration of participants' run-in period and post-treatment follow-up periods is defined in Section 9.1 and section 5.2 (Treatment period).

Change from baseline (Run-In period) to on treatment HAE attack rate, will be summarized by the absolute and percentage change from Baseline. Descriptive statistics (mean, median, standard deviation, Q1, Q3, minimum and maximum values) and 95% CI will be presented. The proportion of participants with a clinical response to treatment will be presented in increments as greater than or equal to 50%, 70%, and 90% reduction of HAE attacks.

A plot of individual participant's HAE attacks over time will display duration and severity by cohort. The plot will begin in the run-in phase through the last HAE assessment. The scheduled dose(s) of each cohort will be represented with dotted-lines. This plot will also be created by HAE attack location or overall cohort plot (combining participants).

HAE attacks per month (attack rate) will be presented at 4-week intervals (28 Days) from treatment start; first dose period, and 3 and 6 month intervals following last dose; and the first 3 and 6 months from Baseline (from initial dose) will also be provided. The mean monthly rate, change from baseline, and 95% CI will be presented; percent change will also be presented for monthly rates. Additional analysis of participants who have completed each interval may be performed.

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Analysis of overall HAE attack rate or certain intervals, will be performed on sub-categories of HAEs: by HAE severities Mild, Moderate, Severe, and Moderate or Severe; and those that required therapy ("rescue medication").

6.4.2 HAE Attack Incidence and Severity

The incidence and proportion of HAE attacks by worst severity (none/attack-free, mild, moderate, and severe) will be summarized.

The proportion of participants who are attack free for the entire treatment period; first dose period, and in 3 month intervals following second/last dose; and the first 3 months and 6 months from Baseline will be summarized.

6.4.3 HAE Attack Duration

The duration of each participant's longest HAE attack will be presented with descriptive statistics and for the following categories: shorter than 12 hours, 12 to 24 hours, 24 to 48 hours, and longer than 48 hours.

6.4.4 HAE Attack Requiring Therapy

The number of HAE attacks and the proportion of participants requiring on-demand therapy at baseline and during the treatment period will be summarized. The type of on-demand therapies used to treat HAE attacks will also be summarized.

6.4.5 HAE Attack Free Days

Descriptive statistics for the number of HAE attack free days will be provided for Baseline and on treatment. Attack Free Days may consider overlapping attacks to count any day on study without an attack. The proportion of HAE attack free days will also be provided, calculated as: the number of HAE attack free days / duration of evaluation period in days. In addition to overall post-treatment summary, the proportion of HAE attack free days will presented in 3 month intervals and 6 months from first dose (for Cohort 1) and 6 months from *second dose* (for Cohorts 2 and 3). Additional analysis of participants who have completed each interval may be performed.

6.4.6 Time to first HAE attack after first and last dosing

The time to first HAE attack will be calculated by: ([First HAE attack or censor date] – Treatment date) +1; If a participant does not have an HAE attack, they will be censored to the end of the treatment period.

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The number of participants with an HAE attack or censored will be presented. Time to first HAE attack after first dose of STAR-0215 will be presented using Kaplan-Meier estimates of 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CI. The proportion of participants with their first HAE attack at 28, 56, 84, and 168 days as applicable per cohort will be calculated. The time to first HAE Attack after last dose, will be presented in the same manner.

The survival curves will be generated using the Kaplan-Meier method.

6.4.7 [redacted].

The changes from baseline in the [redacted] will be presented with descriptive statistics by time point.

The [redacted]

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6.5 Pharmacokinetic pharmacodynamics (PD), immunogenicity and biomarkers Variables Evaluations

6.5.1 Pharmacokinetic Evaluations

Pharmacokinetic analyses will be conducted on participants in the PK Analysis Set and individual plasma concentration summary statistics will be computed using all available PK data. Assays from LC-MS/MS and ELISA will both be analyzed.

Plasma Concentrations:

Cohort 1:

Day1: Predose, 4hr (post -dose); 2, 7, 14, 28, 56, 84, 112, 140, 168 days post-dose

Cohort 2:

Day1: Predose, 4hr (post -dose); 2, 7, 14, 28, 56 day

Day 84: Predose, 4hr (post -dose); 85, 90, 97, 111, 139, 167, 209, 251 days post-initial dose

Cohort 3:

Day1: Predose, 4hr (post -dose); 2, 7, 14 day

Day28: Predose, 4hr (post -dose); 29, 34, 41, 55, 83, 111, 153, 195 days post-initial dose

Individual plasma STAR-0215 concentration data will be listed for each participant and summarized by nominal sampling time point and visit as applicable with descriptive statistics as described below.

Plasma concentrations below the limit of quantification (BLQ) will be flagged as BLQ in the concentration and parameters tables and considered to be 0 for PK and descriptive statistical analysis. BLQ values in between two measurable concentrations will be treated as missing.

If more than 50% of values are below the LLOQ, the mean and standard deviation will be shown as not calculable (NC), and the minimum value will be shown as BLQ. BLQ values between two measurable concentrations are treated as missing. Missing values will be omitted from the calculation of descriptive statistics. Number of missing values will be reported in descriptive statistics.

Individual plasma concentration-time data will be displayed graphically, summarized, and listed. Individual plasma concentrations below the LLOQ will be graphed as ½ LLOQ.

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Plasma concentrations will be summarized by visit / timepoint including all sample assessments. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point. n (number of non-missing observations), arithmetic mean(AM), SD, median, Q1, Q3, minimum, maximum, geometric mean, geometric CV, where GCV% = sqrt(exp(s^2) – 1) *100 and s is the standard deviation of the log-transformed values.

Plasma concentrations vs. time will be displayed graphically in linear and semi-log scale using arithmetic mean and geometric mean. Nominal sampling times will be used in the table summaries and summary figures of plasma concentrations.

Non-Compartmental Analysis:

Pharmacokinetic analyses will be conducted using the PK Set. PK parameters of STAR-0215 will be analyzed based on the actual sampling times. When actual times are not available, nominal times will be used instead if deemed appropriate by the pharmacokineticist.

All parameters will be derived using model-independent methods (non-compartmental analysis – NCA) as implemented in Phoenix® WinNonlin® version 8 or higher (Certara USA Inc., Princeton, New Jersey).

The following PK parameters will be calculated for STAR -0215 based on all available samples:

Cohort 1 Day 1:

Parameter (Units)	CDISC TERM	Definition	Method of Determination
AUC0-t*	AUCLST	AUC from time zero to time t of the last measured quantifiable concentration calculated using the linear-up/logarithmic-down trapezoidal method	Calculated using the linear up/log down variant of the trapezoidal rule
AUC0-∞	AUCIFP	Area under the concentration versus time curve from 0 to infinity	Calculated as AUC0-last + Cest,last/λz, where Cest,last is the estimated last measurable concentration and AUC0 last is the area under the concentration-time curve from 0 to the time of the last quantifiable (above LLOQ) sample after dosing

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			(calculated using the 'linear up, log down' calculation method)
Cmax	CMAX	maximum observed plasma concentration	Observed value
tmax	TMAX	time to reach Cmax	Observed value
Cavg[#]	CAVG	Average Concentration	AUCTAU divided by TAU
t½	LAMZHL	apparent terminal half-life	ln(2)/ λz, where λz is the apparent first-order terminal elimination rate constant. At least three consecutive time points (excluding Cmax) in the terminal phase will be used for apparent terminal half-life determination, with an R^2 vale of 0.85 or greater

***** AUC(0-t) = AUC from time zero to last quantifiable time-point or 168 days
[#] The value of Tau used for this analysis is 168 days

Cohort 2 Dose 1:

Parameter (Units)	**CDISC TERM**	**Definition**	**Method of Determination**
AUC0-84	AUCINT	The area under the curve (AUC) over the interval from 0 to 84 day.	Calculated using the linear up/log down variant of the trapezoidal rule
Cmax	CMAX	maximum observed plasma concentration	Observed value
tmax	TMAX	time to reach Cmax	Observed value

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Cavg[#]	CAVG	Average Concentration	AUCTAU divided by TAU

[#]The value of Tau used for this analysis is 56 days

Cohort 2 Dose 2:

Parameter (Units)	**CDISC TERM**	**Definition**	**Method of Determination**
AUC84-251	AUCINT	The area under the curve (AUC) over the interval from 84 to 251 day.	Calculated using the linear up/log down variant of the trapezoidal rule
AUC0-251	AUCINT	The area under the curve (AUC) over the interval from 0 to 251 day.	Calculated using the linear up/log down variant of the trapezoidal rule
AUC0-∞	AUCIFP	Area under the concentration versus time curve from 0 to infinity	Calculated as AUC0-last + Cest,last/λz, where Cest,last is the estimated last measurable concentration and AUC0 last is the area under the concentration-time curve from 0 to the time of the last quantifiable (above LLOQ) sample after dosing (calculated using the 'linear up, log down' calculation method)
Cmax	CMAX	maximum observed plasma concentration	Observed value
tmax	TMAX	time to reach Cmax	Observed value
Cavg[#]	CAVG	Average Concentration	AUCTAU divided by TAU
CL/F[*]	CLFP	total clearance	Calculated as CLFP = Dose/ AUC0-∞

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t½	LAMZHL	apparent terminal half-life	ln(2)/ λz, where λz is the apparent first-order terminal elimination rate constant. At least three consecutive time points (excluding Cmax) in the terminal phase will be used for apparent terminal half-life determination, with an R^2 vale of 0.85 or greater

*Computed using the AUC(0-inf) over both doses
#The value of Tau used for this analysis is 168 days

Cohort 3 Dose 1:

Parameter (Units)	CDISC TERM	Definition	Method of Determination
AUC0-28	AUCINT	The area under the curve (AUC) over the interval from 0 to 28 day.	Calculated using the linear up/log down variant of the trapezoidal rule
Cmax	CMAX	maximum observed plasma concentration	Observed value
tmax	TMAX	time to reach Cmax	Observed value

Cohort 3 Dose 2:

Parameter (Units)	CDISC TERM	Definition	Method of Determination
AUC0-195	AUCINT	The area under the curve (AUC) over the interval from 0 to 195 day.	Calculated using the linear up/log down variant of the trapezoidal rule
AUC28-195	AUCINT	The area under the curve (AUC) over the interval from 28 to 195 day.	Calculated using the linear up/log down variant of the trapezoidal rule

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AUC0-∞	AUCIFP	Area under the concentration versus time curve from 0 to infinity	Calculated as AUC0-last + Cest,last/λz, where Cest,last is the estimated last measurable concentration and AUC0 last is the area under the concentration-time curve from 0 to the time of the last quantifiable (above LLOQ) sample after dosing (calculated using the 'linear up, log down' calculation method)
Cmax	CMAX	maximum observed plasma concentration	Observed value
tmax	TMAX	time to reach Cmax	Observed value
Cavg[#]	CAVG	Average Concentration	AUCTAU divided by TAU
CL/F[*]	CLFP	total clearance	Calculated as CLFP = Dose/ AUC0-∞
t½	LAMZHL	apparent terminal half-life	ln(2)/ λz, where λz is the apparent first-order terminal elimination rate constant. At least three consecutive time points (excluding Cmax) in the terminal phase will be used for apparent terminal half-life determination, with an R^2 vale of 0.85 or greater

[#]The value of Tau used for this analysis is 195 days
*CL/F computed over the entire time-course of concentrations

In addition to summarization by cohort and dose, the calculated PK parameters will also be summarized by ADA status and dose cohort provided in the dataset. A participant will be considered ADA-positive if, at any time during the dosing interval, anti-drug antibodies are detected. Similarly, treatment-emergent ADA status will be used to summarize PK parameters.

PK parameters will also be summarized graphically by ADA status and dose cohort with either box plots or scatter plots depending on the amount of data.

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The AUC parameters will be calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations ('linear up, log down') calculation method option in WinNonlin.

Onset of the apparent terminal log-linear phase used in the calculation of λz will be determined using WinNonlin Auto Selection and will be reviewed by the pharmacokineticist for reasonableness. No values for AUC0-∞ or Apparent Terminal t1/2 will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Parameters "Rsq_adjusted" (adjusted R2), AUC0-last, and "AUC%extrap_predicted" (predicted percent extrapolated AUC0-∞) will be included as part of WinNonlin parameter output for supportive information on determination of the individual Apparent Terminal t1/2 and AUC0-∞ values. For half-life, only estimates with a minimum of 3 time-points and an R^2 value of 0.85 or greater will be reported.

All PK parameters will be listed by participant and summarized by cohort. The following descriptive statistics will be presented: n (number of non-missing observations), arithmetic mean, SD, median, Q1, Q3, minimum, maximum, geometric mean, geometric CV). Geometric CV (GCV) will be calculated as GCV%=SQRT(exp(s²)-1)*100 and s is the standard deviation of the log-transformed values.

The PK parameters like AUC and Cmax will be represented in 3 significant digits and Tmax (individual, MIN, MED and MAX) in 2 decimals. The descriptive statistics like AM, SD, GM, MED, MIN, MAX will be represented in 3 significant digits and ACV, GCV in1 decimal. For individual concentration summary stats, IQR will be represented in 3 significant digits.

If the pre-dose(before first dose) concentration at Visit 1 is ≤ 5% of Cmax value, the participant's data without any adjustment will be included in all pharmacokinetic calculations. If the pre-dose (before first dose) value is > 5% of Cmax, the participant will be dropped from all PK calculations and descriptive statistics.

6.5.2 Pharmacodynamics Evaluations

Pharmacodynamic analyses will be conducted on data from participants in the PD Analysis Set. Descriptive statistics will be presented for plasma kallikrein activity levels (as measured by %cHMWK), absolute change and percentage change from baseline levels will be analyzed at each visit. A test comparing the percent change and absolute change from baseline within each group will be calculated and a within group p-value will be presented at each visit and timepoint.

Mean and median activity levels versus time, change from baseline, and percent change from baseline profiles will be plotted by treatment on a linear scale. Individual levels versus time plots by cohort and spaghetti plots with subject level versus time profiles by cohort will also be provided on a linear scale.

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Exploratory analyses to assess orthogonal measures of plasma kallikrein enzyme activity (peptide reporter substrate assay) will be performed. Descriptive statistics will be presented for the rate of activity and % inhibition result. A test comparing the % inhibition change and change from baseline to zero within each group will be calculated and a within group p-value will be presented at each visit and timepoint.

The mean and median % inhibition versus time profiles will be plotted by cohort on a linear scale. Individual values versus time plots by treatment and spaghetti plots with subject levels versus time profiles by cohort will also be provided on a linear scale.

6.5.3 Immunogenicity (ADA) Evaluations

Analysis of ADA data will be based on the Safety Analysis Set.

The ADA status will be defined using the baseline and post-baseline results. Anti-drug antibody negative is defined as negative results at all time points. Anti-drug antibody positive is defined as a positive result at any time point, including baseline.

The number and percentage of participants with negative and positive ADA results will be tabulated by cohort.

The number and percentage of participants with ADA negative, positive, and missing results will be tabulated at baseline for the safety analysis set. Additionally, the number of participants with baseline and postbaseline samples will be presented.

Participants with negative baseline result with a positive ADA result post dose are considered treatment induced ADA status; Participants that are ADA positive at Baseline with a post-baseline ADA positive titer result >= 4x Baseline value have treatment boosted ADA status. Treatment-emergent ADA participants have either treatment induced or treatment boosted ADA status.

Data will be summarized for ADA results at all time points. The incidence (defined as treatment induced plus treatment boosted) and prevalence (ADA positive at any time point) will be presented. Treatment induced is defined as negative at baseline and positive at any time point postbaseline. Treatment boosted is defined as positive at baseline and a postbaseline titer of at least 4 times the baseline positive titer result. Descriptive statistics will be presented for the positive titer values.

The incidence and prevalence will be summarized by cohort.

All ADA results will be presented in a data listing, by date for unscheduled or repeated values.

6.5.4 Biomarker Evaluations

The actual value and change from Baseline to each post-baseline evaluation will be summarized. Analysis will be based on the Safety Analysis Set.

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6.6 Safety Evaluations

Safety analyses will be conducted using the Safety Analysis Set.

6.6.1 Adverse Events

Adverse events will be coded using MedDRA and will be graded using the severity scale specified in the protocol. .

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, 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.

Adverse events are summarized by participant, therefore, in any tabulation, a participant contributes only once to the count for a given adverse event (SOC or PT).

Separate tabulations may also be produced for TEAEs assessed as related to study drug (related, probable, or possible relationship), TEAEs that led to discontinuation from study, TEAEs that led to death, TEAEs greater than or equal to Grade 3 in severity and TEAEs by highest grade. 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.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: participant deaths; serious adverse events; and adverse events leading to study discontinuation.

6.6.2 Laboratory Data

The actual value and change from Baseline to each post-baseline evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used.

All laboratory data will be provided in data listings.

A subset listing will be presented for all abnormal laboratory values.

6.6.3 Vital Signs and Weight

Vital signs (body temperature, respiratory rate, heart rate, systolic and diastolic blood pressure, weight and BMI) will be summarized by cohort at each scheduled visit. The actual value and change from Baseline to each post-baseline evaluation will be summarized for vital signs. Height at baseline will be used to calculate BMI.

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By-subject listings of vital sign measurements will be presented in data listings.

6.6.4 Electrocardiogram

Heart rate, PR, QRS, QT, and QTcF will be summarized by cohort at each scheduled visit. The actual value and change from Baseline to each post-baseline evaluation will be summarized for ECGs. A tabulation of the overall ECG interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) will also be presented.

All ECG data for each participant will be provided in data listings.

6.6.5 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. 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 (treatment period) 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.

Run-In period medications are those that began between the date of the Screening Run-In visit and the first STAR-0215 administration date.

If a medication end date is partial, the month or year will be compared to STAR-0215 administration start date. If a medication date is missing, or partially missing, and it cannot be determined whether it was taken on or after STAR-0215 administration, it will be considered a concomitant (treatment period) medication.

Prior, Run-In Period, or Concomitant(Treatment period) medications will each be separately tabulated by Anatomic Therapeutic Class (ATC) and preferred term.

The use of medications will be included in by-subject data listing, designated as Prior, Run-In period, or Concomitant.

HAE medications will be summarized for prior usage, Run-In, and treatment period (based on definitions above). HAE medications will be determined by ATC codes ATC4=B06AC(“DRUGS USED IN HEREDITARY ANGIOEDEMA”) medication with an indication of ‘HAE Attack’ (per EDC) will also be summarized.

The use of HAE medications will be included in by-subject data listing, designated as Prior, Run-In period, or Treatment period medication.

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7 CHANGES TO [redacted]

Protocol text related to Section 2.5/[redacted] was revised: due to fast enrollment each [redacted] will include additional participants and available [redacted] data.

Otherwise, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

A [redacted] will take place when the first 16 participants dosed have completed treatment follow-up. Separate analyses will be performed for the “initial 16 participants’ and for all cumulative data at the time of the data cut-off.

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8 REFERENCES

<add references as appropriate>

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9 APPENDICES

9.1 Schedule of Assessments

Table 6: Schedule of Assessments: Cohort 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] ±7	[redacted] ±7	[redacted] ±7	[redacted] ±7	[redacted] ±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															

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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] ±7	±7	±7	±7	**±7 or ET**
			Pre	**Post**														
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
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											

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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] ±7	±7	±7	±7	±7 or ET
			Pre	**Post**														
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 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

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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] ±7	±7	±7	±7	±7 or ET
			Pre	**Post**														
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).

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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 7: 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	[redacted]					[redacted][18] ±7 or ET
			Pre	Post						Pre	Post									[17] ±7	[17] ±7	[17] ±7	[17] ±7		
Study Assessments																									
Informed Consent	X																								
Inclusion/ Exclusion Criteria	X																								
Medical History/ Demographics	X																								

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	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	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][18] ±7 or ET
			Pre	Post						Pre	Post													
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
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

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	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**	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][18] ±7 or ET
			Pre	**Post**						**Pre**	**Post**													
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					

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	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	[17] ±7	[17] ±7	[17] ±7	[redacted][18] ±7 or ET
Transcriptomics (RNA PAXgene®)	X		X			X		X	X	X			X		X	X	X	X	X					
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.

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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.

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Table 8: Schedule of Assessments: Cohort 3

	Screening	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[1] Pre	28±2[1] Post	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	[8] ±7 or ET
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

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	Scree n-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	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][17] ±7	[redacted][8] ±7 or ET
			Pre	Post				Pre	Post													
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
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					

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	Scree n-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**	[redacted]				**[8] ±7 or ET**
			Pre	**Post**				**Pre**	**Post**									**[17] ±7**	**[17] ±7**	**[17] ±7**	**[17] ±7**	
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					
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

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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.

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18 On-site visit to collect concomitant medication and AE assessments including information regarding pregnancy and HAE attacks.

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Astria STAR-0215-201_SAP_v3.0_09Aug2024

Final Audit Report 2024-08-12

Created:	2024-08-09
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAA8b_2f2HDRX5vuJ41S30jFSqGRPGzXIF7

"Astria STAR-0215-201_SAP_v3.0_09Aug2024" History

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2024-08-09 - 9:03:20 PM GMT- IP address: [redacted]

Signer [redacted] entered name at signing as [redacted]
2024-08-09 - 9:05:34 PM GMT- IP address: [redacted]

[redacted] authenticated with Adobe Acrobat Sign.
2024-08-09 - 9:05:35 PM GMT

Document e-signed by [redacted]
Signing reason: Author
Signature Date: 2024-08-09 - 9:05:36 PM GMT - Time Source: server- IP address: [redacted]

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Email viewed by [redacted]
2024-08-12 - 12:10:55 PM GMT- IP address: [redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-[redacted]
Challenge: The user opened the agreement.
2024-08-12 - 12:11:38 PM GMT

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-[redacted]
Challenge: The user completed the signing ceremony.
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