A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients With Hereditary Angioedema (HAE)

NCT05139810

12 Jul 2022

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Donidalorsen for Hereditary Angioedema

A PLAIN LANGUAGE SUMMARY

THANK YOU

Ionis Pharmaceuticals, the sponsor, would like to sincerely thank the participants who took part in this study, "A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients With Hereditary Angioedema (HAE)," also known as the OASIS-HAE study.

WHAT IS HEREDITARY ANGIOEDEMA (HAE)?

Hereditary angioedema (HAE) is a rare and very serious disease that causes sudden and sometimes dangerous swelling in different parts of the body, like the face, throat, stomach, arms, and legs. The swelling is random, painful, comes back again and again, and can be life-threatening, especially if swelling occurs in the throat. These episodes of swelling can affect the quality of a patient's life.

This long-term illness is due to a problem in a specific gene called SERPING1that encodes a protein called C1 inhibitor. This protein helps to control other proteins in our blood that manage inflammation and swelling. When the SERPING1gene does not work properly, the body either does not make enough of the C1 inhibitor protein (this form of the disease is called HAE-C1INH Type 1) or the protein does not work correctly (this form of the disease is called HAE-C1INH Type 2). When the body does not have enough working C1 inhibitor protein, it produces too much of a molecule called Factor XIIa. Too much Factor XIIa causes another protein called prekallikrein (PKK) to become active and turn into kallikrein. Kallikrein is an enzyme, which is a special protein that helps speed up reactions in the body. Kallikrein cuts a larger protein called high-molecular-weight kininogen into a substance called bradykinin. Large amounts of bradykinin cause blood vessels to widen and cause uncontrolled painful swelling of different body parts called HAE attacks.

WHAT TREATMENT DID REASEARCHERS WANT TO STUDY?

In this study, researchers tested a new medicine called **donidalorsen**. **Donidalorsen** is a type of medicine called an antisense oligonucleotide (ASO). An ASO medication helps reduce the amount of a specific protein in the body called prekallikrein by targeting the messenger RNA (mRNA) that contains instructions to make that protein. **Donidalorsen** specifically attaches to the mRNA that contains instructions for making PKK and signals the cell to break down that mRNA, reducing the amount of PKK produced. This reduction in PKK leads to a decrease in the amount of bradykinin, lowering the chance for swelling.

HOW WAS THIS STUDY DESIGNED?

- **Phase 3**: A Phase 3 study is one of the last studies to be conducted before a new medicine is submitted to government agencies for approval. The study tests the new medicine in participants with the disease to be treated by the medicine to see how well it works and to check for any medical problems.
- **Randomized**: Participants were randomly assigned to a treatment in the study by chance (like rolling a specific number on a die).
- **Placebo-controlled**: Patients were randomly assigned to receive placebo at the same amount and frequency as the patients receiving donidalorsen. All steps of the study were the same for all groups, allowing researchers to see differences between the medicine and no active treatment.
- **Double-Blind**: Neither researchers nor participants knew if the participant was receiving the real medicine (**donidalorsen**) or a placebo.

WHY WAS THIS STUDY DONE?

Researchers wanted to know how well **donidalorsen** could effectively and safely help people suffering from HAE attacks compared with placebo.

What was the main question researchers wanted to answer?

What was the number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 for participants receiving donidalorsen 80 mg every 4 weeks compared with the pooled placebo group?

What happened during this study?

WHAT TREATMENT DID PARTICIPANTS GET?

Donidalorsen Group 1
80 mg of **donidalorsen** every 4 weeks by injection under the skin

Donidalorsen Group 2
80 mg **donidalorsen** every 8 weeks by injection under the skin

Placebo Group
Injection under the skin every 4 or 8 weeks (pooled together). Placebo is an inactive medicine used as a control in the study.

HOW WAS THIS STUDY DONE?

8-WEEK SCREENING PERIOD

Participants were randomly assigned to treatment as soon as they experienced ≥ 2 HAE attacks during this period and completed all evaluations that ensured they were eligible to enroll in the study.

24-WEEK TREATMENT PERIOD

Participants were randomly assigned to receive donidalorsen or placebo:

Donidalorsen Group 1 had 45 participants.

Donidalorsen Group 2 had 23 participants.

Placebo Group: had 22 participants. All patients who received placebo either every 4 weeks or every 8 weeks were pooled together for data analyses.

Participants had check-up visits at certain weeks to see how they were doing and if they had any medical problems. They also filled out questionnaires to talk about any symptoms they experienced while receiving treatment.

13-WEEK FOLLOW UP PERIOD

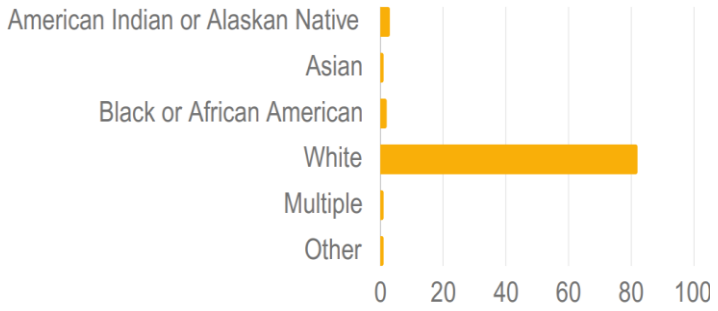
Participants could attend check-up visits at the study clinic sites at weeks 4, 8, and 13 during the 13-week follow-up period, or could choose to enroll in the open-label extension (OLE) study (OASISplus, NCT05392114).

The OLE study allowed participants to receive donidalorsen 80 mg even if they received placebo during this study follow-up period.

WHO PARTICIPATED IN THIS STUDY?

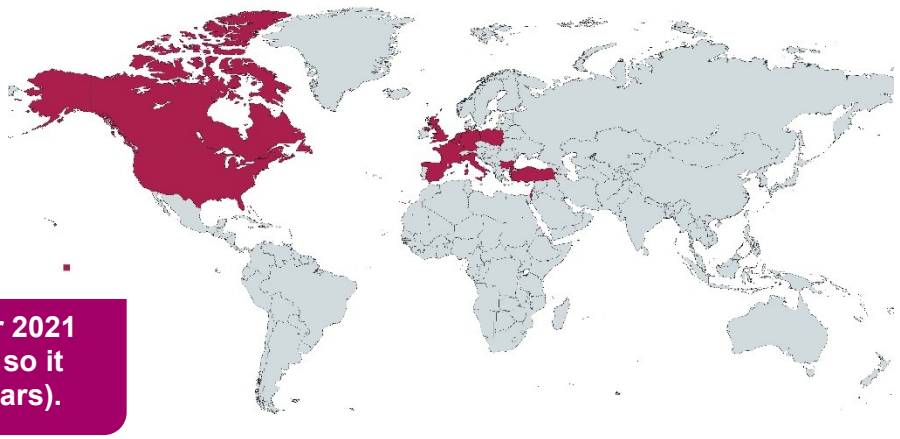
90 total participants, at least 12 years of age or older, with a diagnosis of HAE-1 or HAE-2 who had at least 2 HAE attacks during the Screening Period

DEMOGRAPHICS



WHERE DID THIS STUDY TAKE PLACE AND FOR HOW LONG?

Researchers at 39 clinics across **Belgium, Bulgaria, France, Germany, Italy, Netherlands, Poland, Spain, United Kingdom, United States, Canada, Israel**, and **Turkey** enrolled participants in this study.



This study started in December 2021 and ended in November 2023, so it lasted 23 months (almost 2 years).

What were the results of this study?

Medically Confirmed Number of HAE Attacks (Per 4 Weeks) from Week 1 to Week 25

Donidalorsen – Group 1
(donidalorsen 80 mg every 4 weeks)

The average HAE attack rate (per 4 weeks) from Week 1 to Week 25 for Donidalorsen Group 1 (**donidalorsen** 80 mg every 4 weeks) was 0.44 compared with 2.26 for the placebo group.

Answer to the main question asked:

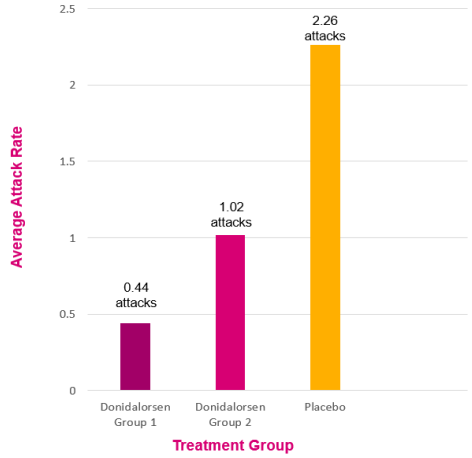
The Donidalorsen Group 1 had an 81% reduction in HAE attacks relative to the placebo group. This reduction was considered significant.

Donidalorsen – Group 2
(donidalorsen 80 mg every 8 weeks)

The average HAE attack rate (per 4 weeks) from Week 1 to Week 25 for Donidalorsen Group 2 (**donidalorsen** 80 mg every 8 weeks) was 1.02 compared with 2.26 for the placebo group. The Donidalorsen Group 2 had a 55% reduction in HAE attacks relative to the placebo group. This reduction was considered significant.

Overall, the results show that **donidalorsen** 80 mg administered every 4 weeks or every 8 weeks significantly reduced the number of HAE attacks (per 4 weeks) compared with the placebo group.

Average HAE Attack Rate (Per 4 Weeks) from Week 1 to Week 25



WHAT MEDICAL PROBLEMS DID PARTICIPANTS HAVE DURING THE STUDY?

MEDICAL PROBLEM REPORTED	GROUP 1 (45 PARTICIPANTS)	GROUP 2 (23 PARTICIPANTS)	PLACEBO (22 PARTICIPANTS)
ANY MEDICAL PROBLEM	33 OUT OF 45 PARTICIPANTS (73%)	14 OUT OF 23 PARTICIPANTS (61%)	18 OUT OF 22 PARTICIPANTS (82%)
ANY MEDICAL PROBLEM RELATED TO TREATMENT	19 OUT OF 45 PARTICIPANTS (42%)	4 OUT OF 23 PARTICIPANTS (17%)	6 OUT OF 22 PARTICIPANTS (27%)
ANY MEDICAL PROBLEM LEADING TO STOPPING TREATMENT	0 OUT OF 45 PARTICIPANTS (0%)	1 OUT OF 23 PARTICIPANTS (4%)	0 OUT OF 22 PARTICIPANTS (0%)
ANY SERIOUS MEDICAL PROBLEM	0 OUT OF 45 PARTICIPANTS (0%)	0 OUT OF 23 PARTICIPANTS (0%)	1 OUT OF 22 PARTICIPANTS (5%)
INJECTION-SITE REACTION	9 OUT OF 45 PARTICIPANTS (20%)	1 OUT OF 23 PARTICIPANTS (4%)	0 OUT OF 22 PARTICIPANTS (0%)
HEADACHE	3 OUT OF 45 PARTICIPANTS (7%)	0 OUT OF 23 PARTICIPANTS (0%)	3 OUT OF 22 PARTICIPANTS (14%)

DID PARTICIPANTS HAVE ANY SERIOUS MEDICAL PROBLEMS RELATED TO THE MEDICINE DURING THE STUDY?

No serious medical problems related to donidalorsen were experienced by participants.

The most common, not serious, medical problems reported were injection-site reactions and headaches.

Where can I learn more about this study?

HOW HAS THIS STUDY HELPED PEOPLE WITH HAE AND RESEARCHERS?

Researchers look at the results of many studies to decide which treatments work and are safest for participants. This summary gives the results of 90 participants in a single study. Other studies may have more participants and may give different results.

Overall, researchers learned that **donidalorsen** at a dose of 80 mg taken every 4 weeks or every 8 weeks made a difference in reducing HAE attack rates compared with placebo.

Researchers also found no serious safety concerns with **donidalorsen** under the conditions of this study.

The results from this study support the use of **donidalorsen** as a possible ongoing (prophylactic) treatment to reduce the number of HAE attacks for people living with HAE. Findings from this study may be used in other studies to learn more about the use of **donidalorsen** in participants with HAE.

ARE THERE PLANS FOR FURTHER STUDIES?

Further clinical studies with **donidalorsen** are ongoing at this time.
You can find them by looking up the following NCT numbers on ClinicalTrials.gov:

- NCT05392114
- NCT04307381
- NCT06415448

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

Sponsor	**Ionis Pharmaceuticals, Inc.**
Treatment Studied	**Donidalorsen**
Protocol Number of Study	**721744-CS5**
ClinicalTrials.gov Study Number	**NCT05139810**
European Study Number (EudraCT)	**2021-002571-19**
Official Title of this Study	**A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients With Hereditary Angioedema (HAE)**
Dates of this Study	**December 2021 to November 2023**
Journal Article of this Study	**Riedl, MA, et al. Efficacy and Safety of Donidalorsen for Hereditary Angioedema. The New England Journal of Medicine. 2024.**
Date of this Report	**18 October 2024**

IONIS: A Force For Life

IONIS PHARMACEUTICALS, INC.

ISIS 721744-CS5

A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Amendment 2 – 12 July 2022

EudraCT No: 2021-002571-19

Trial Sponsor:

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ISIS 721744-CS5

Protocol Amendment 2

EudraCT No: 2021-002571-19

Clinical Phase: 3

A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Protocol History

Original Protocol: 16 June 2021

Amendment 1: 1 October 2021

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

[redacted] Clinical Development [redacted]

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc. that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 721744-CS5
Protocol Title:	A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)
Amendment:	2
Date:	12 July 2022

I hereby acknowledge that I have read and understand the attached clinical protocol, identified above, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and the Declaration of Helsinki.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 721744-CS5

Protocol Title: A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Amendment Number: 2

Amendment Date: 12 July 2022

The following modifications to Protocol ISIS 721744-CS5, dated 12 July 2022, have been made.

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 721744-CS5, Amendment 1, dated 1 October 2021, predominantly around contraceptive use as well as administrative changes and updates.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of changes to the protocol.

Protocol Section	**Description of Change (Additions in bold, deletions in strikethrough)**	**Rationale**
Executive Summary	The ~~hierarchical~~ testing ~~order~~ **sequence** for the secondary endpoints ~~is the order~~ **will be specified** in ~~which they are listed~~ ~~in~~ the ~~secondary endpoints section above~~ **SAP**.	Clarification for statistical analysis.
Executive Summary Section 10.6.3.1	the time normalized run-in period attack rate (continuous) as a covariate, and the logarithm of time in month ~~(days from first dose date to 28 days after last dose administration divided by 28)~~ that each patient was observed ~~during the period~~ **from Week 1 to Week 25** will be used as an offset variable.	Clarification for statistical analysis.
Section 1.2.2	**The number of Investigator-confirmed HAE attacks requiring acute HAE therapy from Week 5 to Week 25 compared to placebo**	Correction of inconsistency in the protocol.
Section 3.4.1	A patient may be randomized after fewer than 56 days from the screening visit if the patient experiences ~~>~~ ≥ 2 HAE attacks	Clarification on how many attacks are required for a patient to be randomized.
Section 5.1	6d). If engaged in sexual relations of childbearing potential, agree to use **acceptable** ~~highly effective~~ contraceptive methods (refer to Section 6.3.1) from the time of signing the ICF and, as applicable, assent form until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo) 7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use a**n acceptable** ~~highly effective~~ contraceptive method (refer to Section 6.3.1)	The reproductive toxicity study performed in mice (combined Seg I and II) indicated no ISIS 721744-related effects on fertility or embryo/fetal development.

Protocol Section	**Description of Change (Additions in bold, deletions in strikethrough)**	**Rationale**
Section 5.2	**14 Recent history (3 years) of, or current drug or alcohol abuse**	Clarification to exclude patients with alcohol or drug abuse
Section 6.2.2	Height will be measured at Screening **and for pediatric patients at Week 25**.	Added collection of Height at Treatment Study Week 25 for pediatric patients.
Section 6.2.3	Electrocardiography will be recorded per the standard practice of the Study Center. ~~Electrocardiography will be performed in triplicate.~~	Correction of inconsistency in the protocol.
Section 6.3.1	All male patients and women of childbearing potential (WOCBP) must refrain from sperm/egg donation and either be abstinent[†] or practice ~~effective~~ **acceptable** contraception from the time of signing the informed consent and, as applicable, assent form until at least 24 weeks after their last dose of Study Drug. For male patients engaged in sexual relations with a female of childbearing potential, if their female partner is using **acceptable** ~~highly effective~~ contraception from the time of the patient signing the informed consent and, as applicable, assent until at least 24 weeks after the patient's last dose of Study Drug, then it is not required for the male patient to also use a**n** ~~highly effective~~ **acceptable** contraceptive method. For the purposes of the study, ~~highly effective~~ **acceptable** contraception is defined as follows: For male patients: • **Acceptable** ~~highly effective~~ male contraception includes a vasectomy with negative semen analysis at Follow-up, **surgically sterile via bilateral orchidectomy, abstinence[†], condom with spermicide** or the non-pregnant female partner of child-bearing potential uses an **acceptable** ~~highly effective~~ contraceptive method (defined below) • Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug For female patients and female partners of male patients, ~~highly effective~~ **acceptable** contraception methods comprise:	The reproductive toxicity study performed in mice (combined Seg I and II) indicated no ISIS 721744-related effects on fertility or embryo/fetal development.

<table>
<tr><th>Protocol Section</th><th>Description of Change
(Additions in bold, deletions in strikethrough)</th><th>Rationale</th></tr>
<tr><td>Section 6.3.1</td><td>Surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception associated with inhibition of ovulation (~~combined estrogen and progestogen containing, or~~ progestogen-only [female patients with HAE] or combined estrogen and progesterone [female partners of male patients]), intrauterine contraception device or intrauterine hormone-releasing system or a vaginal ring (as long as the patient has been using this contraceptive method for at least 3 months before Screening) or vasectomized partner with negative semen analysis at follow-up, male or female condom with spermicide; or cap, diaphragm, or sponge with spermicide. Female patients with HAE cannot use estrogen containing oral, subcutaneous, or transdermal contraceptives in this study.</td><td>This clarification is to note that this exclusion was intended for oral hormonal therapy, and not for intrauterine or intravaginal estrogens. There is significantly more systemic absorption with oral therapy and the purpose of this exclusion criteria was to prohibit that use.</td></tr>
<tr><td>Section 8.6.2</td><td>UPCR >1000 mg/g, ~~Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further~~ confirmed a quantitative total urine protein measurement of > 1.0 g/24 hours</td><td>Updating to a more accurate lab measure.</td></tr>
<tr><td>Section 10.4</td><td>Run-in period is defined as the period from screening to the last day prior to Study Day 1.
For Investigator-confirmed HAE attacks, the baseline rate, i.e., run-in period Investigator-confirmed HAE attack rate, will be calculated for each patient as number of Investigator-confirmed HAE attacks occurred during the run-in period divided by the number of days contributed to the run-in period multiplied by 28 days.</td><td>Clarification of statistical analysis.</td></tr>
<tr><td>Section 10.5</td><td>Final analyses will be conducted after the End of Treatment period when all patients complete Week 25 visit, stay in the study for at least 25 weeks since the Study Day 1 or withdraw from the study before 25 weeks from the Study Day 1. Study results with continuing collected post-treatment data will be updated at the End of Study.</td><td>Clarification that we will perform the final analysis before the follow-up period is completed.</td></tr>
<tr><td>Footnote Table 2</td><td>The suitability of the patient for ~~reduced~~, interrupted and/or continued dosing will be determined by the Investigator or designee in consultation with the Medical Monitor</td><td>Dose reduction is not allowed per protocol.</td></tr>
<tr><td>Appendix A</td><td><table>
<tr><td rowspan="2">Study Week</td><td>Screen</td><td>Treatment</td></tr>
<tr><td>-8 to -1</td><td>25</td></tr>
<tr><td>Study Day</td><td>-56 to -1</td><td>169/ET-L[3] or Tx-ET[4]</td></tr>
<tr><td>Height</td><td>X</td><td>X[20]</td></tr>
</table>
[20] For pediatric patients only.</td><td>Added collection of Height at Treatment Study Week 25 for pediatric patients.</td></tr>
<tr><td>Appendix A</td><td>[8] C1-INH, C4, and C1q will be obtained at Screening. Historical values can be used for the HAE Inclusion Criteria, if already collected in the last ~~tested unless already collected within~~ 5 years ~~of Screening~~.</td><td>Clarification of eligibility laboratory collection.</td></tr>
</table>

Protocol Section	**Description of Change (Additions in bold, deletions in strikethrough)**	**Rationale**
Appendix B	[3] Samples for C4, C1-INH and C1q assays will be obtained at Screening ~~for eligibility assessment unless already collected in the last 5 years~~	Clarification of eligibility laboratory collection.
Appendix C	See Plasma PK Sampling Schedule for clarifications.	To ensure the correct PK sampling schedule and timing of assessments is followed for each respective Cohort, the PK Sampling Schedule will be presented as two separate Cohort-specific tables in this Amendment.

EXECUTIVE SUMMARY

Title: A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Phase: 3

Intended Indication: Hereditary Angioedema (HAE)

Investigational Product: ISIS 721744

Population: HAE-Type I and HAE-Type II

Objectives	Corresponding Endpoints
Primary The primary objective of the study is to evaluate the clinical efficacy of ISIS 721744 in patients with HAE.	The **primary** endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25 compared to placebo
Secondary Evaluate the effects of ISIS 721744 on the quality and pattern of HAE attacks and their impact on Quality of Life.	**Secondary** endpoints include the following: • The time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 compared to placebo • The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo • The time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 compared to placebo • The number of patients with a clinical response defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25 compared to placebo • The number of Investigator-confirmed HAE attacks requiring acute HAE therapy from Week 5 to Week 25 compared to placebo • Percent of patients who are well controlled on the Angioedema Control Test (AECT) at Week 25 • Change in Angioedema Quality of Life (AE-QoL) questionnaire total score at Week 25
Safety To evaluate safety and tolerability of ISIS 721744 in patients with HAE	The number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters
Exploratory Further characterize the effects of ISIS 721744 on health economic and utilization parameters and additional Patient Reported	**Exploratory** endpoints include change or percent change from Baseline compared to placebo in the following: • PKK level in plasma • GAD-7 questionnaire score

Objectives	**Corresponding Endpoints**
Outcomes (PROs) and biomarkers.	• EQ-5D-5L • PGIS • Work Productivity and Impairment (WPAI) questionnaire score Also: • Incidence of all cause emergency room visits, hospitalization and total inpatient days • PGIC • PK: Potential exposure-response analysis using relevant exposure parameters (such as ISIS 721744 plasma C_{trough}) and biomarkers (plasma PKK) and/or clinical endpoints, as appropriate

Study Design

This study is a randomized (ISIS 721744:placebo), double-blind, placebo-controlled trial conducted in multiple centers to evaluate the efficacy and safety of ISIS 721744 in preventing angioedema attacks in patients with HAE-1 (Type I) and HAE-2 (Type II). Patients will be randomized 2:1 to Cohort A (3:1 ISIS 721744 80 mg or placebo every 4 weeks) or Cohort B (3:1 ISIS 721744 80 mg or placebo every 8 weeks).

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Patients must be aged ≥ 12 years at the time of informed consent, and, as applicable, assent
- Patients must have a documented diagnosis of HAE-1/HAE-2 based upon ALL of the following:
  a. Documented clinical history consistent with HAE (subcutaneous [SC] or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018)
  b. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 level is below the lower limit of normal (LLN) or if a known pathogenic mutation in the *SERPING1* gene has been demonstrated
  c. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range

- Patients must:
  a. Experience a minimum of 2 HAE attacks (confirmed by the Investigator) during the Screening Period
  b. Be willing to complete the PRO assessments throughout the study as described in Section 6.2.6.
- Patients must have access to, and the ability to use, ≥ 1 acute HAE medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks

A full list of inclusion criteria is provided in Section 5.1.

Key Exclusion Criteria

- Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening, Treatment or Post-Treatment Periods
- Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III)
- Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks
- Participation in a prior ISIS 721744 study
- Exposure to any of the following medications:
  a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening
  b. Chronic prophylaxis with Takhzyro (lanadelumab), Haegarda (C1-Esterase inhibitor SQ), Cinryze and Ruconest (C1 esterase inhibitor) or Orladeyo (berotralstat) within 5 half-lives prior to Screening (i.e., Takhzyro within 10 weeks prior to Screening, Haegarda/Cinryze/Ruconest within 2 weeks prior to screening, Orladeyo within 3 weeks prior to Screening)
  c. Oligonucleotides (including small interfering ribonucleic acid) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received. This exclusion does not apply to vaccines

A full list of exclusion criteria is provided in Section 5.2.

Statistical Analyses

The power and sample size estimations were calculated using simulations based on a generalized linear model for counting data assuming a Poisson distribution. The primary analysis of the primary endpoint is to compare the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25 between ISIS 721744 80 mg every 4 weeks and pooled placebo. Assuming an HAE attack rate of 13.26 attacks per 6-month period in the pooled placebo group and an HAE attack rate of 1.38 attacks per 6-month period in the ISIS 721744 80 mg every 4 weeks group, the sample size of 54 patients (2:1 ratio [ISIS 721744:placebo]) will provide more than 90% power for the primary endpoint, with a two-sided 0.05 significance level.

A total of approximately 84 patients (42 in the ISIS 721744 every 4 weeks group, 21 in the pooled placebo group, and 21 in the ISIS 721744 every 8 weeks group) will be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations.

Multiplicity Comparisons/Multiplicity

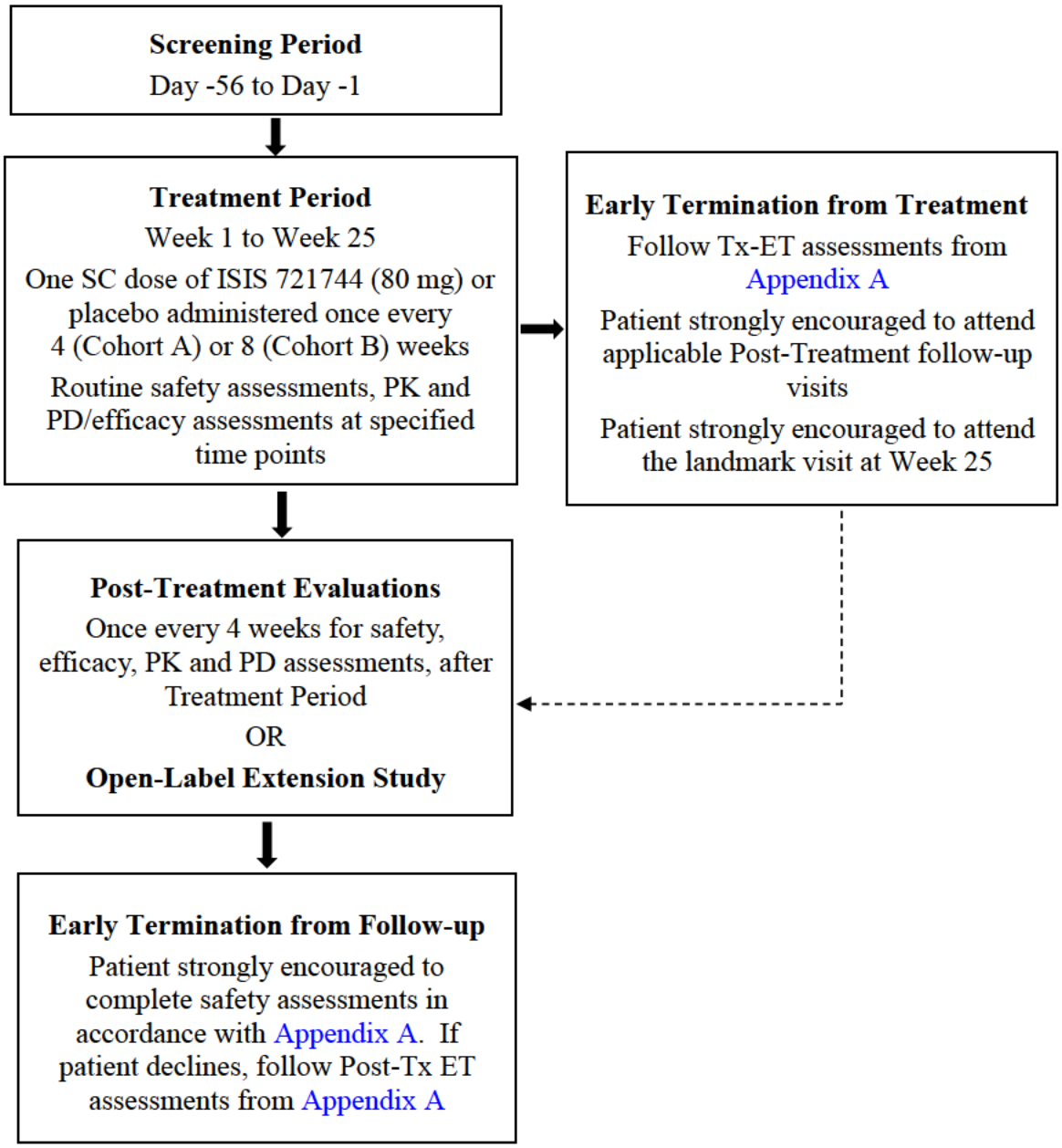
The multiplicity for primary and secondary analyses will be controlled by using the hierarchical testing procedure at 0.05. The testing sequence for the secondary endpoints will be specified in the SAP.

Analysis of Primary Endpoint

The primary analysis of the primary endpoint is to compare the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25 between ISIS 721744 80 mg every 4 weeks and pooled placebo using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effect for treatment group (categorical), the time normalized run-in period attack rate (continuous) as a covariate, and the logarithm of time in month that each patient was observed from Week 1 to Week 25 will be used as an offset variable.

All available data will be included in the analysis. The logarithm of the length of observation time will be included as an offset variable in the Poisson model to adjust for differences in follow-up time. Additional details regarding statistical analyses are provided in Section 10.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AAS	Angioedema Activity Score
ACE	angiotensin-converting enzyme
ADA	Anti-Drug Antibody
ADR	adverse drug reaction
AE(s)	adverse event(s)
AECT	Angioedema Control Test
AE-QoL	angioedema quality of life
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BK	bradykinin
BUN	blood urea nitrogen
C1q	Complement 1q
C1-INH	C1-inhibitor
C4	Complement factor 4
C5a	Complement Factor C5a (activated complement split product)
C_{max}	maximum concentration
cHK	cleaved high molecular weight kininogen
CKD-EPI	Formula for glomerular filtration (> 18 years)
CRF	case report form
CRNMB	clinically relevant non-major bleeding
CRP	C-reactive protein
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ER	emergency room
EQ-5D-5L	EuroQoL-5-Dimensions (5D) quality of life questionnaire
ET	Early Termination
FSH	follicle-stimulating hormone
GAD-7	generalized anxiety disorder 7
$GalNAc_3$	*N*-acetly galactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema

HAE-1	hereditary angioedema type 1
HAE-2	hereditary angioedema type 2
HAE-nC1-INH	hereditary angioedema with normal C1-inhibitor
Hb	hemoglobin
HIV	human immunodeficiency virus
HK	high molecular weight kininogen
hr, hrs	hour(s)
hs-CRP	CRP measured by high sensitivity assay
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IM	immunogenecity
INR	international normalized ratio
IONIS-PKK-L_{Rx}	ISIS 721744
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISIS 721744	antisense inhibitor of prekallikrein
ISIS 721744-CS1	Phase 1 for ISIS 721744
ISIS 721744-CS2	Phase 2 for ISIS 721744
ISIS 721744-CS3	OLE for ISIS 721744
ITT	Intent-to-Treat
IVIG	intravenous immunoglobulin
LCRIS	local cutaneous reaction at injection site
LLN	lower limit of normal
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model with repeated measures
mRNA	messenger ribonucleic acid
NCS	not clinically significant
OLE	open-label extension
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PKa	plasma kallikrein
PKK	prekallikrein
PLT(s)	platelet(s)
Post-Tx-ET	Post-Treatment Early Termination
PROs	Patient Reported Outcomes
PT	prothrombin time
QoL	quality of life

RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 721744 or placebo
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse event(s)
T_{max}	time to maximal concentration
Tx	treatment
Tx-ET	Treatment Early Termination
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
WBC	white blood cell
WOCBP	women of childbearing potential
WPAI	work productivity and impairment

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of ISIS 721744 in patients with hereditary angioedema (HAE).

1.1.2. Secondary Objectives

Evaluate the effects of ISIS 721744 on the quality and pattern of HAE attacks and their impact on Quality of Life.

1.1.3. Safety Objectives

To evaluate safety and tolerability of ISIS 721744 in patients with HAE.

1.1.4. Exploratory Objectives

Further characterize the effects of ISIS 721744 on health economic and utilization parameters and additional Patient Reported Outcomes (PROs) and biomarkers.

1.2. Study Endpoints

1.2.1. Primary Endpoint

The primary endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25 compared to placebo.

1.2.2. Secondary Endpoints

- The time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 compared to placebo
- The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo
- The time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 compared to placebo
- The number of patients with a clinical response defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25 compared to placebo
- The number of Investigator-confirmed HAE attacks requiring acute HAE therapy from Week 5 to Week 25 compared to placebo
- Percent of patients who are well-controlled based on the AECT at Week 25
- Change in AE-QoL questionnaire total score at Week 25

1.2.3. Safety Endpoints

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; electrocardiogram (ECG); and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

1.2.4. Exploratory Endpoints

Exploratory endpoints include change or percent change from Baseline compared to placebo in the following:

- PKK level in plasma
- GAD-7 questionnaire score
- EQ-5D-5L
- PGIS
- WPAI questionnaire score
- Incidence of ER visits, all cause hospitalization and total inpatient days
- PGIC
- PK: Potential exposure-response analysis using relevant exposure parameters (such as ISIS 721744 plasma C_{trough}) and biomarkers (plasma PKK) and/or clinical endpoints, as appropriate

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Hereditary angioedema is a rare genetic disorder that is characterized by disabling recurrent episodes of local skin swellings, painful abdominal attacks, and, occasionally, laryngeal attacks that can be life-threatening. The disorder is classified in 3 subtypes. Hereditary angioedema Type I (HAE-1) and Type II (HAE-2) are caused by an autosomal dominant mutation in the *SERPING1* gene, resulting in either decreased levels of C1-INH (HAE-1) or loss-of-function of this protein (HAE-2) (Bissler et al. 1997). The third form of HAE is associated with normal levels and function of C1-INH (HAE-nC1-INH). This form is currently categorized as 4 subtypes, with either specific genetic mutations in the factor XII gene, the plasminogen gene, or the angiopoietin-1 gene, or due to an unknown cause (Maurer et al. 2018). Extensive evidence from *in vitro* and *in vivo* studies supports the key role of bradykinin (BK) in HAE attacks, although the data linking HAE-nC1-INH with BK are less strong (Zuraw and Christiansen 2016). Diagnosing HAE-nC1-INH can be challenging given the large heterogeneity of this patient population, the lack of diagnostic tests, and the fact that specific genetic mutations account only partially for the occurrence of this type of HAE. Recently, a threshold-stimulated kallikrein activity assay was shown to discriminate BK-mediated angioedema from histamine-mediated angioedema (Lara-Marquez et al. 2018). This technique may, therefore,

enhance the identification of HAE-nC1-INH patients that are likely to benefit from inhibition of the contact activation pathway.

Treatment options for HAE include on-demand treatment of attacks and prophylaxis. On-demand options include supplementation of C1-INH (either plasma-derived or recombinant C1-INH concentrate) and inhibition of BK2 receptor activation (BK2-receptor antagonist). In addition, tranexamic acid may relieve symptoms in non-severe angioedema attacks. Prophylactic regimens for HAE include plasma-derived C1-INH concentrate (administered either intravenously or subcutaneously [SC]), attenuated androgens, antifibrinolytics and a monoclonal antibody directed against plasma kallikrein (PKa) and a small molecule inhibitor of PKa. Kallikrein circulates in plasma as a zymogen (i.e., PKK) which is bound to one of its main substrates, high molecular weight kininogen (HK). Prekallikrein (PKK) is cleaved upon contact activation, forming the active protease PKa. Plasma kallikrein cleaves HK in turn, thereby releasing BK and the split product cleaved high molecular weight kininogen (cHK). The binding of BK to the BK2 receptor leads to activation of various intracellular signaling pathways resulting in vasodilation, chemotaxis of neutrophils, and increased vascular permeability and fluid efflux, which typically characterize an angioedema attack (Zuraw and Christiansen 2016).

2.2. Therapeutic Rationale

ISIS 721744 is a 2′-*O*-(2 methoxyethyl) (2′-MOE) chimeric phosphorothioate (PS)-modified second-generation antisense oligonucleotide (ASO) designed to bind to the messenger ribonucleic acid (mRNA) of PKK, a protease in the contact system. By inhibiting expression of PKK, ISIS 721744 reduces the release of BK, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE attacks.

The Phase 1 clinical data show that ISIS 721744 inhibits plasma PKK effectively in a dose-dependent manner without safety concerns. Validation of this mechanism has been demonstrated in a recently completed 12-week Phase 2 study of ISIS 721744 in adult HAE patients with recurrent attacks, ISIS 721744-CS2, in which once-every-4-weeks ISIS 721744 administration showed 90% reduction in HAE attacks compared to placebo.

2.3. ISIS 721744

2.3.1. Mechanism of Action

ISIS 721744 is a chimeric 2′-MOE ASO targeted to *PKK* mRNA. The ASO is covalently bonded to triantennary GalNAc, a high-affinity ligand for the hepatocyte-specific ASGPR, to form an ASO-GalNAc conjugate. This GalNAc conjugate approach results in enhanced ASO delivery to hepatocytes vs. non-parenchymal cells and has increased ASO potency by approximately 10-fold in mice (Prakash et al. 2014) and up to 30-fold in humans (Crooke et al. 2018) compared to unconjugated ASOs. The ASO portion of ISIS 721744 is fully complementary to a base-pair position 1019-1038 of the Genbank NM_000892.3 sequence spanning a portion of Exon 9 of the PKK-mRNA and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 721744 to the cognate mRNA results in the ribonuclease H1 (RNase H1)-mediated degradation of the *PKK* mRNA, thus preventing production of the PKK protein. Antisense-mediated reduction of target mRNA levels is predictable and dose-dependent. Maximal inhibition of greater than 90% of control levels is

typically achievable in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2. Chemistry

ISIS 721744 is a GalNAc-conjugated 2′-MOE ASO. The oligonucleotide portion of the drug consists of 20 nucleotides (i.e., a 20-mer). Of the nineteen (19) internucleotide linkages, 15 are 3′-*O* to 5′-*O* phosphorothioate diesters, and 4 are 3′-*O* to 5′-*O* phosphate diesters.

Structurally, the conjugated oligonucleotide has 4 regions. Within 2 of the regions, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (i) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (ii) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (iii) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 721744 employs this chimeric structure to enable use of the RNase H1 mechanism for antisense activity. The 2′-MOE modification confers increased stability and affinity but does not support RNase H1 catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy-RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

The fourth region is comprised of a triantennary cluster of GalNAc sugars which is linked to the 5′ end of ISIS 721744 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc cluster enhances delivery of ISIS 721744 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release “free ASO” inside the cell (Prakash et al. 2014).

The internucleosidic linkages are a mixture of phosphorothioate and phosphodiester. The phosphorothioate linkages are introduced into the DNA gap region and at both ends of the oligonucleotide to protect it from nuclease mediated metabolism. The mixed backbone design reduces the total number of phosphorothioate linkages which reduces non-specific interactions with proteins and further enhances the therapeutic index of GalNAc-conjugated ASOs.

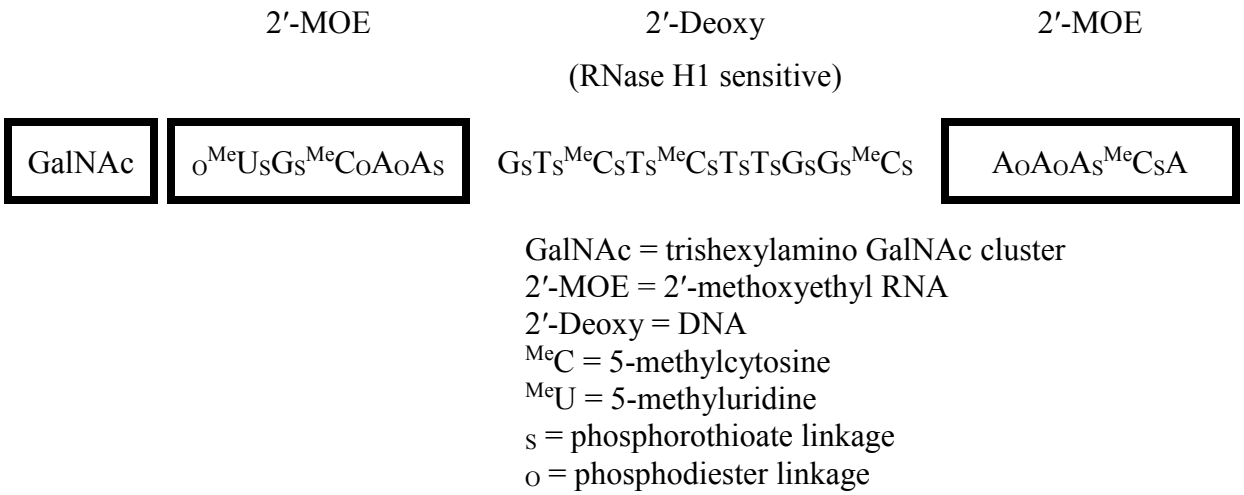


Figure 1: Design of ISIS 721744, a GalNAc-Conjugated Chimeric 2′-MOE Phosphorothioate/Phosphate Oligonucleotide (MOE Gapmer)

The sequence of ISIS 721744 is shown. All of the cytosine bases are methylated at the 5-position. It should be noted that 2′-*O*-(2-methoxyethyl)-5-methyluridine (2′-MOE ^{Me}U) nucleosides are sometimes referred to as 2′-*O*-(2-methoxyethyl) ribothymidine (2′-MOE T).

2.3.3. Preclinical Experience

Detailed information concerning the preclinical studies conducted with PKK ASO ISIS 546254 (parent unconjugated compound), its 5′-GalNAc$_3$-conjugated mixed backbone variant ISIS 721744, and mouse surrogate PKK ASOs can be found in the Investigator's Brochure.

The results support the concept that inhibition of PKK through antisense mechanism may serve as a new and effective strategy for the prophylaxis of HAE. Results also strongly support that GalNAc$_3$-conjugation of PKK ASO significantly increases the potency of ASO for inhibition of PKK hepatic mRNA and circulatory protein expression and thus these ASOs should be a useful therapeutic strategy for the prophylactic treatment of HAE.

2.3.4. Clinical Experience

ISIS 721744 has been evaluated in the clinical setting in a Phase 1 safety study (ISIS 721744-CS1) and Phase 2 study (ISIS 721744-CS2).

Phase 1: ISIS 721744 was studied in 32 healthy volunteers in a double-blind, multiple-dose, dose-escalation study. Of these, 24 subjects received multiple doses of ISIS 721744. The 32 subjects were randomized into 4 cohorts (6 subjects each) to receive once-every-4-week SC doses of ISIS 721744 20, 40, 60, or 80 mg, or placebo (8 subjects) for a total of 12 weeks (4 total doses). All subjects received all planned doses of Study Drug (ISIS 721744 or placebo). The duration of Study Drug exposure was 84 days for each subject.

No serious adverse events (SAEs) were reported in the ISIS 721744-CS1 study. There were no early discontinuations from Study Drug or the study, and all subjects in the ISIS 721744 and placebo arms completed all study procedures. Adverse events at the injection site (defined as

any preferred term containing "injection site") were the most commonly reported treatment-emergent adverse events (TEAEs) in the ISIS 721744 treatment arms; no injection site-related TEAEs were reported in the placebo arm. There were no flu-like reactions or events of local cutaneous reaction at injection site (LCRIS) reported; LCRIS events were defined as (A) moderate or severe injection site erythema, swelling, pruritus, pain, or tenderness that started on the day of injection and persisted for at least 2 days; or (B) any AE at the injection site, regardless of severity, that led to discontinuation of Study Drug, where AE at the injection site was the principal reason for discontinuation. No relationship between incidence of TEAEs and the dose administered was observed.

Thirteen (13) AEs related to study treatment were reported for 4 (16.7%) subjects in the ISIS 721744 arm, and for 1 subject (2 events; 12.5%) in the placebo arm. One (1) subject each in the ISIS 721744 and placebo arm reported AEs of ECG T wave inversion (preferred term) that were assessed as related. Nine (9) of the total 13 related events with ISIS 721744 concerned Injection site-related events and were reported by 1 subject in the 80 mg arm. Additional related events were Tinnitus (1 subject, 1 event in the 60 mg arm), Headache (1 subject, 1 event in the 60 mg arm), and Epistaxis (1 subject, 1 event in the 20 mg arm). All TEAEs related to study treatment were mild in severity, and none were serious.

ISIS 721744 resulted in a dose-dependent reduction of PKK concentration and plasma proenzyme activation. The difference in absolute and percent change from Baseline for ISIS 721744 vs. placebo was statistically significant for PKK concentration for 40, 60, and 80 mg ($p \leq 0.043$) starting at Day 15, the first evaluation, and for 20 mg starting at Day 29, and for plasma proenzyme activation for all doses ($p \leq 0.002$) starting at Day 15. The nadir was generally reached around Day 71, when the percent reduction with the 80 mg dose was -93.2% for PKK concentration and -99.6% for plasma proenzyme activation. The difference in absolute and percent change from Baseline in cHK for ISIS 721744 vs. placebo was not statistically significant at any visit.

Phase 2: ISIS 721744 was evaluated in a double-blind placebo-controlled trial in patient with HAE Type I and II in Part A and in an open-label treated patients with HAE-nC1-INH (or Type III). Clinical data demonstrated a significant degree of efficacy of ISIS 721744 80 mg administered once every-4-weeks for 4 months in reducing the rate of HAE attacks in Type I and Type II HAE patients with recurrent attacks over a 16-week (Week 1-17) period vs. placebo (90% reduction in number of HAE attacks compared to placebo; $p < 0.001$). The percentage of patients who were HAE attack-free from Week 5 to Week 17 was 92.3% as compared to none of the patients treated with placebo. There was also a significant reduction, 95%, in patient treated with ISIS 721744 in the need for use of acute therapies to treat HAE attacks vs. placebo treated patients. Additionally, the number of moderate to severe attack was also markedly reduced with a 96% reduction in ISIS 721744 treated group vs. placebo. There was also a statistically significant reduction in plasma PKK, plasma proenzyme activation and cHK.

ISIS 721744 was well-tolerated with most AEs being mild in severity, and similar in frequency between active and placebo treated patients. The most common TEAE was headache. All the TEAEs had resolved by the end of the study. No LCRIS or flu-like reactions were reported. No deaths or SAEs were reported. There were no clinically relevant changes in the safety laboratories, such as chemistry, hematology, coagulation, complement, inflammatory markers, urinalysis, ECG, or vital sign.

Overall, ISIS 721744 was efficacious and well-tolerated in these patients with HAE.

Eligible patients from ISIS 721744-CS2 are continuing to receive the drug for an additional 2 years in the open-label extension (OLE) study, ISIS 721744-CS3.

Investigator Initiated Trial: Additionally, evidence was provided of efficacy in 2 patients in the Netherlands with severe BK-mediated forms of angioedema who were administered drug as treatment use, first with the unconjugated parent ASO, IONIS-PKK$_{Rx,}$ (ISIS 546254) followed by treatment with the ligand-conjugated ASO, IONIS-PKK-L$_{Rx}$ (ISIS 721744; (Cohn et al. 2020). In both patients, IONIS-PKK$_{Rx}$ and IONIS-PKK-L$_{Rx}$ showed clinical efficacy by markedly reducing the rate of breakthrough attacks.

2.4. Rationale for Dose and Schedule of Administration

The dose level of 80 mg every 4 weeks was selected based on the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from the ISIS 721744-CS1 study in healthy volunteers and ISIS 721744-CS2 study in patients with HAE as well as the clinical efficacy data of the ISIS 721744-CS2 study. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered to healthy volunteers once every 4 weeks for a total of 12 weeks. All dose levels were generally well-tolerated and induced a dose- and exposure-dependent reduction in plasma PKK, a biomarker for BK and vascular permeability. The highest dose level of 80 mg produced near complete reduction of plasma PKK levels (a mean reduction of 93.6% from Baseline on Day 99 [2 weeks after the last dose]) in healthy volunteers. In the Phase 2 study in HAE patients, the dose level of 80 mg resulted in a mean plasma PKK reduction of about 60% from Baseline on Day 113, 4 weeks after a total of 4 doses (administered every 28 days) with no corresponding attacks reported for most patients. This suggests that the 80-mg dose administered every 4 weeks results in sufficient target knockdown to achieve near-complete prevention of attacks in these patients. Additionally, the mean plasma PKK levels correlated well with the mean attacks/month (clinical endpoint) over time. A second dosing regimen of 80 mg every 8 weeks is included in this study to evaluate the efficacy and safety of a reduced dosing frequency. This dosing schedule was selected based on the ISIS721744-CS3 open-label study (open-label study extension of the ISIS 721744-CS2 study) that evaluated the same dosing regimen. In the CS3 study, 5 out of the 17 HAE Type II patients that rolled over to the CS3 study switched to 80 mg every 8 weeks. Currently 4 out of these 5 patients have remained attack free. This suggests that patients could potentially benefit from this alternative dosing regimen with a reduced dosing frequency. Both dosing schedules (80 mg every 4 weeks and 80 mg every 8 weeks) have been generally well-tolerated in these patients. The estimated half-life ($t_{½}$) of ISIS 721744 is approximately 4 to 5 weeks, thus supporting these dosing schedules as well. Minimal to no correlation was observed between ISIS 721744 clearance and exposure with body weight across healthy volunteers and patients combined suggesting that a flat dose of 80 mg is appropriate across the entire population of this study. The dose and schedule are also supported by sub-chronic and chronic toxicity studies in mice and monkeys of up to 6- and 9-months dosing duration, respectively. For an 80-mg monthly dose in adult humans (70 kg), the safety margin is approximately 21-fold and 32-fold based on the dose and area under the curve (AUC) respectively at NOAEL in the 9-month monkey study. Additionally, the safety margin would still be over 20-fold for patients with lower body weight

(~35 kg patients) based on a conservative body weight- based AUC predicted from population PK modeling.

2.5. Benefit-Risk Assessment

2.5.1. Overall Assessment of Benefit:Risk

The preclinical, Phase 1, and Phase 2 studies of ISIS 721744 have demonstrated a favorable risk-benefit profile, with no safety signals identified in clinical trials on hematological parameters, liver function, or renal function. In the completed Phase 2 study of ISIS 721744 in HAE patients, AEs, including those at the injection site, were balanced between groups and no severe AEs were reported and all TEAEs had resolved by the end of the study. There were no clinically relevant changes in the safety laboratories, such as chemistry, hematology, coagulation, complement, inflammatory markers, urinalysis, or ECGs, nor in vital signs. No safety or stopping rules were met for renal function, liver or bleeding. No deaths or SAEs were reported. Overall, in this trial, ISIS 721744 was safe and well-tolerated in patients with HAE. In the ongoing Phase 2 OLE study of ISIS 721744, a continued favorable safety and tolerability profile has been demonstrated, with no platelet (PLT), liver function, or renal function signals identified.

The conjugated nature of ISIS 721744 allows specific targeting of ASO to hepatocytes so, that for similar hepatocyte exposure, reduced exposure to both non-parenchymal liver cells and systemic exposure has the potential to lower PKK with an enhanced tolerability profile over the parent molecule, ISIS 546254.

Nevertheless, regular monitoring of PLT counts, liver chemistry, and renal function, and stopping rules will be included in the clinical study as described in Section 8.5 and Section 8.6.

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ISIS 721744 are justified by the anticipated benefits that may be afforded to patients with HAE.

Detailed information concerning the benefit-risk assessment of ISIS 721744 can be found in the Investigator's Brochure.

2.5.2. Additional Risks During the COVID-19 Pandemic

HAE patients should continue any approved pharmaceutical interventions for treating acute attacks as no risks have been identified that would cause termination of treatment during the COVID-19 Pandemic at this time.

There could be risk however, for patients who are participating in a clinical trial such as ISIS 721744-CS5. There may be risks to patients traveling to research sites. Sites should follow their specific regional guidance (i.e., institutional, local, state, federal, country-level, as applicable) with regard to receiving patients for clinical trials. Visits should continue as long as it is deemed safe to do so. Provision will be available for patients to be treated or evaluated in their homes by a home healthcare professional. Additional mitigation steps and a study pause may be necessary as conditions warrant. If a study patient becomes infected with COVID-19 or develops COVID-19-related symptoms, the patient should notify the study staff/Investigator or

designee and notify their treating Physician that they are participating in a clinical trial with ISIS 721744.

3. EXPERIMENTAL PLAN

3.1. Study Design

This study is a randomized (ISIS 721744:placebo), double-blind, placebo-controlled trial conducted in multiple centers to evaluate the efficacy and safety of ISIS 721744 in preventing angioedema attacks in patients with HAE-1 (Type I) and HAE-2 (Type II) HAE. Patients will be randomized in a 2:1 ratio to Cohort A (ISIS 721744 or placebo every-4-weeks) or Cohort B (ISIS 721744 or placebo every 8 weeks), respectively. Within each Cohort, patients will be randomized in a 3:1 ratio to receive 80mg of ISIS 721744 or matching volume of placebo. Patients who discontinue treatment will attend the Early Termination (ET) Visit and will be encouraged to complete the Post-Treatment Period unless consent or assent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.

3.2. Number of Study Centers

This study will be conducted at multiple Study Centers worldwide.

3.3. Number of Patients

Approximately 84 patients are planned to be enrolled in the study.

3.4. Overall Study Duration and Follow-up

The study will consist of Screening, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in Appendix A.

Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator or designee.

The length of each patient's participation in the study is approximately 11 months, which includes an up to 56-day Screening Period, a 25-week Treatment Period, and an up to 13-week Post-Treatment Period, unless the patient chooses to enroll in the OLE study.

3.4.1. Screening

After the informed consent (ICF) and, in the case of participants not of legal age, assent is signed, the patient will be assessed for eligibility according to the Schedule of Procedures in Appendix A. The Screening Period is up to 56 days in duration. A patient may be randomized after fewer than 56 days from the screening visit if the patient experiences ≥ 2 HAE attacks in less than 56 days, has completed all other screening activities, and has met all other eligibility requirements.

3.4.2. Treatment

Eligible patients will report to the Study Center for the first administration of Study Drug on Study Day 1 and will continue to receive Study Drug once every 4 (Cohort A) or 8 (Cohort B) weeks during the 25-week Treatment Period. Patients will return to the Study Center (or Home Healthcare, if available) for treatment visits to complete assessments and dosing per the Schedule of Procedures in Appendix A. In regions where Home Healthcare is available to patients, a training curriculum will be developed with input from the Sponsor and all Home Healthcare providers will be trained prior to conducting any study related assessments/procedures. This training will be documented and filed as appropriate.

3.4.3. Post-Treatment

Patients are to return to the Study Center for post-treatment follow-up visits (or Home Healthcare, if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A. Alternatively, patients who complete Study Visit Week 25, and meet eligibility requirements, may enroll in the OLE study any time after the Week 25 visit. If a patient chooses to enroll in the OLE study, the patient will discontinue participation in the CS5 Post-Treatment Period prior to the first visit in the OLE study. Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator or designee.

The final study visit for patients not enrolling in the OLE will be the Week 13 Post-Treatment Period Visit.

Throughout the study including during the Post-Treatment Period, patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator or designee.

3.5. End-of-Study

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

For individual patients, End-of-Study is defined as completion of their last study visit.

3.6. Data and Safety Monitoring Board or Independent Data Monitoring Committee

A Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 721744 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter and Statistical Analysis Plan (SAP).

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval of the protocol, ICF and, as applicable, assent form, and all other patient information and/or recruitment material.

Patients, or their legally appointed and authorized representatives, will sign and date an ICF, and when appropriate, an assent form before any screening tests or assessments are performed. Race and Ethnicity data will be collected as part of the demographic information for all screened patients during the Screening Period. At the time of consent and, as applicable, assent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire study.

In the event the patient is re-consented and as applicable, re-assented and re-screened, the patient must be given a new screening number. Screening numbers, once assigned, will not be re-used.

4.2. Randomization

Patients will be randomized, after all screening assessments have been completed and after the Investigator or designee has verified that they are eligible per the criteria in Section 5.1 and Section 5.2. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Approximately 84 patients with HAE-1/HAE-2 will be randomized via the IRT system to SC injections of ISIS 721744 80 mg or placebo. Approximately 56 patients will be randomized to every-4-week dosing (Cohort A) and 28 patients will be randomized to every-8-week dosing (Cohort B). Within each Cohort, patients will be randomized in a 3:1 ratio to receive 80 mg of ISIS 721744 or matching volume of placebo. For purposes of planned analyses, the placebo patients from each Cohort will be pooled for comparison to ISIS 721744 treated patients.

Randomization information will be concealed from the Investigators or designees and patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

4.4. Unblinding of Treatment Assignment

The Sponsor and all patients, monitors, and Study Center personnel related to the study (except for the DSMB, statistical/programming support staff) will be blinded throughout the study until all patients have completed the study and the database has been locked. Representatives from

the Sponsor may be unblinded after the last patient has completed the end of the Treatment Period (Week 25/Tx-ET) as described in the Unblinding Plan. Those Sponsor representatives will no longer be involved in the conduct of the study after they have been unblinded. However, if a patient has suffered an SAE (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient via the IRT system.

The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's designated vendor. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for the purpose of unblinded regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the ET study procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 56 days of the Study Day 1 Visit or at the time point specified in the eligibility criteria listed.

5.1. Inclusion Criteria

1. Patients, or their legally appointed and authorized representatives, must provide written and signed ICF, and when appropriate, an assent form and any authorizations required by local law and be able to comply with all study requirements for the duration of the study
2. Patients must be aged ≥ 12 years at the time of informed consent and, as applicable, assent
3. Patients must have a documented diagnosis of HAE-1/HAE-2 based upon ALL of the following:
    a. Documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018)
    b. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 level is below the lower limit of normal (LLN) or if a known pathogenic mutation in the SERPING1 gene has been demonstrated
    c. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range
4. Patients must:
    a. Experience a minimum of 2 HAE attacks (confirmed by the Investigator) during the Screening Period

b. Be willing to complete the PRO assessments throughout the study as described in Section 6.2.6

5. Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks
6. Female patients must be non-pregnant (and not planning a pregnancy during the study) and non-lactating, and be either:
   a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)
   b. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the post-menopausal range for the laboratory involved)
   c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception)
   d. If engaged in sexual relations of childbearing potential, agree to use acceptable contraceptive methods (refer to Section 6.3.1) from the time of signing the ICF and, as applicable, assent form until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo)
7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo)

5.2. Exclusion Criteria

1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening, Treatment or Post-Treatment Periods
2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired, idiopathic angioedema or HAE with normal C1-INH (also known as HAE Type III)
3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks
4. Any clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following laboratory values are exclusionary:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN)
   b. Total bilirubin > 1.5 × ULN OR, if due to Gilbert's syndrome, > 5 mg/dL
   c. Platelet count < 130 K/mm^3

d. For patients ≥18 years old: Estimated glomerular filtration rate < 45 mL/min (as determined by the CKD-EPI formula for creatinine clearance)

e. For patients 12 and <18 years old: Estimated glomerular filtration rate < 60 mL/min (as determined by the Bedside Schwartz formula for creatinine clearance)

5. Patients with a history of acquired coagulopathies or bleeding diathesis (e.g., thrombocytopenia, disseminated intravascular coagulation, coagulopathy of liver disease, drug-induced PLT dysfunction, hyperfibrinolysis, acquired clotting factor inhibitors) and inherited bleeding disorders (e.g., hemophilia A, hemophilia B, other clotting factor deficiencies, qualitative PLT disorders, inherited thrombocytopenia, vascular abnormalities) and hypercoagulability
6. Any clinically significant (CS) renal or hepatic diseases
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
10. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening
11. Participated in a prior ISIS 721744 study
12. Exposure to any of the following medications:
    a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening
    b. Chronic prophylaxis with Takhzyro (lanadelumab), Haegarda (C1-esterase inhibitor SQ), Cinryze and Ruconest (C1 esterase inhibitor) or Orladeyo (berotralstat) within 5 half-lives prior to Screening (i.e., Takhzyro within 10 weeks prior to Screening, Haegarda/Cinryze/Ruconest within 2 weeks prior to screening, Orladeyo within 3 weeks prior to Screening)
    c. Oligonucleotides (including small interfering ribonucleic acid [siRNA]) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received. This exclusion does not apply to vaccines
13. Any condition that, in the opinion of the Investigator or designee, may compromise the patient's safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of results
14. Recent history (3 years) of, or current drug or alcohol abuse

6. STUDY PROCEDURES

6.1. Study Schedule

All required study procedures are outlined in Appendix A.

The safety of ISIS 721744 will be continually monitored throughout the study by the Investigator or designee and the Sponsor Medical Monitor.

The length of each patient's participation from Screening to the last study visit is up to approximately 11 months.

6.1.1. Screening

Written and signed informed consent and, as applicable, assent for the study will be obtained prior to the performance of any study related procedures including screening procedures. An up to 56-day period is provided for completing screening assessments and determining patient eligibility for the study. Abnormal screening results may be re-tested once for determination of patient eligibility after consultation with the Sponsor Medical Monitor. Patients may have laboratory procedures repeated 1 time in order to determine eligibility.

A list of assessments to be completed during Screening is provided in Appendix A. All patient-reported outcomes assessments should be completed at the beginning of each (as appropriate) visit.

During the Screening Period (up to 56 days), patients must experience a minimum of 2 HAE attacks (confirmed by the Investigator) to be eligible for the study; patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening Period, site personnel will contact the patient approximately weekly in order to inquire about any attack that may have occurred. The patient should be randomized as soon as possible after the second attack occurs, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 56 days. Once eligibility has been confirmed, patients will be randomized to receive ISIS 721744 80 mg or placebo once every 4 (Cohort A) or 8 (Cohort B) weeks for a total Treatment Period of up to 25 weeks.

6.1.2. Treatment Period

The first dose of ISIS 721744 or placebo will be administered at the Study Center on Day 1. Self-administration of Study Drug (ISIS 721744 or placebo), or administration by other qualified individuals (e.g., family member), may be allowed after dosing instructions and training have been provided by qualified site personnel. If a dose is to be administered outside the Study Center, site personnel must also confirm that a home healthcare nurse is available to complete all pre-dosing procedures and that the patient has been instructed not to administer a dose until the home healthcare nurse has completed all protocol required pre-dose procedures. ISIS 721744 or placebo will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm. Study visits will be performed at the Study Center (or by Home Healthcare, if available) throughout the Treatment Period approximately every 28 days. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. During the Treatment and Post-Treatment Periods, the following data will be collected:

Angioedema Activity Score (AAS) and number of HAE attacks (confirmed by the Investigator); number of HAE attacks that required on demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Treatment and Post-Treatment Periods, site personnel will contact the patient approximately weekly in order to inquire about any attack that may have occurred. In addition, during study visits, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks.

Additional assessments will be performed throughout the study as indicated in the Schedule of Procedures table in Appendix A.

Patients who experience at least 5 attacks/month for 2 consecutive months after Week 5 will have the opportunity to terminate from the Treatment Period and either continue in the Post-Treatment Period or enter into an OLE. A decision to terminate a patient from the Treatment Period for this reason will be made by the Investigator or designee in consultation with the Sponsor Medical Monitor. Patients who complete Study Visit Week 25, and meet eligibility requirements, may enroll in an OLE study after the Week 25 visit. If a patient chooses to enroll in the OLE study, the patient will discontinue participation in ISIS 721744-CS5 prior to the first visit in the OLE study.

Patients who discontinue treatment will attend the ET Visit and will be encouraged to complete the Post-Treatment Period, unless consent/assent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.

6.1.3. Post-Treatment Period

Each patient will be followed for safety assessments for up to 13 weeks after completion of, or ET from, the Treatment Period. During the Post-Treatment Period, patients will return to the Study Center (or have Home Healthcare, if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A for safety and clinical laboratory evaluations and for blood sampling for PK/PD analyses. Alternatively, after completion of the Week 25 visit, eligible patients may elect to enroll in the OLE study, pending study approval by the IRB/IEC and the appropriate regulatory authority, and will need to sign the IRB/IEC approved informed consent and, as applicable, assent prior to enrollment. Patients who complete Study Visit Week 25, and meet eligibility requirements, may enroll in the OLE study any time after the Week 25 visit. If a patient chooses to enroll in the OLE study, the patient will discontinue participation in ISIS 721744-CS5 prior to the first visit in the OLE study.

Assessments will be performed throughout the Post-Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

6.2. Study/Laboratory Assessments

6.2.1. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

If the PLT value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) or missing, a repeat blood specimen should be redrawn as soon as possible (ideally within 7 days) either in clinic or by Home Healthcare (if available) or local laboratory.

All PLT count results, and liver and renal function tests, must be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the result has not met the stopping rule.

All lab alerts received, including those related to PLT, liver, or renal function monitoring/stopping rules, are also reviewed promptly by the Sponsor and the CRO Medical Monitors who will agree on actions to be taken. Within 24 hours of receiving an actionable lab alert the CRO Medical Monitor will communicate instructions to the Investigator or designee and the study personnel by emailing them the Safety Surveillance Form that needs to be completed and signed by the Investigator or designee /study personnel and promptly returned to the Sponsor and CRO Medical Monitor. In urgent cases, such as PLTs results below 50,000/mm^3, or liver or renal test results reaching a critical stopping rule, the Investigator or designee must also be contacted by phone.

Investigators or designees may, at their discretion, test specific laboratory parameters which may be prone to clotting, clumping or hemolysis (e.g., hematology samples) at their local laboratory, in addition to the required central laboratory samples. In these instances, the local laboratory results should be recorded by the site into the electronic database. Assays which are blinded should not be locally tested and recorded into the database (e.g., PKK). All lab sample results from the site's local laboratories are received by the Study Center staff per the local laboratories' standard reporting time, and should be entered as soon as possible (ideally within 1 week) into the electronic Case Report Form (eCRF) to inform the Sponsor and CRO study monitoring teams

Further information on safety monitoring and actions to be taken by the Study Investigator or designee in the event of reduced PLT count are provided in Section 8.5.3 and Section 8.6.3.

6.2.2. Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded per the standard practice of the Study Center. Blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at Screening and for pediatric patients at Week 25.

6.2.3. Electrocardiography

Electrocardiography will be conducted at Screening, Day 1 (prior to the first dose of Study Drug), and again during the Treatment Period and at the Post-Treatment Period visits as outlined in Appendix A.

Electrocardiography will be recorded per the standard practice of the Study Center.

6.2.4. Pharmacokinetic Sampling

Blood samples for the determination of plasma ISIS 721744 concentrations will be collected prior to dosing on Day 1 and at various times throughout the Treatment and Post-Treatment Periods as noted in the table in Appendix C.

6.2.5. Collection of Hereditary Angioedema Attack Details

Historical HAE attack information will be collected at Screening. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient approximately weekly in order to inquire about any attack that may have occurred. In addition, during study visits, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site.

During the Screening, Treatment, and Post-Treatment Periods, detailed information on each HAE attack will be collected including the number of HAE attacks that required on-demand treatment and the details of any on-demand treatment used (frequency and dosing). For each HAE attack, the following data will be collected:

- Date/time of symptom onset
- Location and description of symptoms:
  - Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region
  - Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhea
  - Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx
- HAE attack severity:
  - Mild: transient or mild discomfort
  - Moderate: mild to moderate limitation in activity, some assistance needed
  - Severe: marked limitation in activity, assistance required
- Need for assistance, medical intervention, ER visit, or hospitalization
- Medications to treat the attack
- HAE attack course, including if the HAE attack(s) in question was a typical attack for the patient, or if there was an alternative diagnosis
- Date/time symptoms resolved

The presence of these symptoms, including symptoms in one or more of the above locations, will not automatically be considered an HAE attack unless such a diagnosis is confirmed by the Investigator. The investigator may feel that the presence of these symptoms does not represent a HAE attack if there are features that strongly refute such a diagnosis. For example, if the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g., urticaria); if the reported event persists well beyond the typical course of time for an HAE attack (e.g., greater than 7 days); or if there is a likely alternative etiology for the event (e.g., viral gastroenteritis).

An HAE attack will be defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations noted above. A discrete attack will be counted if there is at least 24-hour symptom-free period between attacks.

6.2.6. Patient-Reported Outcomes

6.2.6.1. Angioedema Quality of Life (AE-QoL) Questionnaire

Quality of life (QOL) will be assessed by the AE-QoL questionnaire during Screening, Treatment, and Post-Treatment Periods as outlined in Appendix A.

The AE-QoL questionnaire is a validated tool to assess symptom-specific health-related QOL impairment in patients suffering from recurrent angioedema (Weller et al. 2013). The AE-QoL is a self-administered questionnaire that can be completed in less than 5 minutes; it comprises 17 questions across 4 domains: functioning, fatigue/mood, fears/shame, and food. The AE-QoL can be used to calculate scores for the 4 individual domains and can also be used to determine a total score. The AE-QoL will be completed by the patient.

6.2.6.2. Angioedema Control Test (AECT) Questionnaire

The AECT is a validated patient-reported outcome instrument to assess disease activity in patients with recurrent angioedema (Weller et al. 2020) which will be assessed during the Treatment and Post-Treatment Periods as outlined in Appendix A. The AECT is easy to administer and fast to complete. The questionnaire consists of four questions asking about the frequency and severity of angioedema experienced in the prior month. Each question has 5 response choices. The AECT can be used to identify patients with poorly controlled disease by working with a cutoff value of greater than or equal to 10 points. Patients who score less than 10 points (0-9) in the AECT have poorly controlled disease whereas patients with controlled disease score 10-16 points. The AECT will be completed by the patient.

6.2.6.3. Angioedema Activity Score (AAS)

Patients will be instructed on the use of the AAS questionnaire during Screening and will record their HAE attacks using the AAS questionnaire to confirm study eligibility. The AAS questionnaire will be completed by patients daily (minimum of 4 daily assessments per week) during the Screening, Treatment, and Post-Treatment Periods.

During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study.

The AAS is a validated patient-reported outcome instrument to assess disease activity in patients with recurrent angioedema. The AAS was designed as a diary-type tool and is easy to administer and fast to complete. Using the AAS questionnaire, patients score each of 5 key symptoms-related factors from 0 to 3, resulting in a total daily score of 0 to 15 (Weller et al. 2013).

6.2.6.4. Additional PROs

Additional instruments that will be used to collect information from patients during the Treatment and Post-Treatment Periods are summarized in this section. Timing of these assessments is outline in Appendix A. Generic health-related QOL will be assessed using the EQ-5D-5L. The PGIC and the PGIS scales will also be administered throughout the study. The PGIC and PGIS scales are administered for purposes of PRO validation and estimation of minimal important difference (MID). A Generalized Anxiety Disorder (GAD-7) questionnaire will be administered to evaluate anxiety experienced by patients. The GAD-7 is a self-administered patient questionnaire, and it is used as a screening tool and severity measure for generalized anxiety disorder. Pharmacoeconomics will be assessed by the Work Productivity and Activity Impairment (WPAI) questionnaire. ER visits, hospitalization and total inpatient days will be assessed at each study visit starting at Day 1.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male patients and women of childbearing potential (WOCBP) must refrain from sperm/egg donation, and either be abstinent[†] or practice acceptable contraception from the time of signing the informed consent and, as applicable, assent form until at least 24 weeks after their last dose of Study Drug.

For male patients engaged in sexual relations with a female of childbearing potential, if their female partner is using acceptable contraception from the time of the patient signing the informed consent and as applicable, assent until at least 24 weeks after the patient's last dose of Study Drug, then it is not required for the male patient to also use an acceptable contraceptive method.

For the purposes of this study, females of childbearing potential are defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post-hysterectomy

For the purposes of the study, acceptable contraception is defined as follows:

For male patients:

- Acceptable male contraception includes a vasectomy with negative semen analysis at Follow-up, surgically sterile via bilateral orchidectomy, abstinence†, condom with spermicide or the non-pregnant female partner of child-bearing potential uses an acceptable contraceptive method (defined below)
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug

For female patients and female partners of male patients, acceptable contraception methods comprise:

- Surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception associated with inhibition of ovulation (progestogen-only [female patients with HAE] or combined estrogen and progesterone [female partners of male patients]), intrauterine contraception device or intrauterine hormone-releasing system or a vaginal ring (as long as the patient has been using this contraceptive method for at least 3 months before Screening) or vasectomized partner with negative semen analysis at follow-up, male or female condom with spermicide; or cap, diaphragm, or sponge with spermicide. Female patients with HAE cannot use estrogen containing oral, subcutaneous, or transdermal contraceptives in this study.

†**Note:** Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

Note: A female condom and a male condom should not be used together as friction between the 2 can result in either or both products failing

6.4. Emergency Provisions

During an emergency, such as a pandemic, natural or man-disasters (i.e., earthquake, industrial accident), weather events (i.e., hurricanes, typhoons), terrorist acts/acts of war, etc., the following changes to this protocol are allowed without formal amendment to the protocol, provided all International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and regulatory requirements associated with the study are upheld.

- **Remote Assessments and At-Home visits**: Scheduled clinic visits may be replaced by remote assessments (via video conference or telephone call), or at-home visits, or a combination thereof, provided that these are properly documented. This may be accomplished by at-home visits by Study Center staff or home healthcare providers, with incorporation of videoconference or telephone assessments by Study Center staff or designee

- **Randomization:** When a participant is found to be eligible for the study, the decision regarding if and when randomization will occur is based on the judgment of the Investigator or designee in consultation with the Sponsor. Randomization may be delayed by up to 1 month without rescreening
- **Study Drug Administration**: To support Study Drug administration at home, delivery of Study Drug to a participant may be undertaken at the discretion of the Investigator or designee, based on local and regional regulations for transporting investigational product
- **Safety Assessments**: Every effort should be made to continue performing safety assessments on schedule. This may require remote assessments (e.g., for adverse events and concomitant medications) by Study Center staff, and it may require at home visits (e.g., for blood draws, urine samples, physical examination, vital signs) by Study Center staff or home healthcare providers. Which safety assessments are considered critical, for example to support a decision on whether to administer the next scheduled dose of Study Drug, is to be determined on a case-by case basis by the Investigator or designee in consultation with the Sponsor
- **Other Assessments:** Every effort should be made to perform the assessments related to primary or secondary endpoints on schedule
- **Reporting of Protocol Deviations:** All protocol deviations that are caused by a public health emergency should be documented as such; for example, include in the description of the protocol deviation that it is related to COVID-19. The impact of such protocol deviations on the study is to be summarized in the clinical study report. This summary is considered sufficient notification of the EC/IRB for minor protocol deviations that were caused by a public health emergency
- **Immunization:** Immunization of participants with a vaccine for an epidemic/pandemic may occur while participants are on study, however it is preferable that a separation of at least 7 days occurs between administration of the vaccine and administration of Study Drug. Adjustment of the Study Drug schedule may be considered in order to achieve this separation in consultation with the Sponsor

An event requiring institution of emergency provisions is based on the judgement of the Investigator or designee in consultation with the Sponsor. The determination of when an emergency has resolved to sufficient extent such that these allowances are no longer needed is also based on the judgment of the Investigator or designee in consultation with the Sponsor.

7. STUDY DRUG

7.1. Study Drug Description

Study Drug (ISIS 721744 or placebo) characteristics are listed in Table 1.

The Study Drug (ISIS 721744 or placebo) is contained in 2 mL stoppered glass vials. The Study Drug (ISIS 721744 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 721744 or placebo) must be stored securely at 2 °C to 8 °C and be protected from light.

During the Treatment Period, Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection once every 4 (Cohort A) or 8 (Cohort B) weeks.

Table 1: Study Drug Characteristics

Study Drug	**ISIS 721744**	**Placebo**
Strength	100 mg/mL	Not Applicable
Volume/Formulation	0.8 mL solution per vial	0.8 mL solution per vial
Route of Administration	SC	SC

7.2. Packaging and Labeling

The Sponsor will provide the Investigator or designee with packaged Study Drug (ISIS 721744 or placebo) labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drug (ISIS 721744 or placebo) supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. Study Drug Administration

Study Drug (ISIS 721744 or placebo) will be administered as a single SC injection once every 4 (Cohort A) or 8 (Cohort B) weeks by blinded study staff during on-site visits at the Study Centers or by Home Healthcare professional. Self-administration of ISIS 721744 or placebo may be allowed after dosing instructions and training are provided by qualified site personnel and home healthcare nurse is available to complete all pre-dosing procedures.

Vials of Study Drug (ISIS 721744 or placebo) are for single use only.

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 721744 or placebo) preparation and administration.

8.2. Other Protocol-Required Drugs

Patients must have access to, and the ability to use, ≥ 1 acute HAE medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks. During the course of the study, the use of acute HAE medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4. Treatment Precautions

There are no specific treatment precautions required.

8.5. Safety Monitoring Rules

Stopping rules are described below in Section 8.6.

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

- For the purposes of safety monitoring baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1
- In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations
- In case of discrepancy between the test results from 2 sources, such as between the central and local lab, safety-mandated action must be initiated based on the more critical (lower or higher, as relevant) of the 2 values

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug (ISIS 721744).

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator or designee and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described in Section 8.6 are met, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 721744), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the Protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

All patients will have liver chemistry tests monitored every 4 weeks during the Treatment Period. Upon completion of the study Treatment Period, liver chemistry tests should be monitored as per visit schedule in Appendix A.

In the event of appearance of symptoms or signs of hepatic injury (jaundice, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, abnormal bleeding or bruising, or eosinophilia > ULN) liver enzymes and bilirubin should be tested as soon as possible (ideally within 3 days). Testing at a lab that is local to the patient is permissible for this purpose.

In the event of an ALT or AST measurement that is > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, Alkaline Phosphatase (ALP), international normalized ratio [INR], and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 × ULN or 1.2 × baseline value if the baseline value was > ULN].

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (hepatitis A virus immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], Hepatitis C Virus antibody, cytomegalovirus IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computerized tomography (CT) or magnetic resonance imaging (MRI) scans, may be performed at the discretion of the Investigator or designee, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 × ULN.

The Study Drug must be interrupted until all evaluations and consultation with the Sponsor Medical Monitor is complete.

All lab alerts for abnormal liver function tests must be promptly reviewed by the Investigator or designee (within 48 hours of receipt) and Medical Monitor(s) (within 24 hours of receipt) as described in Section 6.2.1.

Lab alerts for abnormal liver chemistry tests will be issued for: 1) ALT or AST > 3 × ULN; 2) ALT or AST > 2 × baseline; 3) total bilirubin > ULN. These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance referenced in Section 8.5 above.

8.5.2. Safety Monitoring Rules for Renal Function Test Results

While on treatment, all patients will have renal function tests monitored every 4 weeks during the Treatment and Follow-up Periods as per visit schedule in Appendix A.

In the event of appearance of symptoms or signs consistent with renal dysfunction such as hematuria, polyuria, anuria, flank pain, new-onset hypertension, nausea and/or anorexia, renal function should be tested as soon as possible (ideally within 3 days). Testing at a lab that is local to the patient is permissible for this purpose.

If a patient's results meet criteria 1 or 2 below, the Investigator or designee should confirm the results and initiate weekly monitoring if confirmed. If the event a persistent elevation is observed over 2 consecutive weeks, then refer to Stopping Rules for Renal Function Test Results in Section 8.6.2.

1. Serum creatinine increase that fulfills all of the following: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section Stopping Rules Section 8.6)
2. Proteinuria, urine protein/creatinine ratio (UPCR) > 750 mg/g for baseline values ≥ 200 mg/g, or 4 × baseline value for baseline values < 200 mg/g that are confirmed by repeated urine protein/creatinine ratio or by a quantitative total urine protein measurement of > 1.0 g/24 hours

8.5.3. Safety Monitoring Rules for Platelet Count Results

Platelet count will be monitored at least every 4 weeks during the Treatment and Post-Treatment Periods as per visit schedule in Appendix A.

The Investigator or the designee should review all PLT count results within 48 hours of receipt. Any unreportable PLT count result must be rechecked ideally within 7 days and determined not to have met a stopping rule before dosing can continue.

Actions to be taken in the event of reduced PLT count are shown in Table 2.

Table 2: Actions in Patients with Confirmed Low Platelet Count

Platelet count (K/mm^3)	**Dosing**	**Monitoring frequency**
≥ 125	No action	At least every 4 weeks.
> 100 to < 125	Dosing every 4 (Cohort A) or 8 (Cohort B) weeks should be continued.	At least every 2 weeks until 2 successive values > 125K/mm^3.
≥ 75 to ≤ 100	Dosing every 4 (Cohort A) or 8 (Cohort B) weeks may be continued if approved by the Sponsor Medical Monitor.	Every week until 2 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.*
≥ 50 to < 75	Pause dosing. When PLT count returns to > 100K/mm^3, restart dosing only if approved by the Sponsor Medical Monitor.	Twice weekly until 2 successive values > 75K/mm^3, then weekly until 2 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.*
≥ 25 to < 50	Permanently discontinue Study Drug. Consider corticosteroids if additional risk factors for bleeding are present.**	Twice weekly until 2 successive values > 75K/mm^3, then weekly until 2 successive values > 100/mm^9. Consider more frequent monitoring if additional risk factors for bleeding are present.*
< 25	Permanently discontinue Study Drug. Corticosteroids strongly recommended.**	Daily until 2 successive values > 25K/mm^3, then twice weekly until 2 successive values > 75K/mm^3, then weekly until 2 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.*

* The suitability of the patient for interrupted and/or continued dosing will be determined by the Investigator or designee in consultation with the Medical Monitor and will be based on factors such as the original rate of decline in the patient's PLT count, whether any bleeding events were experienced by the patient, and the speed of recovery of PLT count after interruption of dosing.

** Recovery in platelet count may be accelerated by administration of high-dose glucocorticoids. Treatment as recommended by the American Society of Hematology (ASH) (2019) guidelines for immune thrombocytopenia (Blood Advances, 10 DECEMBER 2019, Volume 3, Number 23) includes initial therapy with either dexamethasone 40 mg per day for 4 days, or prednisone 0.5 to 2.0 mg/kg per day. Prednisolone or prednisone may be administered for up to 2 to 4 weeks with taper; alternatively, intravenous immunoglobulin (IVIG) may be administered at 0.4 g/kg/d for 5 days, or infusions of 1 g/kg/d for 1-2 days (Provan et al. 2010; Provan et al. 2019).

There will be lab alerts for PLT values under 100,000/mm^3.

8.5.4. Safety Monitoring for Bleeding Events

Patients will be evaluated for occurrence of bleeding events continuously after the start of Study Drug treatment (Day 1) up to the end of the Follow-up Period. All bleeding events are considered AEs and reported on the AE case report form (CRF).

If an event of major bleeding (MB) or clinically relevant non-major bleeding (CRNMB) event occurs (as defined below), the Investigator or designee must notify the Medical Monitor (or designee) and the patient should be treated, as needed, immediately and closely monitored (vital signs, lab tests such as hemoglobin (Hb), hematocrit, and PLT count, additional visits, overnight stays and coagulation tests may be needed if deemed appropriate by the treating physician) throughout the Treatment and Post-Treatment Periods and an (S)AE CRF will be completed. In addition, approximately 2 mL of K2 EDTA anticoagulated blood will be collected and resulting plasma must be stored allowing for a centralized assessment of ISIS 721744 concentrations.

If a minor bleeding event occurs, the Investigator or designee should notify the Medical Monitor (or designee) and additional testing of coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], INR), PLT count, and PLT volume may be performed.

Major bleeding is defined as one of the following (Schulman and Kearon 2005):

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed RBCs or whole blood or a fall in Hb of 20 g/L (1.24 mmol/L) or more within 24 hours

Clinically relevant non-major bleeding is defined as any sign or symptom of hemorrhage (e.g. more bleeding that would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for MB but does meet at least one of the following criteria (Kaatz et al. 2015):

1. Requiring medical intervention by a healthcare professional
2. Leading to hospitalization or increased level of care
3. Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Minor bleeding events are those that do not fulfill the criteria for MB or CRNMBs (defined above), for example excess bruising, petechiae, gingival bleeding on brushing teeth.

8.6. Stopping Rules

Monitoring rules are described above in Section 8.5.

For the purposes of the stopping rules, Baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1.

8.6.1. Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with Study Drug (ISIS 721744 or placebo) will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 × ULN, which is confirmed
2. ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 × ULN (or the greater of 2 x baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 1.5 × ULN or INR > 1.5
4. ALT or AST > 3 × ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, **and** the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a patient with Study Drug (ISIS 721744 or placebo) may be stopped temporarily:

1. Serum creatinine increase that fulfills all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. UPCR >1000 mg/g, confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hours

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator or designee **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3. Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low PLT count are summarized in Table 2 above.

8.6.4. Stopping Rules for Bleeding Events

In the event of MB or CRNMB (see definitions in Section 8.5.4 as assessed by the Investigator or designee, dosing of a patient with Study Drug (ISIS 721744 or placebo) may be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined, including the suitability of the patient for resumption of dosing by the Investigator or designee in consultation with the Medical Monitor (or designee).

8.7. Adjustment of Dose and/or Treatment Schedule

Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study.

Dose adjustments for PLT count reduction must be made in accordance with Table 2.

Other adjustments, including dose interruptions, will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

8.8. Discontinuation of Study Drug/Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent or assent
- The patient withdraws from treatment (but does not withdraw consent or assent)
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6
- The patient experiences an AE that necessitates unblinding of the Investigator or designee or Sponsor to the patient's treatment assignment

The reason for discontinuation of Study Drug must be recorded in the eCRF and source documentation.

Patients who discontinue Study Drug will remain in the study and attend the Tx-ET Visit (Week 25 visit assessments), unless consent or assent is withdrawn. Any patient who discontinues early from the Treatment Period should be strongly encouraged to complete the Post-Treatment Period study visits, procedures and observations (see Appendix A).

8.8.1. Follow-up Visits for Early Termination from Treatment Period or Post-Treatment Period

If a patient discontinues early from the Treatment Period, Treatment Early Termination (Tx-ET) visit assessments should be performed 28 days from the last dose of Study Drug, and patients should start the 13 weeks Post-Treatment Period to collect the study assessments in accordance with the Schedule of Procedures in Appendix A. Patients should also be strongly encouraged to attend the landmark visit at Week 25 if they discontinue prior to Week 25 to collect HAE attacks and conduct safety assessments in accordance with Appendix A. Depending on the day of discontinuation, Post-Treatment visits and the landmark visit may overlap and can be combined.

Any patient who chooses to discontinue early from the Post-Treatment Period should be strongly encouraged to complete safety procedures and observations in accordance with Appendix A. If the patient declines or is unable to participate in the above, final Post-Treatment Early Termination (Post-Tx ET) assessments should be performed at the time of withdrawal in accordance with Appendix A.

8.8.2. Temporary Pause/Safety Review

The trial should be halted for a safety review based on the following criteria:

- Death in any subject in which the cause of death is judged to be probably or definitely related to the study drug by the treating investigator
- The occurrence in any subject of a life-threatening SAE that is assessed to be related to the study drug by the treating investigator
- Two occurrences of Grade 3 or higher toxicities that are assessed to be related to the study drug by the treating investigator
- Two occurrences of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by the treating investigator

8.9. Withdrawal of Patients from the Study Procedures

Patients must be withdrawn from study procedures for any of the following:

- Withdrawal of consent or assent
- The patient is unwilling or unable to comply with the protocol
- The patient meets any of the Exclusion Criteria (see Section 5.2) after enrolling in the study that in the opinion of the Investigator represents a safety risk to the patient

Other reasons for withdrawal of patients from the study may include the following:

- At the discretion of the Investigator or designee for medical reasons
- At the discretion of the Investigator or designee or Sponsor for non-compliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent or assent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the respective ET study procedures (Week 25 or Post-Treatment Week 13 visit assessments) and observations at the time of withdrawal (see Appendix A).

For patients withdrawn for reasons other than withdrawal of consent or assent, every effort should be made to complete the ET study procedures and observations at the time of withdrawal (see Appendix A) and ideally within 4 weeks from the last dose of Study Drug.

8.10. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

A concomitant therapy is any non-protocol-specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered between Screening and the end of the Post-Treatment Period.

Allowed Concomitant Therapy

During the course of the study, the use of acute HAE medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

All other stable medications (if not excluded below) are allowed, so long as the dose and type is not expected to change during the study.

Disallowed Concomitant Therapy

1. Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens or tranexamic acid. Any chronic use of other HAE prophylactic agents such as lanadelumab or berotralstat will not be permitted during the Treatment Period.

   NOTE: The use of acute HAE medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated
2. ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy)
3. Any oligonucleotides (including siRNA) other than ISIS 721744
4. Any other investigational drug or device

Patients should consult with the Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any non-drug therapy.

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between Screening and the end of the Post-Treatment Period.

Disallowed Concomitant Procedures

Plasma apheresis is not allowed during the study.

8.11. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the applicable Ionis and/or designee Standard Operating Procedures throughout the conduct of the clinical study.

9.2. Regulatory Reporting Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators or designees of SAEs including SUSARs per the ICH guidelines E2A and ICH GCP. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards/Independent Ethics Committees will be notified of any SAE according to applicable regulations. The DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's or designee's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug (ISIS 721744 or placebo) is causally related to a reported SAE and, therefore, meets the definition of an SUSAR. While the Sponsor's independent causality assessment may differ from the Investigator's or designee's assessment, the country-specific regulatory requirements must be followed for expedited reporting of SUSAR to local regulatory authorities.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators or designees in a blinded fashion.

For the purpose of regulatory reporting of SUSARs, there are not "expected" AEs in this study population. Investigator's Brochure (provided separately) for expected adverse events.

SAEs due to HAE attacks will not be reported on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of the Study Drug (ISIS 721744 or placebo) exposure. The Investigator or designee still has the responsibility to report all SAEs to the Sponsor as described in Section 9.4.1 to Section 9.4.3.5.

HAE attacks will be reported on a HAE attack CRF page and will not be reported as AEs.

The Sponsor or designee and DSMB will monitor these protocol-specified SAEs using the incidence rate of the event in the study compared to the expected incidence rate in a non-Study Drug exposed patient population. If the aggregate analysis indicates that an event is occurring more frequently or at a greater severity than expected, then the event will be reported.

9.3. Definitions

9.3.1. Adverse Event

An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2. Adverse Drug Reaction and Suspected Unexpected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the adverse event has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event (SAE)

A SAE is any adverse event that in the view of either the Investigator or designee or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or designee or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ER or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; OR Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

9.3.4. Adverse Event of Special Interest (AESI)

For the purpose of this study, severe reductions in PLT count < 50,000/mm^3 accompanied by a MB event or CRNMB event, or PLT count of < 25,000/mm^3 independent of a MB or CRNMB event, are considered as AEs of special interest (AESIs) and are subject to 15-day expedited reporting by the Sponsor to the regulatory agencies.

Adverse events of special interest are required to be reported by the Investigator or designee to the Sponsor immediately, within 24 hours of the Study Center's first knowledge of the event, for expedited reporting to Regulatory Authorities.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent and, as applicable, assent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator or designee should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1. Serious Adverse Events (SAE)

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 13 Visit of the Post-Treatment Period, or patient has Day 1/Week 1 in the OLE study. Serious adverse events should be reported using electronic SAE submission (via Electronic Data Capture [EDC]) whenever possible. In situations where electronic SAE submission is unavailable, a paper Initial Serious Adverse Event Form should be completed, and a copy should be faxed or emailed to the Sponsor or designee. The SAE reporting instructions, including the fax number and email address, can be found in the Investigator Site File for the study.

Detailed information should be actively sought and included as Follow-Up as soon as additional information becomes available. All SAEs will be followed until resolution. Serious adverse events that remain ongoing past the patient's last protocol-specified visit will be evaluated by the Investigator or designee and Sponsor. If the Investigator or designee and Sponsor agree that the patient's condition is unlikely to resolve, the Investigator or designee and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 13 Visit of the Post-Treatment Period, or patient has Day 1/Week 1 in the OLE study. The Investigator or designee will monitor each patient closely and record all observed or volunteered AEs on the eCRF.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's or designee's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 721744 or placebo) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug (ISIS 721744 or placebo), e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 721744 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 721744 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator or designee believes no relationship exists between the event and Study Drug (ISIS 721744 or placebo)

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests will be graded based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept. 2007 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

The severity of AEs and SAEs relating to AEs at the injection site will be graded based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 (refer to Appendix D).

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3.

9.4.3.3. Action Taken with Study Drug

Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study.

Action taken with Study Drug (ISIS 721744 or placebo) due to an AE is characterized by 1 of the following:

- **None:** No changes made to Study Drug (ISIS 721744 or placebo) administration and dose
- **Not Applicable:** AE reported during the Screening Period prior to Study Drug (ISIS 721744 or placebo) administration or during the Post-Treatment Period
- **Permanently Discontinued:** Study Drug (ISIS 721744 or placebo) discontinued and not restarted
- **Temporarily Interrupted, Restarted - Same Dose:** Dosing and/or dosing frequency temporarily interrupted/changed or delayed due to the AE and restarted at the same

9.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6. Follow-up of Adverse Event

Investigator or designee **Follow-Up**

During the study, the Investigator or designee should follow each AE until the event has resolved to Baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent or assent. Every effort should be made to follow all SAEs considered to be related to Study Drug or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

Investigator or designee should follow-up or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available.

Sponsor Follow-Up

For SAEs, AESIs, and pregnancy cases in patients who have completed or terminated the study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of these case.

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator or designee, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator or designee until the parameter returns to its baseline value or until agreement is reached between the Investigator or designee and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator or designee should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator or designee should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's or designee's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent and, as applicable, assent to participate in the study

- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator or designee between the patient's consent and, as applicable, assent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3. Dosing Errors

Study Drug (ISIS 721744 or placebo) dosing errors (including overdose, underdose, and administration error) should be documented as protocol deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing eCRF. If the patient takes a dose of Study Drug (ISIS 721744 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the Investigator or designee should refer to the "Guidance for Investigator" section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use acceptable contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including the Post-Treatment Period), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient will be encouraged to complete the Post-Treatment Period of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the

progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations, e.g., pregnancy ICF may be required.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations, e.g., partner ICF may be required.

10. STATISTICAL CONSIDERATIONS

The sections below indicate the overall structure and approach to the analysis of this study. A detailed SAP incorporating these sections below will be prepared separately. The SAP will outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis. The study objectives and endpoints are listed in Section 1.1 and Section 1.2, respectively.

10.1. Stratification, Subsets, and Covariates

There are no stratification factors in this study. Subset analyses are not planned. The covariate used in the model for the primary efficacy analysis is described in Section 10.6.3.1.

10.2. Sample Size Considerations

The power and sample size estimations were calculated using simulations based on a generalized linear model for count data assuming a Poisson distribution. The primary endpoint is the time-normalized- number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25. Assuming an HAE attack rate of 13.26 attacks per 6-month period in the placebo group and an HAE attack rate of 1.38 attacks per 6-month period in the ISIS 721744 80 mg every 4 weeks group, the sample size of 54 patients (2:1 ratio [ISIS 721744:placebo]) will provide at least 90% power for the primary endpoint, with a 0.05 significance level. A total of approximately 84 patients (42 in the ISIS 721744 every 4 weeks group, 21 in the pooled placebo group, and 21 in the ISIS 721744 every 8 weeks group) will be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations.

10.3. Populations

The Safety Population will include all randomized patients who receive at least 1 dose of Study Drug (ISIS 721744 or placebo).

The Intent-to-Treat (ITT) Population will include all randomized patients.

The Per-Protocol (PP) Population will include all patients in the ITT Population who are treated according to the protocol without any major deviations that could compromise the interpretation of efficacy. Significant deviations will be determined prior to unblinding for statistical analysis.

The PK Population will include all patients who are randomized and receive at least 1 dose of Study Drug and have at least 1 evaluable PK sample.

10.4. Definition of Baseline

Run-in period is defined as the period from screening to the last day prior to Study Day 1.

For Investigator-confirmed HAE attacks, the baseline rate, i.e., run-in period Investigator-confirmed HAE attack rate, will be calculated for each patient as number of Investigator-confirmed HAE attacks occurred during the run-in period divided by the number of days contributed to the run-in period multiplied by 28 days.

For PLTs, Baseline will be defined as the average of all non-missing pre-dose assessments.

For other assessments, if there are 2 or more pre-dose values available, baseline will be defined as the average of the pre-dose Study Day 1 value and the last pre-dose value prior to Study Day 1. If there is only 1 pre-dose measurement available, then it will be assigned as Baseline.

10.5. Interim Analysis, Multiplicity, and Early Stopping Guidelines

No interim analysis is planned for this study. Final analyses will be conducted after the End of Treatment period when all patients complete Week 25 visit, stay in the study for at least 25 weeks since the Study Day 1 or withdraw from the study before 25 weeks from the Study Day 1. Study results with continuing collected post-treatment data will be updated at the End of Study.

The multiplicity for primary and secondary analyses will be controlled by using the hierarchical testing procedure at 0.05.

The following secondary endpoints will be tested if the primary endpoint is statistically significant ($p < 0.05$). The testing sequence for the secondary endpoints will be specified in the SAP.

- The time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 compared to placebo
- The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo
- The time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 5 and Week 25 compared to placebo

- The number of patients with a clinical response defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25 compared to placebo
- The number of Investigator-confirmed HAE attacks requiring acute HAE therapy from Week 5 to Week 25 compared to placebo
- Percent of patients who are well controlled based on the AECT at Week 25
- Change in AE-QoL questionnaire total score at Week 25

The early stopping guidelines are described in Section 8.6.

10.6. Planned Methods of Analysis

All eCRF data, lab data transfers, and any outcomes derived from the data will be provided in the patient listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, SD, standard error, interquartile range (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

All primary and secondary endpoints will be assessed on ITT and PP Populations, with the former being the basis for the primary efficacy analysis. Placebo patients from Cohort A and Cohort B will be pooled for analysis. All safety assessments will be performed on the Safety Population.

10.6.1. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. Patient randomization will be summarized by cohort and treatment group. The patient disposition will be summarized. All patients enrolled will be included in a summary of patient disposition.

10.6.2. Safety Analysis

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

Treatment duration and amount of Study Drug (ISIS 721744 or placebo) received will be summarized by treatment group. Patient incidence rates of all adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, and by MedDRA term. Tables and/or narratives of treatment emergent deaths, serious and significant adverse events, including early withdrawals due to adverse events, will also be provided.

All treatment emergent AEs, all treatment emergent AEs potentially related to Study Drug, all treatment emergent serious AEs, and all treatment emergent serious AEs potentially related to Study Drug (ISIS 721744 or placebo) will be summarized.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 721744 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

10.6.3. Efficacy Analysis

10.6.3.1. Primary Efficacy Analysis

The primary endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25.

The primary analysis of the primary endpoint is to compare the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25 between ISIS 721744 80 mg every 4 weeks and pooled placebo using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion on the ITT population. The model will include fixed effect for treatment group (categorical), the time-normalized run-in period attack rate (continuous) as a covariate, and the logarithm of time in months that each patient was observed from Week 1 to Week 25 will be used as an offset variable.

All available data, including data after participants received androgens or on demand acute medications to manage attacks during the Treatment Period, up to either the start of the open-label period or Week 25, whichever is earlier, will be used to account for missing values in the primary analysis. The logarithm of the length of observation time will be included as an offset variable in the Poisson model to adjust for differences in follow-up time. All patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, will have the time-adjusted attack rate included in the analysis.

Sensitivity analyses will be conducted for all patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, using multiple imputation (MI) to impute the unobserved attack rate. A pattern mixture model may be included. In addition, a tipping-point analysis will be conducted to measure the potential effect of missing data on the reliability of the primary efficacy analysis.

10.6.3.2. Secondary Efficacy Analysis

The secondary endpoints include the time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25; the percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25; the time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 1 to Week 25; the number of patients with a clinical response defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25

compared to placebo; the number of Investigator-confirmed HAE attacks requiring acute therapy from Week 5 to Week 25; percent of patients who are well controlled on the AECT at Week 25; and change in AE-QoL questionnaire total score at Week 25.

The time-normalized number of Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25, the time normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25, and the time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per month) from Week 5 to Week 25 will be analyzed in a similar way to the primary efficacy endpoint.

Continuous variables will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment group. Continuous variables will also be analyzed using a mixed effects model with repeated measures (MMRM). The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

Categorical variables will be summarized by frequency and percentage for the treatment group and placebo group. Categorical variables will be analyzed using the Chi-squared test or Fisher's Exact test.

10.6.4. Pharmacokinetic Analysis

The plasma PK of ISIS 721744 will be assessed following SC administration. For all patients, pre-dose (trough) and post-treatment plasma ISIS 721744 concentrations will be determined and summarized using descriptive statistics. Plasma terminal elimination half-life will also be calculated using the Post-Treatment Follow-up ISIS 721744 plasma concentrations, if data permits.

Metabolite identification and profiling may be conducted on select plasma samples.

Plasma PK parameters will be summarized using descriptive statistics. Additional details regarding the PK analysis along with immunogenicity (IM) analysis will be described in the SAP.

Analysis of potential exposure-response relationship between biomarkers and PK measures may also be explored.

Population PK and PK/PD analyses may be performed using PK and PD data from this study, and/or combined with other ISIS 721744 clinical PK/PD data in the development timeline.

10.6.5. Pharmacodynamic Analysis

The change from Baseline in PKK levels at each visit during the Treatment Period will be compared between ISIS 721744 80 mg and placebo using the MMRM. The response variable is the change or percent change from Baseline at post-baseline visit up to Week 25. The MMRM model will include effects of treatment (ISIS 721744 or placebo), time (categorical), treatment-by-time interaction, and baseline value.

10.6.6. Additional Analyses

Exploratory efficacy endpoints include change in GAD-7, change in EQ-5D-5L, PGIC, PGIS, change in WPAI, and incidence of ER visits, all cause hospitalization, and total inpatient days.

The change from Baseline in PGIS will be analyzed using a proportional odds model with treatment as a factor and baseline value as covariate.

The value in PGIC will be analyzed using a proportional odds model with treatment as a factor.

All other exploratory efficacy endpoints will be analyzed using the same methods as described for the secondary efficacy endpoints. Additional psychometric analyses may be conducted for selected PROs.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent and Assent

The written informed consent and, as applicable, assent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the study, the Investigator or designee is responsible for obtaining written informed consent and, as applicable, assent from the patient or their legally appointed and authorized representatives after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 721744 or placebo) are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and, as applicable, assent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient and by the person who conducted the informed consent and, as applicable, assent discussion (not necessarily an Investigator). The original signed ICF should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent and, as applicable, assent form should be provided to the patient.

11.2. Ethical Conduct of the Study

All applicable regulations and guidelines of current GCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator or designee must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent and assent document. The Investigator or designee should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The Investigator or designee should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator or designee will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4. Patient Confidentiality

The Investigator or designee must ensure that the patient's confidentiality is maintained. On the CRFs or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed ICFs) should be kept in strict confidence by the Investigator or designee.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator or designee and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator or designee is obligated to inform and obtain the consent and, as applicable, assent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator or designee must be obtained for all protocol amendments and amendments to the informed consent and assent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the study. The Investigator or designee **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2. Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator or designee reserves the right to terminate their participation in the study, according to the terms of the Study Center contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the study's completion or ET and send a copy of the notification to the Sponsor or designee.

12.3. Study Documentation and Storage

An eCRF utilizing an EDC application will be used for this study.

The Investigator or designee should ensure that all appropriately qualified persons to whom he/she has delegated study duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, imaging, and correspondence. In this study, eCRFs may not be used as source documents.

The Investigator or designee and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with ICH GCP, suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include the following:

- Patient files containing completed CRFs, informed consents and, as applicable, assents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator or designee. Should the Investigator or designee wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator or designee agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5. Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

APPENDIX A. SCHEDULE OF VISITS AND PROCEDURES

Appendix A SCHEDULE OF VISITS AND PROCEDURES

Study Week	Screen	Treatment Period							Post-Treatment Period		
	-8 to -1	1	5[1]	9[1]	13[1]	17[1]	21[1]	25	4[1, 2]	8[1, 2]	13[1, 2]
Study Day	-56 to -1	1	29	57	85	113	141	169/ET-L[3] or Tx-ET[4]	28	56	91/ Post-Tx-ET[5]
Visit Windows	0	± 3 days									
Informed Consent/Assent	X										
Inclusion/Exclusion	X										
Medical History	X										
HAE Attack History	X										
FSH[6]	X										
Pregnancy Test[7]	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B, C, HIV	X										
C1-INH, C1q and C4 Testing[8]	X										
Height	X							X[20]			
Body weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination/Body Assessments[10]	X	X	X[18, 19]	X[18]	X	X[18]	X[18, 19]	X			X
12-lead ECG	X	X			X	X[17]	X[16]	X	X		X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab Parameters[11, 12]	X	X	X	X	X	X	X	X	X	X	X
C5a		X						X			X
Inflammatory Panel		X			X			X			X
Anti-drug Antibody		X	X		X		X	X	X		X
PK Blood Sampling		See Appendix C									
Plasma PKK		X	X	X	X	X	X	X	X	X	X
Archived serum samples	X	X	X	X	X			X	X		X
AE-QoL		X			X			X			X
GAD-7		X			X			X			X
EQ-5D-5L		X			X			X			X
WPAI	WEEKLY THROUGHOUT ENTIRE STUDY										
PGIS		X			X			X			X
PGIC								X			X
AECT		X	X	X	X	X	X	X	X	X	X

Appendix A SCHEDULE OF VISITS AND PROCEDURES (CONTINUED)

Study Week	**Screen**	**Treatment Period**							**Post-Treatment Period**		
	-8 to -1	**1**	**5[1]**	**9[1]**	**13[1]**	**17[1]**	**21[1]**	**25**	**4[1, 2]**	**8[1, 2]**	**13[1, 2]**
Study Day	**-56 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169/ET-L[3] or Tx-ET[4]**	**28**	**56**	**91/ Post-Tx-ET[5]**
Visit Windows	**0**	**± 3 days**									
AAS	DAILY THROUGHOUT ENTIRE STUDY										
HAE Attack Assessment[13, 14]	X	X	X	X	X	X	X	X	X	X	X
ER visits, hospitalizations, total inpatient days		X	X	X	X	X	X	X	X	X	X
Study Drug (ISIS 721744 or placebo) Administration[15]		X	X[19]	X	X[19]	X	X[19]				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

All procedures and study samples collections are to be done pre-dose at respective visits, unless specified otherwise

1 Assessments and procedures may be conducted by a Home Healthcare professional (if available).
2 Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (i.e., 4 weeks/28 days for Cohort A and 8 weeks/56 days for Cohort B) post-last dose.
3 Landmark visit for patients who discontinue early from the Treatment Period.
4 For patients who discontinue early from the Treatment Period.
5 For patients who discontinue early from the Post-Treatment Period.
6 For confirmation of menopause at Screening per Inclusion Criteria.
7 For WOCBP only. Serum pregnancy will be performed at Screening, but urine pregnancy will be performed at all other time points. A positive result from a urine pregnancy test will be confirmed with a serum pregnancy test.
8 C1-INH, C4, and C1q will be obtained at Screening. Historical values can be used for the HAE Inclusion Criteria, if already collected in the last 5 years.
9 Vital signs may include blood pressure, heart rate, respiratory rate, and body temperature.
10 Physical Exam will be done as a Body Assessment if conducted by a nurse or Home Healthcare professional.
11 Including chemistry, hematology, and coagulation.
12 If the platelet value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days); for a complete list of laboratory tests refer to Appendix B.
13 Site personnel will contact the patient approximately weekly to inquire about HAE attacks experienced by the patient. HAE attacks will also be assessed at each study visit.
14 Patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. The following details relating to each HAE attack will be collected: localization, severity, course of attack, required on-demand treatment(s), and the frequency and dose of on-demand treatment.

Appendix A SCHEDULE OF VISITS AND PROCEDURES (CONTINUED)

[15] Self-administration of Study Drug, or administration by other qualified individuals (e.g., family member), may be allowed after completion of training provided by qualified site personnel. A Home Healthcare professional must be available to complete all pre-dosing procedures prior to Study Drug administration.

[16] Cohort A ONLY: Measure ECG at pre-dose and at 2-hours post-dose.

[17] Cohort B ONLY: Measure ECG at pre-dose and at 2-hours post-dose.

[18] Targeted physical exam/body assessment which must include examination of the skin (including injection site), chest and mouth following Study Drug administration.

[19] Cohort A ONLY.

[20] For pediatric patients only.

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 721744 or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Cholesterol
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- ALP
- Creatinine kinase
- GGT

Screening Tests

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (only women who are not surgically sterile)
- Serum βhCG (only women who are not surgically sterile or post-menopausal)

Coagulation

- aPTT (sec)
- PT (sec)
- INR
- D-dimer

Complement

- C5a
- C4[3]
- C1-INH[3]
- C1q[3]

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1]

- ISIS 721744 concentration in plasma

Immunogenicity

- Anti-ISIS 721744 antibodies (Anti-Drug Antibody [ADA])

Inflammatory

- hs-CRP

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- P/C Ratio
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

PD Biomarkers

- Plasma PKK levels

[1] Plasma and urine PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 721744 with plasma constituents.
[2] Will be performed on abnormal findings unless otherwise specified.
[3] Samples for C4, C1-INH and C1q assays will be obtained at Screening.

APPENDIX C. PK SAMPLING SCHEDULE

Appendix C PK Sampling Schedule

Blood samples for the determination of plasma ISIS 721744 concentrations will be collected prior to dosing, and at various time points throughout the Dosing and Post-Treatment Period as noted in the table below. Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of ISIS 721744 with plasma constituents.

Plasma PK Sampling Schedule

Cohort A: Plasma PK Sampling Schedule

Study Week	**Treatment Period**							**Post-Treatment Period**		
	1	**5**	**9**	**13**	**17**	**21**	**25**	**4[1]**	**8[1]**	**13[1]**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169/ ET-L or Tx-ET**	**28**	**56**	**91 or Post-Tx-ET**
Time Point	Pre-dose, 2 hr[2]	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 2 hr[2]	Anytime	Anytime	Anytime	Anytime

[1] Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (i.e., 4 weeks/28 days post-last dose.

[2] 2 hrs after dose of Study Drug. Window of ± 15 minutes. Record actual time of collection in CRF.

Cohort B: Plasma PK Sampling Schedule

Study Week	**Treatment Period**							**Post-Treatment Period**		
	1	**5**	**9**	**13**	**17**	**21**	**25**	**4[1]**	**8[1]**	**13[1]**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169/ ET-L or Tx-ET**	**28**	**56**	**91 or Post-Tx-ET**
Time Point	Pre-dose, 2 hr[2]	Anytime	Pre-dose	Anytime	Pre-dose, 2 hr[2]	Anytime	Anytime	Anytime	Anytime	Anytime

[1] Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (i.e., 8 weeks/56 days) post-last dose.

[2] 2 hrs after dose of Study Drug. Window of ± 15 minutes. Record actual time of collection in CRF.

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept. 2007.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	1.0 – 1.2 x ULN	>1.2 – 1.4 x ULN	> 1.4 x ULN
Eosinophils increased	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	150 – 200 mg/dL	125 – 149 mg/dL	< 125 mg/dL
Fibrinogen increased	400 – 500 mg/dL	501 – 600 mg/dL	> 600 mg/dL
Hemoglobin decreased Male Female	 12.5 – 13.5 g/dL 11.0 – 12.0 g/dL	 10.5 – 12.4 g/dL 9.5 – 10.9 g/dL	 < 10.5 g/dL < 9.5 g/dL
INR increased[†]	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	750 – 1,000 cell/mm^3	500 – 749 cell/mm^3	< 500 cell/mm^3
Neutrophil count decreased	1,500 – 2,000 cell/mm^3	1,000 – 1,499 cell/mm^3	< 1,000 cell/mm^3
Platelet count decreased	125,000 – 140,000 cell/mm^3	100,000 – 124,000 cell/mm^3	< 100,000 cell/mm^3
Prothrombin time (PT)	1.0 – 1.1 x ULN	>1.1 – 1.2 x ULN	> 1.2 x ULN
White blood cell decreased	2,500 – 3,500 cell/mm^3	1,500 – 2,499 cell/mm^3	< 1,500 cell/mm^3
White blood cell increased	10,800 – 15,000 cell/mm^3	15,001 – 20,000 cell/mm^3	>20,000 cell/mm^3
Chemistry			
Alanine aminotransferase increased[†]	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	1.1 – 2.0 x ULN	>2.0 – 3.0 x ULN	> 3 x ULN

Adverse Event	Mild	Moderate	Severe
Aspartate aminotransferase increased†	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased			
When accompanied by any increase in liver function test	1.1 – 1.25 x ULN	>1.25 – 1.5 x ULN	> 1.5 x ULN
When liver function test is normal	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN
Blood urea nitrogen	23 – 26 mg/dL	27 – 31 mg/dL	>31 mg/dL
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	1.5 – 1.7 mg/dL	1.8 – 2.0 mg/dL	≥ 2.1 mg/dL
GGT increased†	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	10.5 – 11.0 mg/dL	11.1 – 11.5 mg/dL	≥ 11.6 mg/dL
Hyperglycemia†	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	5.1 – 5.2 mmol/L	5.3 – 5.4 mmol/L	≥5.5 mmol/L
Hypernatremia	144 – 145 mmol/L	146 – 147 mmol/L	≥148 mmol/L
Hypoalbuminemia	2.8 – 3.1 g/dL	2.5 – 2.7 g/dL	< 2.5 g/dL
Hypocalcemia	8.0 – 8.4 mg/dL	7.5 – 7.9 mg/dL	< 7.5 mg/dL
Hypoglycemia	65 – 69 mg/dL	< 64 mg/dL	< 55 mg/dL AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	3.5 – 3.6 mmol/L	3.3 – 3.4 mmol/L	< 3.3 mg/dL
Hypomagnesemia	1.3 – 1.5 mg/dL	1.1 – 1.2 mg/dL	< 1.1 mg/dL
Hyponatremia	132 – 134 mmol/L	130 – 131 mmol/L	<130 mg/dL
Hypophosphatemia	2.3 – 2.5 mg/dL	2.0 – 2.2 mg/dL	< 2.0 mg/dL
Hypoproteinemia	5.5 – 6.0 g/dL	5.0 – 5.4 g/dL	< 5.0 g/dL
Lipase increased	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN
Serum amylase increased	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria	Trace	1+	≥ 2+
Hematuria	1 - 10 cells per high power field	11 – 50 cells per high power field	> 50 cells per high power field

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

†Grading for this parameter is derived from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

The following grading recommendations for adverse events (AEs) at the injection site are based upon the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007.

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	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* 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.

APPENDIX E. PATIENT REPORTED OUTCOME ASSESSMENTS

Angioedema Activity Score (AAS)

Angioedema Quality of Life (AE-QoL)

Angioedema Control Test (AECT)

Generalized Anxiety Disorder 7 (GAD-7)

Work Productivity and Impairment (WPAI)

Patient Global Impression of Change (PGIC)

Patient Global Impression of Severity (PGIS)

Protocol

Version:	1
Version Date:	12 Jul 2022
Title:	ISIS 721744-CS5 Protocol Amendment 2: A Phase 3 Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

APPROVALS:

[redacted] Clinical Development [redacted] [redacted] 12-Jul-2022 23:06:33 GMT+0000

Parexel International

Ionis Pharmaceuticals, Inc.

ISIS 721744-CS5

A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Statistical Analysis Plan

Version: 2.0

Parexel Project Number: [redacted]

SPONSOR SIGNATURE PAGE

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PAREXEL SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role: [redacted] Biostatistician

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Major Changes
1.0	11 Apr 2022	New document
2.0	08 Dec 2023	• Section 1: Updated the list of Study Protocol and Amendments. • Section 3.2.2 (and later related sections): Updated the primary analysis set from intent-to-treat (ITT) population to Full Analysis Set (FAS). • Section 3.2.5 (and later related sections): Added the following exploratory endpoints and analyses methods: o Change in each angioedema quality of life (AE-QoL) questionnaire domain scores o Time-normalized number of Investigator-confirmed HAE attacks from Week 17 to Week 25 o Investigator-confirmed HAE attacks that involves the larynx • Section 4.2.2: Clarified baseline definitions with more details. • Section 4.9.1.3 (and later related sections): Angioedema Control Test (AECT) total score missing data handling is changed to LOCF in the main analysis. MI based on J2R will be a sensitivity analysis. • Section 4.9.1.4: Adjusted testing hierarchical rank. • Section 4.9.2.1: Added interaction of baseline and treatment group as a covariate in efficacy analysis models. • Section 4.9.2.6: Added typical patients as subgroup analyses. • Section 4.9.3 (and later related sections): Updated responder analyses methods by using a logistic regression instead of Chi-square. Added the analysis handling in case the logistic regression models with convergence issue. Section 4.9.3: Clarified continuous data analyses methods, i.e., mixed effects model with repeated measures (MMRM) or Wilcoxon Rank Sum test.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE(s)	adverse event(s)
AECT	Angioedema Control Test
AE-QoL	angioedema quality of life
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ER	emergency room
EQ-5D-5L	EuroQoL-5-Dimensions quality of life questionnaire
EQ VAS	EQ Visual analog scale
FSH	follicle-stimulating hormone
GAD-7	generalized anxiety disorder 7
HAE	hereditary angioedema
Hb	hemoglobin
HIV	human immunodeficiency virus
INR	international normalized ratio
ISIS 721744	antisense inhibitor of prekallikrein
ITT	Intent-to-Treat
J2R	Jump-to-Reference
LCRIS	local cutaneous reaction at injection site
MAR	Missing at Random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov chain Monte Carlo
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MID	minimal(ly) important difference
MMRM	mixed effects model with repeated measures
NA	not applicable
NB regression	Negative Binomial regression
OLE	open-label extension
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PD	pharmacodynamics
PK	pharmacokinetic(s)

PKK	prekallikrein
PT	preferred term
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 721744 or placebo
TEAE(s)	treatment-emergent adverse event(s)
ULN	upper limit of normal
WBC	white blood cell
WPAI	work productivity and impairment
WPAI4	work productivity and impairment every-4-week score
WS	Weight of school
WW	Weight of work

1. INTRODUCTION

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings, and Figures. It describes the variables and analysis sets, anticipated data transformations and manipulations and other details of the analyses not provided in the Study Protocol.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Amendment 1 (1 October 2021)
- Study Protocol, Amendment 2 (UK only, 29 March 2022)
- Study Protocol, Amendment 2 (Germany, 11 April 2022)
- Study Protocol, Amendment 2 (Spain, 21 April 2022)
- Study Protocol, Amendment 2 (12 July 2022)
- Study Protocol, Amendment 3 (UK, 22 August 2022)
- Study Protocol, Amendment 3 (Germany, 24 August 2022)
- Study Protocol, Amendment 3 (Spain, 22 August 2022)
- electronic Case Report Form (eCRF) (12 October 2023)

Additional requests in Study Protocol amendment 3 (UK only) include 1) assessments of growth development and sexual maturity (i.e., Tanner Staging) for adolescent patients (12-17 years) and 2) extending the last post-treatment visits from Week 13 to Week 17. This SAP describes these requests in the corresponding section below.

Revision(s) of this SAP will be required for any subsequent amendments to the protocol which may change the analyses described in this SAP. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP Addendum and/or documented in the final clinical study report.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of ISIS 721744 in patients with Hereditary Angioedema (HAE).

2.2. Secondary Objectives

To evaluate the effects of ISIS 721744 on the quality and pattern of HAE attacks and their impact on Quality of Life.

2.3. Safety Objectives

To evaluate safety and tolerability of ISIS 721744 in patients with HAE.

2.4. Exploratory Objectives

To further characterize the effects of ISIS 721744 on health economic and utilization parameters and additional Patient Reported Outcomes (PROs) and biomarkers.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is a phase 3, randomized (ISIS 721744:placebo), double-blind, placebo-controlled trial conducted in multiple centers to evaluate the efficacy and safety of ISIS 721744 in preventing angioedema attacks in patients with HAE-1 (Type I) and HAE-2 (Type II).

Approximately 84 patients are planned to be enrolled in the study. Patients will be randomized in a 2:1 ratio to Cohort A (ISIS 721744 or placebo every 4 weeks) or Cohort B (ISIS 721744 or placebo every 8 weeks), respectively. Within each Cohort, patients will be randomized in a 3:1 ratio to receive 80 mg of ISIS 721744 or matching volume of placebo.

Detailed information regarding the study procedures is presented in the Study Protocol.

The study will consist of Screening, Treatment, and Post-Treatment Periods. Patients may be required to attend additional visits for monitoring of adverse events (AEs) or abnormal investigation results.

The length of each patient's participation in the study is approximately 11 months (or 12 months for UK), which includes an up to 56-day Screening Period, a 24-week Treatment Period, and an up to 13-week (or up to 17-week, in UK only) Post-Treatment Period, unless the patient chooses to enroll in the open-label extension (OLE) study.

Patients who experience at least 5 attacks/month for 2 consecutive months after Week 5 will have the opportunity to terminate from the Treatment Period and either continue in the Post-Treatment Period or enter into an OLE study. Patients who complete Study Visit Week 25, and meet eligibility requirements, may enroll in an OLE study after the Week 25 visit. If a patient chooses to enroll in the OLE study, the patient will discontinue participation in ISIS 721744-CS5 prior to the first visit in the OLE study.

Patients who discontinue treatment will attend the Early Termination Visit and will be strongly encouraged to complete the Post-Treatment Period, unless consent/assent is withdrawn.

Endpoints related to "Investigator-confirmed HAE attacks (per month)" in the protocol is intended to be an attack rate per every-4-week. To be accurate, these endpoints are rephrased as "Investigator-confirmed HAE attacks (per every-4-week)" throughout this SAP.

3.2. Study Estimand and Endpoints

3.2.1. Intercurrent events

The following intercurrent events will be considered when define estimand:

1. Treatments are early terminated, e.g.
   a. Patients escaping early to the OLE study due to experiencing ≥ 5 recurrent HAE attacks per month for 2 consecutive months during the Treatment Period;
   b. Patients discontinuing the study treatment early due to recurrent HAE attacks and not enrolling in the OLE study;
   c. Patients discontinuing the study treatment early due to COVID-19 or war-related events.
2. Not allowed concomitant therapy or procedures defined in the Protocol Section 8.10 are used.

3.2.2. Estimand and Main Estimator/Primary Endpoint for the Primary Objective

The estimand for the primary objective is to evaluate the difference between randomized study medication of ISIS 721744 80 mg once every 4 weeks and Placebo in the Investigator-confirmed HAE attack count from Week 1 to Week 25 irrespective of intercurrent events on the Full Analysis Set (FAS).

The main estimator, i.e. primary endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25 compared to placebo.

Investigator-confirmed HAE attacks will be continuously collected until Week 25 no matter which intercurrent event is occurred. The primary analysis will be performed based on the treatment policy strategy.

3.2.3. Secondary Endpoints

- The time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 compared to placebo
- The percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 compared to placebo
- The time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 compared to placebo
- The number of patients with a clinical response defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate between Week 5 to Week 25 compared to placebo

- Percent of patients who are well controlled based on the Angioedema Control Test (AECT) at Week 25
- Change in Angioedema Quality of Life (AE-QoL) questionnaire total score at Week 25
- The number of Investigator-confirmed HAE attacks requiring acute therapy from Week 5 to Week 25

3.2.4. Safety Endpoints

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; electrocardiogram (ECG); and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

3.2.5. Exploratory Variables

Exploratory endpoints include change or percent change from Baseline compared to placebo in the following:

- Prekallikrein (PKK) level in plasma
- Generalized anxiety disorder 7 (GAD-7) questionnaire score
- EuroQoL-5-Dimensions quality of life questionnaire (EQ-5D-5L)
- Patient Global Impression of Severity (PGIS)
- Work productivity and impairment (WPAI) questionnaire score
- Change in each AE-QoL questionnaire domain score
- Time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 17 to Week 25
- Investigator-confirmed HAE attacks that involves the larynx
- Incidence of emergency room (ER) visits, all cause hospitalization, and total inpatient days
- Patient Global Impression of Change (PGIC)
- Pharmacokinetic (PK): Potential exposure response analysis using relevant exposure parameters (such as ISIS 721744 plasma C_{trough}) and biomarkers (plasma PKK) and/or clinical endpoints, as appropriate

4. STATISTICAL METHODS

4.1. Data Management and Quality Assurance

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study. Data will be continuously collected no matter which intercurrent events defined in the Section 3.2.1 have occurred.

4.1.1. Case Report Form Data

BioClinica (or designee) is responsible for creating the EDC data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc (Ionis). Ionis (or designee) is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

4.1.2. Laboratory Data

Ionis and Medpace are responsible for the format of the laboratory electronic data transfers and the transfer schedule. Central laboratory data results are not stored in the EDC system. Medpace and Ionis are responsible for the review of the clinical laboratory data. This process involves reviewing the patient and visit identifiers in the central laboratory data results data against the central lab data identifiers collected in the EDC system. Investigator sites have access to the data via lab reports sent directly from the laboratory or through the laboratory's web portal (in which case Investigators only have access to data from their site).

4.1.3. Patient Reported Outcome (PRO) Assessments

The PRO assessments will be captured by YPrime eCOA System. Patients will enter their assessments into the system using a study-dedicated tablet and handheld devices. Ionis and YPrime are responsible for the format of the electronic data transfers and the transfer schedule. The PRO assessments will not be stored in the EDC system. Ionis and YPrime are also responsible for the review of the data. This process involves reviewing the patient and visit identifiers in the assessment data against the data identifiers collected in the EDC system. The YPrime system for data collection includes built-in measures to prevent missing items for any completed questionnaire.

4.1.4. Plasma Prekallikrein (PKK) Level Data

PPD is contracted and responsible for analyzing plasma PKK. Ionis is responsible for the management and review of the plasma PKK data. Final data, which has been approved by Quality Assurance, will be stored in version-controlled repository.

4.1.5. Pharmacokinetics (PK) Data and Immunogenicity (IM) Data

PPD is contracted and responsible for plasma drug concentration and Immunogenicity sample analysis. Ionis is responsible for the management and review of the PK data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

4.2. General Considerations

4.2.1. Data Presentation

Placebo patients from Cohort A and Cohort B will be pooled for analyses.

Continuous data will be summarized in terms of the number of patients, mean, standard deviation (SD), standard error of mean (SEM), median, interquartile range (25th percentile, 75th percentile), minimum, and maximum, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD and SEM will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for all summary statistic. Raw values presented in listings will be displayed to the measured precision, unless specified.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. P-values less than 0.001 may be presented as "< 0.001".

Confidence intervals will be presented to 2 more decimal place than the raw data.

4.2.2. Definition of Study Day and Baseline

Study Day will be calculated relative to the date of first dose, i.e.,:

- For assessments after the first dose date, Study Day = Assessment Date – Date of first dose + 1. Study Day 1 is the first dose date.
- For assessments before the first dose date, Study Day = Assessment Date – Date of first dose.

Run-in period is defined as the period from screening to the first dose date/time. The treatment period for this summary is defined as the period from the first dose date/time to the last dose date/time + 28 days for Cohort A and + 56 days for Cohort B.

For Investigator-confirmed HAE attacks, the baseline rate, i.e., run-in period Investigator-confirmed HAE attack rate, will be calculated for each patient as number of

Investigator-confirmed HAE attacks occurred during the run-in period divided by the number of days contributed to the run-in period multiplied by 28 days.

For Angioedema Activity Score (AAS), 2 baseline scores will be calculated. The daily AAS of the last week before the first dose date/time is summed up to 7-day scores (AAS7) baseline. The daily AAS of the last 28 days before the first dose date/time is summed up to 4-week scores (AAS28) baseline. More details are described in Section 4.13.11.

For questionnaires, including AE-QoL, GAD-7, EQ-5D-5L, PGIS, and AECT, baselines are defined as scores collected on Study Day 1.

For WPAI, the baseline is defined as the score collected before or on Study Day 1. Additionally, a baseline of WPAI every-4-week mean score (WPAI4) will be derived as a mean of 4 consecutive weekly scores prior to Study Day 1. The last week WPAI prior to Study Day 1 is collected on Study Day 1.

For platelet count, the baseline is defined as the average of all non-missing assessments prior to the first dose.

For other assessments including chemistry, hematology, urinalysis, coagulation, weight, and plasma PKK levels, if there are 2 or more pre-dose values available, Baseline will be defined as the average of the pre-dose Study Day 1 value and the last pre-dose value prior to Study Day 1. If there is only 1 pre-dose measurement available, then it will be assigned as Baseline. For ECG, if the triplicates are taken, the average of the triplicates will be calculated first before averaging assessments from multiple visits. If only 1 or 2 assessments are available, the single assessment or average of the 2 assessments will be calculated first before averaging assessments from multiple visits.

4.2.3. Analysis Visit Window

Data collected by visit, including scheduled and unscheduled visits, will be mapped to analysis visit specified in the table below. The intent of these visit windows is not to align with those prescribed for visit scheduling in the clinical study protocol but, rather, based on the protocol-defined target study day, to delineate mutually exclusive windows so that all assessments proximal to a particular study period can be integrated to best represent the patient's status during that period of the study. If a patient has discontinued early from the treatment period but attended Early Termination Post-Treatment follow-up visit to collect assessments, then those assessments collected at Early Termination visit and during Post-Treatment Follow-Up Period should be mapped to analysis visits as well and included in the analysis and summaries, unless otherwise described. If there are multiple assessments within a visit window, the visit nearest the scheduled date will be used unless 2 visits are equally near, in which case the average will be used.

Assessment	Analysis Visit[1,2] (Week)	Target Day[2]	Study Day Window[2]
PKK level, AECT, Clinical Laboratory Evaluations, Vital Sign, Weight	Tx Week 5	Tx Day 29	2-43
	Tx Week 9	Tx Day 57	44-71
	Tx Week 13	Tx Day 85	72-99
	Tx Week 17	Tx Day 113	100-127
	Tx Week 21	Tx Day 141	128-155
	Tx Week 25	Tx Day 169	156-186
	Post-Tx Week 4	Post-Tx Day 28	15-42
	Post-Tx Week 8	Post-Tx Day 56	43-73
	Post-Tx Week 13 (or Post-Tx Week 17 for UK)	Post-Tx Day 91 (or Post-Tx Day 119 for UK)	74-105 (or 74-127)
AE-QoL, GAD-7, EQ-5D-5L, PGIS, Height	Tx Week 13	Tx Day 85	30-127
	Tx Week 25	Tx Day 169	128-186
	Post-Tx Week 13 (or Post Tx Week 17 for UK)	Post-Tx Day 91 (or Post-Tx Day 119 for UK)	45-105 (or 45-127)
PGIC	Tx Week 25	Tx Day 169	128-186
	Post-Tx Week 13 (or Post Tx Week 17 for UK)	Post-Tx Day 91 (or Post-Tx Day 119 for UK)	45-105 (or 45-127)
12-lead ECG	Tx Week 13	Tx Day 85	72-99
	Tx Week 17	Tx Day 113	100-127
	Tx Week 21	Tx Day 141	128-155
	Tx Week 25	Tx Day 169	156-186
	Post-Tx Week 4	Post-Tx Day 28	15-42
	Post-Tx Week 13 (or Post Tx Week 17 for UK)	Post-Tx Day 91 (or Post-Tx Day 119 for UK)	74-105 (or 74-127)

Assessment	Analysis Visit[1,2] (Week)	Target Day[2]	Study Day Window[2]
WPAI	Tx Week 2	Tx Day 8	2-11
	Tx Week 3	Tx Day 15	12-18
	Tx Week 4	Tx Day 22	19-25
	Tx Week 5	Tx Day 29	26-32
	Tx Week 6	Tx Day 36	33-39
	Tx Week 7	Tx Day 43	40-46
	Tx Week 8	Tx Day 50	47-53
	Tx Week 9	Tx Day 57	54-60
	Tx Week 10	Tx Day 64	61-67
	Tx Week 11	Tx Day 71	68-74
	Tx Week 12	Tx Day 78	75-81
	Tx Week 13	Tx Day 85	82-88
	Tx Week 14	Tx Day 92	89-95
	Tx Week 15	Tx Day 99	96-102
	Tx Week 16	Tx Day 106	103-109
	Tx Week 17	Tx Day 113	110-116
	Tx Week 18	Tx Day 120	117-123
	Tx Week 19	Tx Day 127	124-130
	Tx Week 20	Tx Day 134	131-137
	Tx Week 21	Tx Day 141	138-144
	Tx Week 22	Tx Day 148	145-151
	Tx Week 23	Tx Day 155	152-158
	Tx Week 24	Tx Day 162	159-165
	Tx Week 25	Tx Day 169	166-173
	Post-Tx Week 1	Post-Tx Day 7	3-10
	Post-Tx Week 2	Post-Tx Day 14	11-17
	Post-Tx Week 3	Post-Tx Day 21	18-24
	Post-Tx Week 4	Post-Tx Day 28	25-31
	Post-Tx Week 5	Post-Tx Day 35	32-38
	Post-Tx Week 6	Post-Tx Day 42	39-45
	Post-Tx Week 7	Post-Tx Day 49	46-52
	Post-Tx Week 8	Post-Tx Day 56	53-59
	Post-Tx Week 9	Post-Tx Day 63	60-66
	Post-Tx Week 10	Post-Tx Day 70	67-73
	Post-Tx Week 11	Post-Tx Day 77	74-80
	Post-Tx Week 12	Post-Tx Day 84	81-87
	Post-Tx Week 13	Post-Tx Day 91	88-94
	Post-Tx Week 14[3]	Post-Tx Day 98[3]	95-101[3]
	Post-Tx Week 15[3]	Post-Tx Day 105[3]	102-108[3]
	Post-Tx Week 16[3]	Post-Tx Day 112[3]	109-115[3]
	Post-Tx Week 17[3]	Post-Tx Day 119[3]	116-122[3]

[1] Tx = Treatment Period; Post-Tx = Post-Treatment Period [2] For Tx, Weeks/days from the first dose date; for Post-Tx, Weeks/days from end of treatment. End of treatment is defined as 1 dosing interval (i.e., 4 weeks for Cohort A and 8 weeks for Cohort B) post-last dose. [3] UK only.

4.3. Software

All report outputs will be produced using SAS® version 9.4 or higher in a secure and validated environment.

4.4. Study Patients

4.4.1. Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- The number and percentage of randomized patients, screen failed patients and major screen failure reason will be summarized based on all screened patients. Additionally, the number and percentage of patients who failed the screening due to COVID-19 related impact will also be provided.
- The number and percentage of treated patients with at least one dose of Study Drug (ISIS 721744 or placebo), patients terminated from the treatment, and major reasons of treatment termination will be summarized by treatment group (ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks, pooled placebo) and overall based on all randomized patients. Additionally, the number and percentage of patients who terminated from treatment due to COVID-19 related impact will also be summarized.
- The number and percentage of patients completed the post-treatment follow-up, terminated from the post-treatment follow-up, and major reasons of termination from the post-treatment follow-up will be summarized by treatment group and overall based on all randomized patients. Additionally, the number and percentage of patients who terminated from study due to COVID-19 related impact will also be summarized.
- The number and percentage of patients within each analysis population, as defined in Section 4.5, by treatment group and overall, will be summarized based on all randomized patients.

A by-patient listing of disposition data will be provided based on the randomized patients. A listing of eligibility criteria will also be provided. A separate by-patient listing for screen failures will also be provided.

4.4.2. Protocol Deviations

After all data are entered, reviewed, and queried, the database is closed and sent to the statistics group for review and for identification of protocol deviations.

Protocol deviations will be classified to major or minor based on the study protocol deviation process plan. Protocol deviations will be provided in the by-patient listing. Major protocol deviations will be summarized by deviation category. Additional table may be provided to summarize the major protocol deviations related to COVID-19 public health emergency.

A listing of all patients affected by the COVID-19 public health emergency related study disruption by patient number identifier and by investigational site, and a description of how the individual's participation was altered will be provided.

4.5. Analysis Sets

Screened patients will be defined as those patients who signed informed consent/assent forms.

The Safety Set will include all randomized patients who received at least 1 dose of Study Drug (ISIS 721744 or placebo). Analyses or summaries on the Safety Set will be performed by actual treatment group.

The Full Analysis Set (FAS) will include all randomized patients who received at least 1 dose of Study Drug (ISIS 721744 or placebo). Analyses or summaries on FAS will be performed by randomized treatment group.

The Per-Protocol Set (PPS) will include all patients in the FAS who are treated according to the protocol without any major deviations that could compromise the interpretation of efficacy. Other major deviations that could compromise the interpretation of efficacy will be determined prior to unblinding for statistical analyses. Analyses or summaries on the PPS will be performed by randomized treatment group.

The PK Population will include all patients who are randomized and received at least 1 dose of Study Drug of ISIS 721744 and have at least 1 evaluable PK sample.

The FAS is the basis for the primary efficacy analysis. All efficacy and pharmacodynamics (PD) endpoints will be assessed based on the FAS. Efficacy endpoints may be analyzed based on the PPSs which is specified in the Section 4.9.

All safety assessments analyses or summaries will be performed on the Safety Population.

The number of patients in each analysis population will be summarized by treatment group (ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks or pooled placebo) and overall for all randomized patients. A summary of reasons for patients to have been excluded from the PPS will be provided. A by-patient listing for analysis populations and reason for exclusion will be provided.

4.6. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics, including regions, age, age category (12 to 17, 18 to 39, 40-64, ≥ 65), sex, ethnicity, race, weight at baseline, height at screening, and body mass index (BMI) at baseline, will be descriptively summarized by treatment group and overall for the FAS, PP and Safety Populations.

For race summary, if multiple races are recorded in database, 'Multiple Race' will be used in the summary table. Detailed records will be presented in a by-patient listing.

Summaries will be provided for HAE attack history, including family history of HAE attacks (yes or no), the number of attacks the patient has had in the past 12 months (i.e., the past year), historical C1-INH activity (%), years from diagnosis to informed consent, age at onset, HAE

type, type of attack(s) experienced, treatment history of lanadelumab, berotralstat, C1-esterase inhibitor (yes or no), run-in period Investigator-confirmed HAE attack rate (attacks/4 weeks), and run-in period Investigator-confirmed HAE attack rate group (≤ 2, 2–5, > 5 attacks/4 weeks).

By-patient listings for demographics and baseline characteristics will be presented based on the FAS. Screen failures will also be listed per data availability.

4.7. Medical History

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 24.1 or higher and will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall for the Safety Population. Medical history will also be provided in a by-patient listing.

4.8. Prior and Concomitant Medication

Prior and concomitant medications will be coded using WHO Drug dictionary version September 2023 or later. Medications will be summarized by anatomical therapeutic chemical (ATC) class and PT by treatment group and overall.

Prior medications include medications that started prior to the first dose of Study Drug (ISIS 721744 or placebo) regardless of whether they continued while on treatment or not. Concomitant medications include medications that patients are exposed to (on or after the first dose) Study Drug (ISIS 721744 or placebo). Partial or missing medication start date or end date will be imputed by the following imputation rules:

Start date:

- If year, month and day are all missing then assign it as the date of Study Day 1
- If month and day are missing and year is:
  - earlier than the year of Study Day 1 then assign it as December 31
  - otherwise, assign it as January 1
- If only day is missing, and month-year is:
  - earlier than the month-year of Study Day 1 then assign it as the last day of the month
  - otherwise, assign it as the first day of the month

End date: imputation will be performed for the end date only if the day or month is missing (i.e., year is present):

- If month and day are missing, then assign December 31
- If only day is missing, then assign the last day of the month

If the imputed start date is later than the imputed end date, then set the imputed start date to the imputed end date.

The definitions for prior, concomitant medication defined relative to use of study drug are shown schematically in the diagram below.

Scenario	First Dose Date		Prior Medication	Concomitant
1	x----------x		Y	N
2	x----------x/*		Y	Y
3		x-------x/*	N	Y
4	?----------x		Y	N
5	?----------x/*		Y	Y
6	x----------?		Y	Y
7		x----------?/*	N	Y

Y = yes
N = no
x = start/stop date/time
? = missing date/time
*= ongoing

4.9. Efficacy Evaluation

The FAS is the basis for the primary efficacy analysis and the main efficacy analyses for all other efficacy endpoints. Analyses based on the PPS, if applicable, are described for each endpoint within this section. By-patient listings will be provided.

4.9.1. Analysis and Data Conventions

4.9.1.1. Multicenter Studies

This study will be conducted at multiple study centers worldwide. Study centers or regions are not stratified during randomization. No formal adjustments for centers will be conducted. The primary endpoint will be analyzed by adding regions and the interaction of region and treatment group as covariates as a subgroup analysis (see Section 4.9.2.6).

4.9.1.2. Adjustments for Covariates

The primary efficacy endpoint is time-normalized number Investigator-confirmed HAE attacks. Run-in period time-normalized attack rate as a baseline as well as the interaction of baseline and treatment will be included in the model as a covariate.

Baselines and the interaction of baseline and treatment may be a covariate in change from baseline analyses models for secondary endpoints, if applicable.

4.9.1.3. Handling of Dropouts or Missing Data Dropouts

Investigator-confirmed HAE attacks will be considered as missing when the study termination date for a patient is earlier than 24 weeks since Study Day 1.

Other endpoints will be considered as missing when assessment is not available at a specific visit.

Handling of Dropouts

Missing **primary and secondary endpoints** data will be handled as following:

- For time-normalized Investigator-confirmed HAE attack endpoints, the primary analysis for the primary endpoint and the main analyses for secondary endpoints will have the time-adjusted attack rate included in the analysis; sensitivity analyses will be performed based on imputed data by using multiple imputation (MI) methods assuming Jump-to-Reference (J2R).
- For number of patients with a clinical response on HAE and HAE attack-free, responder is derived based on time-adjusted Investigator-confirmed HAE attack rate per every-4-week. The main analysis will consider the HAE attack rate per every-4-week are the same before and after withdrawal; sensitivity analysis will be performed based on imputed data by using the MI method assuming J2R.
- For the AECT total score, the main analysis will be performed based on imputed data by last observation carried forward (LOCF). Additionally, sensitivity analyses will be performed based on imputed data by using MI methods assuming J2R.
- For the AE-QoL total score, main analysis will be performed by using MMRM model without missing data imputation; sensitivity analyses will be performed based on imputed data by using MI methods assuming J2R.

For **exploratory endpoints**, including plasma PKK level, GAD-7, EQ-5D-5L, PGIS, PGIC, WPAI, missing data will not be imputed.

Multiple Imputation – Investigator-confirmed HAE attack

Patients with the study termination date earlier than 25 weeks since the Study Day 1 will have two portions of treatment period, the pre-withdrawal part and the post-withdrawal part. Investigator-confirmed HAE attacks observed in the study will be combined with the imputed data to estimate the event rates for each treatment group. Missing data during the post-withdrawal part will be imputed by the following methods assuming J2R.

First, the Poisson regression model used for the primary analysis will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in this model.

Second, Independent samples will then be drawn from the posterior distributions of model parameters fit using the Bayesian analysis. For each patient with missing data during the post-withdrawal part, these sampled values of the model parameters are then used to generate a set of values for the expected unobserved attack.

Last, the expected number of attacks for the post-withdrawal part is added to the number of attacks in the pre-withdrawal part to get the total number of attacks over treatment period for patients who have missing data.

The post-withdrawal part of each pattern-specific distribution may be modelled using approaches discussed below:

Jump-to-Reference (J2R)

The J2R approach is an extremely conservative imputation approach that assumes that a patient receiving active Study Drug (ISIS 721744) does not sustain benefit after discontinuing study treatment. In J2R, missing event rate in both the ISIS 721744 treatment group and the pooled placebo group will be imputed by setting to the event rate of the pooled placebo group during the pre-withdraw part.

Tipping Point

The tipping point approach is known to progressively shift the imputed analysis results towards a point where the analysis conclusion is reversed (i.e., the analysis yields a non-significant p-value). The study adopts a two-way tipping point approach where a series of shift (denoted as δ) is applied to both active Study Drug (ISIS 721744) and placebo treatment arm. As the underlying distribution of primary endpoint is a Poisson distribution, the parameter of Poisson distribution (denoted as λ) is adjusted by δ as follows:

$\lambda_{\text{(ISIS 721744, tipping point)}} = \lambda_{\text{(ISIS 721744, MAR-imputed)}} \times \delta_{\text{(ISIS 721744)}}$

$\lambda_{\text{(Placebo, tipping point)}} = \lambda_{\text{(Placebo, MAR-imputed)}} \times \delta_{\text{(ISIS 721744)}}$

The sequences of both λ starts at 1, where $\lambda_{\text{(ISIS 721744, tipping point)}}$ is increased by 0.25 upwards and $\lambda_{\text{(Placebo, tipping point)}}$ goes backwards to 0. The increment of 0.25 may be subject to adjust in case the tipping points are not yet to be discovered. The upper limit may expand further in case the 'tipping-point' that yields non-significant conclusion has not appeared yet. Under each combination of $\lambda_{\text{(ISIS 721744, tipping point)}}$ and $\lambda_{\text{(Placebo, tipping point)}}$, the same analysis method as Missing at Random (MAR) is applied to acquire the p-value of the analysis. For example, if there are 6 numbers (from 1 to 2.25 by 0.25) set as δ, there should be in total 36 corresponding p-values in the whole tipping point analysis.

For each imputation method used, at least 100 imputed datasets will be generated.

Multiple Imputation Jump-to-Reference (J2R) – AECT Total Score and AE-QoL Total Score

The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing AE-QoL total score and AECT total score by treatment group. The variable list for imputations will include the baseline score, as well as all available post-baseline scores within the treatment period, in the order of protocol defined visits. The SAS procedure PROC MI will be used in the multiple simulation. EM algorithm will be used to derive a set of initial parameter estimates for MCMC method. A non-informative prior (Jeffreys' prior) will be used to derive the posterior distribution of the parameters. In case there are missing baselines, it will be imputed first by the average of available baselines across all patients in the FAS. In the case of non-monotone missing pattern, MCMC method will be used first so that each imputed data set has a monotone missing pattern based on the order of the variable list.

The J2R approach is detailed in (Carpenter *et al.* 2013) and is an extremely conservative imputation approach that assumes that a patient receiving active Study Drug (ISIS 721744) does not sustain benefit after discontinuing study treatment. In J2R, missing data in the pooled placebo group will be imputed under a within treatment arm MAR assumption. For a patient with missing data in the ISIS 721744 treatment group, their AE-QoL total score or AECT total score distribution is set to equal that of the pooled placebo group.

For each imputation method used, at least 100 imputed datasets will be generated.

Last Observation Carried Forward (LOCF) – AECT Total Score

For each subject, the missing AECT total score at Week 25 will be imputed by the available value at the nearest previous post-baseline visit. For example, if a subject early withdraws at Week 13, the subject's Week 25 will be imputed by the available total score at Week 13.

Missing Dates for Investigator-confirmed HAE attacks

Missing start or end date and time for Investigator-confirmed HAE attacks will be imputed. In general, missing start time will be imputed as 0:00 and missing end time will be imputed as 23:59. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in between:

- For Investigator-confirmed HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous Investigator-confirmed HAE attack to ensure there are 24 hours in between the 2 attacks.
- For Investigator-confirmed HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack
- For Investigator-confirmed HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next Investigator-confirmed HAE attack to ensure there are 24 hours in between the 2 attacks.
- For Investigator-confirmed HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack.

For Investigator-confirmed HAE attacks with a non-missing start date and time and a missing stop date and time:

- The stop date and time will be imputed as the earlier of the following 2 date and time:
  - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.
  - 24 hours before the start date and time of the next attack.

  After imputation, in the case of earlier than the start date/time, impute the time to be one second after the start date/time.

4.9.1.4. Multiple Comparisons/Multiplicity

The multiplicity will be controlled by using a hierarchical ranking strategy in the following testing sequence. Should the null hypothesis for the primary efficacy endpoint be rejected, other endpoints will be tested in order. If any test is not statistically significant, the test(s) at the lower rank will be considered exploratory. Other statistical analyses planed in this SAP but not listed below are considered as exploratory analyses. No adjustment will be made. All tests will be conducted at a two-sided alpha level of 0.05.

1. Primary efficacy endpoint analysis: Comparison of the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25 between ISIS 721744 80 mg every 4 weeks group and pooled placebo group
2. Comparison of the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
3. Comparison of the number of patients with a ≥ 70% reduction from baseline in Investigator-confirmed HAE attacks (per every-4-week) from Week 5 and Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
4. Comparison of the percentage of Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
5. Comparison of the time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
6. Comparison of the number of Investigator-confirmed HAE attacks requiring acute therapy (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
7. Comparison of the change in AE-QoL total score at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
8. Comparison of the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
9. Comparison of the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
10. Comparison of the number of patients with a ≥ 70% reduction from baseline in Investigator-confirmed HAE attacks (per every-4-week) from Week 5 and Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
11. Comparison of the percentage Investigator-confirmed HAE attack-free patients from Week 5 to Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group

12. Comparison of the time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
13. Comparison of the number of Investigator-confirmed HAE attacks requiring acute therapy (per every-4-week) from Week 5 to Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
14. Comparison of the change in AE-QoL total score at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
15. Comparison of the change in AE-QoL domain score of Functioning at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
16. Comparison of the change in AE-QoL domain score of Fears/Shame at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
17. Comparison of the change in AE-QoL domain score of Fatigue/Mood at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
18. Comparison of the change in AE-QoL domain score of Nutrition at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
19. Comparison of the change in AE-QoL domain score of Functioning at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
20. Comparison of the change in AE-QoL domain score of Fears/Shame at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
21. Comparison of the change in AE-QoL domain score of Fatigue/Mood at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
22. Comparison of the change in AE-QoL domain score of Nutrition at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group
23. Comparison of the percent of patients who are well controlled on the AECT at Week 25 between ISIS 721744 80 mg every-4-weeks group and pooled-placebo group
24. Comparison of the percent of patients who are well controlled on the AECT at Week 25 between ISIS 721744 80 mg every-8-weeks group and pooled-placebo group

4.9.1.5. Interim Analyses

No interim analysis is planned for this study. Primary analyses will be conducted after the End of Treatment period when all patients complete Week 25 visit, stay in the study for at least 166 days since the Study Day 1 or withdraw from the study before Week 25 visit. Study results with continuing collected post-treatment data will be updated at the End of Study.

4.9.1.6. Examination of Subgroups

To evaluate the consistency of analysis results in the primary endpoint over parameters such as demographic and baseline characteristics, summaries by subgroup will be provided. Exploratory

subgroup analyses may be performed if supported by data. More details are described in the Section 4.9.2.6. The subgroups include the following:

- Age Category (12 to 17, 18 to 39, 40–64, ≥ 65)
- Sex (Male, Female)
- Race (Caucasian, Other),
- Regions (North America, Europe, Middle East)
- Taken any predefined prophylactic therapy, including lanadelumab, berotralstat, C1-esterase inhibitor? (Yes, No)

4.9.2. Primary Efficacy Variable

The primary endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25.

Hereditary Angioedema Attack (HAE Attack)

During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient approximately weekly in order to inquire about any attack that may have occurred.

The presence of these symptoms, including symptoms in one or more predefined locations in the protocol will not automatically be considered an HAE attack unless such a diagnosis is confirmed by the Investigator.

An Investigator-confirmed HAE attack will be defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations noted above. A discrete attack will be counted if there is at least 24-hour symptom-free period between attacks.

Unique Investigator-confirmed HAE Attacks

To be counted as a unique Investigator-confirmed attack distinct from the previous attack, there must be at least 24 hours between the stop date/ time of the first event and the start date/time of the next event, for the attacks to be considered distinct. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be combined and counted as one unique attack.

When 2 or more events are combined as one unique Investigator-confirmed attack for efficacy analysis, parameters of the derived unique attack with combined multiple events will be defined in a conservative way.

- Events: Investigator-confirmed attacks.
- Dates: The start date/time will be the earliest start date/time of those multiple events; and the end date/time will be the latest end date/time of those multiple events.
- The severity will be defined as the highest severity among those multiple events.

- The primary location will be determined by the primary location of individual event, and by following the hierarchy of laryngeal attack, peripheral attack, and abdominal attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the combined attack.
- Regarding the concomitant (allowed or not allowed) medications for the derived unique Investigator-confirmed HAE attack, all records from individual events will be included.

4.9.2.1. Primary Analysis

The primary efficacy endpoint will be tested by the following hypothesis:

H_0: $\lambda_{ISIS\ 721744} / \lambda_{placebo} = 1$ versus H_1: $\lambda_{ISIS\ 721744} / \lambda_{placebo} \neq 1$

$\lambda_{ISIS\ 721744}$ refers to the Investigator-confirmed HAE attack rate from Week 1 to Week 25 in the ISIS 721744 80 mg every 4 weeks group and $\lambda_{placebo}$ refers to the Investigator-confirmed HAE attack rate during the treatment period in the placebo group. The null hypothesis is that the Investigator-confirmed HAE attack rate ratio from Week 1 to Week 25 is 1 (no difference between treatment groups), versus the alternative hypothesis that the Investigator-confirmed HAE attack rate ratio is not 1. Estimated attack rate ratios less than 1 would indicate that patients treated with ISIS 721744 80 mg every 4 weeks, on average, have a lower incidence of Investigator-confirmed HAE attacks from Week 1 to Week 25. The hypothesis will be tested using a Poisson regression model.

The primary analysis will be performed using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion on the FAS. The model will include fixed effect for treatment group (categorical), baseline (the time-normalized run-in period attack rate, continuous), and the treatment-by-baseline interaction as covariates, and the logarithm of time in every-4-week that each patient was observed from Week 1 to Week 25 will be used as an offset variable.

All patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, will have the time-adjusted attack rate included in the analysis.

The primary analysis will be performed based on the treatment policy strategy. Treatment effect will be estimated regardless of intercurrent events, which are defined in the Section 3.2.1.

From this model, the least squares mean rate, the standard error and the corresponding 95% confidence interval for each treatment group as well as, the model adjusted mean rate ratios of ISIS721744 80 mg every 4 weeks relative to the pooled placebo group and the corresponding 95% confidence interval will be estimated. These estimates will be reported as mean event rates per every-4-week by transforming the estimates using the exponential function. The p-value of the Wald-based chi-square test will be reported for testing the hypothesis.

The percentage difference in mean Investigator-confirmed HAE attack rate between ISIS 721744 80 mg every 4 weeks and the pooled placebo will be calculated as 100% × (model adjusted mean rate ratio –1). Similarly, the estimated upper and lower confidence limits for the model adjusted

mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

In the case when the Poisson regression model cannot be converged, e.g., when all patients within one treatment group have 0 post-baseline Investigator-confirmed HAE event, Fisher's Exact Test will be used for the analysis instead of Poisson regression. The odds ratio, corresponding 95% CI, and p-value will be provided. Sensitivity analyses on FAS described below for the primary endpoint analysis may not be performed.

The comparison between ISIS 721744 80 mg every-8-weeks group and the pooled-placebo group in the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25 will be analyzed in the same way including sensitivity analyses and supportive analyses discussed in sections from 4.9.2.1 to 4.9.2.4

4.9.2.2. Sensitivity Analysis 1 – Negative Binomial (NB) Regression

The Poisson regression model assumes that the mean and variance are equal. When the variance in the data is larger than the mean, the model is said to be over-dispersed. The primary analysis using Pearson chi-square scaling of standard errors to account for potential overdispersion. A sensitivity analysis will be performed by fitting a NB regression (Negative Binomial regression) model, which allows the variance in a different function of the mean. The model will include fixed effects for treatment group (categorical), baseline (the time normalized run-in period attack rate, continuous), and the treatment-by-baseline interaction as covariates, and the logarithm of time in every-4-week that each patient was observed will be used as an offset variable.

All patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, will have the time-adjusted attack rate included in the analysis.

Strategy used for the primary analysis, the treatment policy, will be used for this sensitivity analysis. Treatment effect will be estimated regardless of intercurrent events, which are defined in the Section 3.2.1.

4.9.2.3. Supportive Analysis – Per-Protocol Set (PPS)

Primary analysis and sensitivity analysis 1 described above will be repeated on the PPS. In the case when Poisson regression cannot be converged, e.g., when all patients within one treatment group have 0 post-baseline Investigator-confirmed HAE event, Fisher's Exact Test will be used for the analysis instead of Poisson regression. The odds ratio, corresponding 95% CI, and p-value will be provided.

4.9.2.4. Sensitivity Analysis 3 – Multiple Imputation Incorporating Pattern Mixture Model

For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and lost to follow-up before Week 25, the primary analysis assumes that the missing data is MAR. To evaluate the robustness of inferences made on MAR, a sensitivity analysis on FAS will be performed based on imputed data by using MI

method assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the Poisson regression model used for the primary analysis will be performed. Results will be combined using Rubin's rules.

4.9.2.5. Sensitivity Analysis 4 – Tipping-Point Analysis

A tipping-point analysis will be conducted to measure the potential effect of missing data on the reliability of the primary efficacy analysis.

In this analysis, a range of progressively more conservative assumptions about the number of events occurring in the post-withdrawal period will be explored in order to find the assumption which will reverse the conclusion (i.e., yield a non-significant p-value) of the primary analysis. The assumption that will reverse the conclusion is referred to as the tipping point. Once the tipping point is identified, the clinical plausibility of the assumption can be assessed.

Missing event rate will be imputed by using the MI method described in Section 4.9.1.3. In each run, the Poisson regression model used for the primary analysis will be performed. Results will be combined using Rubin's rules.

The range of assumptions will be determined after treatment unblinding to ensure an appropriate range is explored based on the magnitude of treatment effect and pattern of missing data.

4.9.2.6. Supplementary Analyses of Primary Endpoints

4.9.2.6.1. Subgroup Analyses

Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25 will be summarized by each subgroup defined in the Section 4.9.1.6.

Typical Patients Subgroup Analyses

During the study conduction, patients that have a clinical history and/or screening period which is atypical for patients with Type I/II HAE may be found that could compromise the interpretation of the efficacy. The list of atypical patients will be determined prior to unblinding for statistical analyses.

Subgroup analyses based on typical patients, i.e., excluding atypical patients mentioned above, will be performed for the following endpoints by using the same methods as described for the primary efficacy endpoint in Sections 4.9.2.1.

- Time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25
- Time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25
- Time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25
- Time-normalized number of Investigator-confirmed HAE attacks requiring acute therapy (per every-4-week) from Week 5 to Week 25

4.9.2.6.2. Descriptive Summaries

Investigator-confirmed HAE attack rates as well as change and percent change from baseline in the run-in period will be summarized by treatment group.

The Investigator-confirmed HAE attack rate will be calculated for each patient as the following:

Rate from Week 1 to Week 25: the number of Investigator-confirmed HAE attacks occurring during from Week 1 to Week 25 divided by number of days the patient contributed to the period multiplied by 28 days.

Rate every 4 weeks: Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date/time of the Investigator-confirmed HAE attack. First dose date/time will be used as the start of the first interval and end of the interval will be First dose date/time + 28 days. Each successive interval will start from the end of the prior interval, exclusively, and end 28 days later. The Investigator-confirmed HAE attack rate will be calculated for each patient as the number of Investigator-confirmed HAE attacks occurring during each 28-day intervals.

Rate standardized to every-4-week per each week: First, as described above, Investigator-confirmed HAE attack rate will be derived for every 7 days. It then standardized to every-4-week rate by multiply by 4.

4.9.3. Secondary Efficacy Variables

Strategy used for the primary analysis, the treatment policy, will be used for each second efficacy endpoint analysis. Treatment effect will be estimated regardless of intercurrent events, which are defined in the Section 3.2.1.

For secondary endpoints which are count data, i.e., number of HAE related data, in the case when Poisson regression models cannot be converged, e.g., when all patients within one treatment group have 0 event, Fisher's Exact Test will be used as the main analysis. Sensitivity analyses on FAS described below may not be performed.

For secondary endpoints which are responder data, e.g., number of patients with a clinical response on HAE or AECT or with HAE attack-free, in the case when logistic regression models cannot be converged, e.g., when all patients within one treatment group are responders, Fisher's Exact Test will be used as the main analysis. Sensitivity analyses on FAS described below may not be performed.

In the case of convergence problems with the repeated measures mixed model, Section 4.9.3.7 provides alternative model options.

4.9.3.1. Time-Normalized Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks (per Every-4-week) from Week 5 to Week 25

The time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 will be analyzed using the same methods as described for the primary efficacy endpoint in sections from 4.9.2.1 to 4.9.2.4.

Main analysis will be based on Poisson regression model on FAS with the treatment policy strategy. For patients who discontinued the Treatment Period early and started OLE, and

patients who discontinued the Treatment Period early and were lost to follow-up before Week 25 but after Week 5, will have the time-adjusted attack rate included in the analysis. For patients who were lost to follow-up before Week 5, assuming there is no change on the Investigator-confirmed HAE attack rate, the baseline Investigator-confirmed HAE attack rate in run-in period will be used.

Sensitivity Analyses

A NB regression on FAS will be performed as a sensitivity analysis.

To evaluate the robustness of inferences made on MAR, a sensitivity analysis on FAS will be performed based on imputed data by using multiple AE) methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the Poisson regression model used for the primary analysis will be performed. Results will be combined using Rubin's rules .

4.9.3.2. Time-Normalized Number of Moderate or Severe Investigator-Confirmed Hereditary Angioedema (HAE) Attacks (per Every-4-week) from Week 5 to Week 25

The time-normalized number of moderate or severe Investigator-confirmed HAE attacks (per every-4-week) from Week 5 to Week 25 will be analyzed using the same method as described for the primary efficacy endpoint in Sections 4.9.2.1, 4.9.2.2 and 4.9.2.4.

Main analysis will be based on Poisson regression model on FAS with the treatment policy strategy. For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, will have the time-adjusted attack rate included in the analysis.

Sensitivity Analyses

A NB regression on FAS will be performed as a sensitivity analysis.

To evaluate the robustness of inferences made on MAR, a sensitivity analysis based on FAS will be performed based on imputed data by using MI methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the Poisson regression model used for the primary analysis will be performed. Results will be combined using Rubin's rules (Rubin 1987).

Similar descriptive summaries described in Section 4.9.2.6 will be provided for this endpoint as well.

4.9.3.3. Number of Patients with A Clinical Response between Week 5 and Week 25

A clinical response is defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from baseline in Investigator-Confirmed HAE attack rate. The patient who archives a clinical response is a responder.

Percentage reduction = (Post-baseline rate - Baseline rate) / Baseline rate × 100%,

where

Post-baseline = the Investigator-confirmed HAE attack rate from Week 5 to Week 25 and

Baseline = run-in period Investigator-confirmed HAE attack rate.

For each of the clinical response, the odds ratio, corresponding 95% confidence intervals and p-value will be provided by using a logistic regression model with the baseline, and the treatment-by-baseline interaction as covariates. Odds Ratio is showing the strength of the association between the treatment effect and the clinical response.

Odds Ratio = $(p_1/(1- p_1)) / (p_2/(1- p_2))$

Where

p_1 = proportion of responder of ISIS 721744 80 mg every 4 weeks (or every 8 weeks)

p_2 = proportion of responder of the pooled Placebo

Odds Ratio ranges from 0 to infinity. When Odds Ratio = 1, there is no association; when Odds Ratio > 1, patients in the active treatment group are more likely than patients in the placebo group to be responders.

The responder is derived based on time-adjusted Investigator-confirmed HAE attack rate per every-4-week. For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, the HAE attack rate per every-4-week for each treatment group is considered as the same before and after withdrawal.

Main analysis will be based on FAS.

Sensitivity Analysis

To evaluate the robustness of inferences made on the main analysis, a sensitivity analysis on FAS will be performed based on imputed data by using MI methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the percentage reduction will be calculated and main analysis described above will be performed. Results will be combined using Rubin's rules.

4.9.3.4. Percentage of Investigator-Confirmed Hereditary Angioedema (HAE) Attack-Free Patients from Week 5 to Week 25

The clinical response of Investigator-confirmed HAE attack-free from Week 5 to Week 25 will be analyzed using the same method as described for clinical responses in Section 4.9.3.3.

For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, the HAE attack rate per every-4-week for each treatment group is considered as the same before and after withdrawal.

Main analysis will be based on FAS and PPS.

Sensitivity Analysis

To evaluate the robustness of inferences made on the main analysis, a sensitivity analysis on FAS will be performed based on imputed data by using MI methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the percentage reduction will be calculated and main analysis described above will be performed. Results will be combined using Rubin's rules.

4.9.3.5. Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks Requiring Acute Therapy from Week 5 to Week 25

HAE attacks requiring acute therapy include those attacks with the following concomitant medication.

C1 Esterase Inhibitors (human)	Berinert Cinryze
C1 Esterase Inhibitor (recombinant)	Ruconest
Plasma Kallikrein Inhibitor (human)	Kalbitor (ecallantide)
Bradykinin antagonist	Firazyr (icatibant)

The time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) requiring acute therapy from Week 5 to Week 25 will be analyzed using the same methods as described for the primary efficacy endpoint in Sections 4.9.2.1, 4.9.2.2 and 4.9.2.4.

Main analysis will be based on Poisson regression model on FAS with treatment policy strategy. For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, will have the time-adjusted attack rate included in the analysis.

Sensitivity Analyses

A NB regression on FAS will be performed as a sensitivity analysis.

To evaluate the robustness of inferences made on MAR, a sensitivity analysis based on FAS will be performed based on imputed data by using multiple imputation (MI) methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the Poisson regression model used for the primary analysis will be performed. Results will be combined using Rubin's rules .

4.9.3.6. Percent of Patients who are Well-Controlled on the Angioedema Control Test (AECT) at Week 25

The AECT is a validated patient-reported outcome instrument to assess disease activity in patients with recurrent angioedema (Weller *et al.* 2020) which will be assessed during Treatment and Post-Treatment Periods as outlined in Protocol Appendix A. The questionnaire consists of four questions asking about the frequency and severity of angioedema experienced in the last 4 weeks. Each question has 5 response choices. Scored as the following:

1. How often have you had angioedema?	Very often = 0, Often = 1, Sometimes = 2, Seldom = 3, Not at all =4
2. QOL been affected by angioedema?	Very much = 0, Much = 1, Somewhat = 2, A little = 3, Not at all =4
3. Unpredictability of angioedema?	Very much = 0, Much = 1, Somewhat = 2, A little = 3, Not at all =4
4. Angioedema been controlled?	Not at all = 0, A little = 1, Somewhat = 2, Well = 3, Very well =4

The AECT total score is the summation of scores of 4 questions and can be used to identify patients with poorly controlled disease by working with a cutoff value of greater than or equal to 10 points. Patients with the total score less than 10 points (0–9) in the AECT have poorly controlled disease whereas patients with controlled disease score 10–16 points. The AECT will be completed by the patient.

The number and percentage of patients who are well-controlled on the AECT at Week 25 will be summarized by treatment group.

The clinical response of well controlled patients on AECT at Week 25 will be analyzed on all patients with at least one non-missing AECT value at a post-baseline visit, using the same method as described for clinical responses in Section 4.9.3.3. However, the baseline and treatment-by-baseline interaction is not included for AECT (i.e., no covariates in the logistic regression).

For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, before calculating the responder of well controlled on the AECT at Week 25, missing AECT total score will be imputed by LOCF which is described in Section 4.9.1.3.

Sensitivity Analyses

To evaluate the robustness of inferences made on the imputed data using LOCF, a sensitivity analysis on all patients with at least one non-missing AECT value at a post-baseline visit will be performed based on imputed data by using MI methods assuming J2R which is described in Section 4.9.1.3. For each imputed data set, the responder will be derived, and main analysis described above will be performed. Results will be combined using Rubin's rules.

A sensitivity analysis on all patients with at least one non-missing AECT value at a post-baseline visit based on imputed data by using LOCF in Section 4.9.1.3 will also be performed. In the sensitivity analysis, the logistic regression will include the baseline AECT total score (continuous) as a covariate. Missing baselines will be imputed first by the average of available baselines across all patients in the FAS.

4.9.3.7. Change from Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score at Week 25.

Quality of life will be assessed by the AE-QoL questionnaire during Screening, Treatment, and Post-Treatment Periods as outlined in Protocol Appendix A.

The AE-QoL questionnaire is a validated tool to assess symptom specific health-related quality of life impairment in patients suffering from recurrent angioedema (Weller *et al.* 2012). The AEQoL is a self-administered questionnaire that can be completed in less than 5 minutes; it comprises 17 questions across 4 domains: functioning, fatigue/mood, fears/shame, and food. Each domain includes the following questions:

Functioning	How often have been restricted in the area of Q1. Work; Q2. Physical activity; Q3. Leisure time; Q4. Social relations
Fatigue/mood	Q6. Difficulty falling asleep; Q7. Wake up during the night; Q8. Tired since not sleeping well; Q9. Trouble on concentrating; Q10. Depressed
Fears/shame	Q12. Swelling episode burden you; Q13. Afraid swelling could occur suddenly; Q14. Afraid frequency of the swelling increase; Q15. Ashamed to go out in public because of swelling; Q16. Embarrassed or self-conscious because of swelling; Q17. Afraid treatment has negative long-term effects
Food	Q5. Restrict eating and drinking; Q11. Limit your choices of food/beverage

The AE-QoL can be used to calculate scores for the 4 individual domains and can also be used to determine a total score. The AE-QoL will be completed by the patient.

AE-QoL will be evaluated by determining its four individual domain scores and a total score. Each item answered by the patient scores between 0 and 4 points depending on the answer option chosen by the patient: Never = 0, Rarely = 1, Occasionally = 2, Often = 3, Very often = 4. The AE-QoL domain scores and total score are calculated by using the following formula:

(Sum score of all completed items) / (maximum sum score of all possible items) × 100

Computation of AE-QoL Total Score

Example 1: All items were completed (maximum possible sum: 68 points)
Sum of all 17 completed items: 41 points
Total score = 100 × (41/68) = 60 (out of a possible 100 points)
Example 2: 2 items were not completed (maximum possible sum: 60 points)
Sum of all 15 completed items: 41 points
Total score = 100 × (41/60) = 68 (out of a possible 100 points)

Computation of Domain Scores (Example: Fears/Shame)

Example: Sum of all 6 completed items: 14 points
Maximum possible sum: 24 points
Domain Score = 100 × (14/24) = 58 (out of a possible 100 points)

Remarks

Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0-to-100 scale), the calculated scores are not or only little influenced by missing items.

An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items

(>4 items) are left unanswered. For AE-QoL each derived domain score and total score, missing baseline or post-baseline handling are described in the Section 4.9.1.3.

The minimal and highest possible domain and total scores are 0 and 100, respectively.

AE-QoL total score, the change, and the percent change from baseline will be summarized by visit and treatment group.

The change from baseline in AE-QoL total score at Week 13 and Week 25 will be compared between ISIS 721744 80 mg every 4 weeks and pooled placebo using the MMRM model. The MMRM model will include effects of treatment, time, treatment-by-time interaction, baseline value at Study Day 1, and treatment-by-baseline interaction. Missing baselines will be imputed first by the average of available baselines across all patients in the FAS . The analysis will be conducted in the FAS. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997). If there are convergence problems with the repeated measures mixed model, this will be explored with the following methods in order: 1) the SCORING = 4 option could be used in the PROC MIXED statement in SAS. This makes SAS use Fisher scoring for the first 4 iterations. 2) If the convergence problem cannot be resolved, the unstructured covariance matrix will be replaced by the homogeneous compound symmetry covariance matrix (Type = CS in SAS).

The comparison between ISIS 721744 every 8 weeks and pooled placebo will also be analyzed in the same way as above mentioned.

The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

Sensitivity Analyses

To evaluate the robustness of inferences made on MAR, a sensitivity analysis on FAS based on imputed data by using MI methods assuming J2R which is described in Section 4.9.1.3 will be performed. For each imputed data set, total score will be derived. The change from baseline in AE-QoL total score will be compared between ISIS721744 80 mg every 4 weeks and pooled placebo using ANCOVA with baseline as a covariate. Results will be combined using Rubin's rules.

In addition, a responder analysis will be performed for AE-QoL total score as an exploratory analysis:

A clinical response is defined as a ≥ 6-point improvement from baseline in AE-QoL total score at Week 25, i.e., Post-baseline – Baseline ≤ -6. The patient who archives a clinical response is a responder. Patients with non-missing response will be analyzed. The odds ratio, corresponding 95% confidence intervals and p-value will be provided by using a logistic regression model with the baseline, and the treatment-by-baseline interaction as covariates.

For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, the treatment termination reason will be checked. Due to reasons of adverse events or lack of efficacy, patients will be considered as a non-responder; due to other reasons, patient will be

categorized as missing and excluded from the analysis. Patient with missing baseline will also be excluded from the analysis.

Exploratory analysis for each AE-QoL domain score is described in Section 4.13.8.

4.10. Safety Evaluation

All safety summaries and analyses will be based on the Safety Set as defined in Section 4.5.

4.10.1. Extent of Exposure

Study drug will be administered as subcutaneous injections. A descriptive summary of exposure variables will be provided for patients who took ISIS 721744 80 mg:

- Amount of active Study Drug (ISIS 721744) (mg)
- Duration of active Study Drug (ISIS 721744) exposure (days) from the first dose date/time to the last dose date/time + pre-specified duration in days, or to the study termination date, which occurred earlier.
  - for cohort A, the pre-specified duration is 28 days
  - for cohort B, the pre-specified duration is 56 days

4.10.2. Adverse Events (AEs)

AEs will be coded using the MedDRA Version 26.1 or higher.

Treatment-emergent adverse events (TEAEs) will be tabulated and are defined as those AEs that either start or worsen in severity on or after the date/time of first dose of study treatment.

In addition, if severity of an AE changes during the study, a separate AE will be recorded for each severity on the AE CRF. “first” and “second” AE will be identify based on AE start date. AE start date of the second record is AE stop date of first record. AE severity (mild/moderate/severe) are compared between these 2 linked records in a pair for further defining TEAE. Consider 2 cases below:

- Case 1: The first AE record in the pair occurs before first dosing, and the second AE record occurs after first dosing.

  If the AE severity of the second record is worse than that of the first record, then only the second AE is deemed as a TEAE. Otherwise, neither record is considered as TEAE.

- Case 2: Both AE records in the pair occur after first dosing.

  If the AE severity on the second record is worse than the severity on the first record, then count both records as treatment-emergent. But, if the severity improves, then only count the first record as treatment-emergent.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or complete missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

The incidence of AEs will be summarized by MedDRA PT and SOC for:

- Any TEAEs
- Potentially Related TEAEs. Related is defined as "Related", "Possible", or missing relationship to Study Drug (ISIS 721744 or placebo)
- Any TEAEs by severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported one or more events. AEs with missing severity will categorized as "Missing" for this summary
- Related TEAEs by severity
- Serious AEs (SAEs)
- Serious and related TEAEs

AE summaries will be ordered alphabetically for SOC, and PT within SOC and decreasing frequency for SOC, and PT within SOC, in the overall column.

A by-patient listing of all AEs (including non-treatment-emergent events) will be provided. AEs that lead to study discontinuation or investigational drug discontinuation will also be listed separately. Non-treatment emergent adverse event will be flagged in the data listing.

4.10.3. Deaths, and Other Serious or Significant Adverse Events

4.10.3.1. Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe AEs with the PTs including Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection, persisted for at least 2 days or ongoing; or (B) any AE at the Study Drug injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the Study Drug injection site is the principal reason for discontinuation. LCRIS will be summarized using the MedDRA coding system, by PT and by treatment group. Patients with moderate, severe and any LCRIS will also be summarized. Discontinuations of Study Drug (ISIS 721744 or placebo) due to AE at the injection site will be summarized separately.

Percentage of injections leading to those events will be summarized by PT and overall using the descriptive statistics. Additionally, percentage of injections leading to events will be summarized by moderate, severe severity and overall discontinuation of study drug due to AE at injection site.

Percentage of injections leading to LCRIS will be calculated as follows for each patient: (A/B) × 100, where A = number of injections with a LCRIS, and B = total number of injections. Doses that are split across multiple injections are counted as a single injection.

LCRIS will be provided in a subject data listing.

4.10.3.2. Flu-like Reactions

Flu-like reactions are defined as adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least 2 of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day.

Flu-like reactions will also be summarized using the MedDRA coding system, by PT and by treatment group.

Percentage of injections leading to flu-like reactions will be summarized by treatment group using the descriptive statistics.

Percentage of the injections leading to flu-like reactions will be calculated as follows for each patient: (A/B) × 100, where A = number of injections leading to flu-like reactions, and B = total number of injections.

Flu-like reactions will also be listed.

4.10.3.3. Bleeding Adverse Events

Bleeding AEs will be identified based on the Haemorrhages (SMQ) Export from MedDRA and summarized by MedDRA SOC and PT and by treatment group. A by-patient listing will be provided.

4.10.4. Clinical Laboratory Evaluation

The following is the list of lab analytes that will be collected throughout the study:

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, BUN, creatinine, cholesterol, uric acid, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine kinase, gamma-glutamyl transferase (GGT)
- Hematology: red blood cells, hemoglobin (Hb), hematocrit, platelets, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cells (WBC), and WBC differential (percentage and absolute count) (basophils, eosinophils, lymphocytes, monocytes and neutrophils)
- Coagulation: activated partial thromboplastin time (aPTT) (sec), prothrombin time (sec), international normalized ratio (INR), D-dimer

- Complement: Complement Factor 5a (C5a). (At screening, Complement factor 4 (C4), C1-inhibitor (C1-INH) level and function, Complement 1q (C1q) will be collected.)
- Inflammatory: C-reactive protein (CRP) measured by high sensitivity assay (Hs-CRP)
- Screening tests: hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV) antibody, follicle-stimulating hormone (FSH) (women only, if applicable), and serum beta-subunit of human chorionic gonadotropin (βhCG) (women only). The data will be displayed in by-patient listings.
- Urinalysis (other): color, appearance, specific gravity, pH, P/C ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrate, microscopic examination. The data will be displayed in by-patient listings.

Missing WBC differential absolute counts and percentages will be derived:

- If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If WBC differential absolute counts are missing, and manual count values are available, then manual count values will be used. If neutrophils count and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils, if only segmented neutrophil result is available, then neutrophils will be set to segmented neutrophils result.

All lab data will be displayed in by-patient listings.

Chemistry, hematology, coagulation, and complement, (result, change and percent change from baseline) will be summarized using descriptive statistics (n, mean, median, standard error, standard deviation, 25th percentile, 75th percentile, minimum, and maximum) by treatment group and analysis visit. Only central lab data will be summarized in by-visit summary. Both central and local lab data will be used in the abnormal summaries described below.

For ALT and AST, the number and percent of patients falling in each of the following categories based on the confirmed results (both central and local lab data will be used) will be tabulated by treatment group:

- ALT or AST > 3 × upper limit of normal (ULN), which is confirmed
- ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed
- ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed

  and

total bilirubin > 1.5 × ULN or INR > 1.5, where "and" required to be based on the same sample

- ALT or AST > 5 × ULN, which is confirmed
- ALT or AST > 5 × ULN, which is confirmed

  and

  persists for ≥ 2 weeks
- ALT or AST > 8 × ULN, which is confirmed

For platelet (K/mm^3), the number and percentage of patients falling in each of the following categories based on the confirmed results (both central and local lab data will be used) will be tabulated by treatment group for ≥ 125, >100 to <125, ≥75 to ≤ 100, ≥ 50 to < 75, ≥ 25 to < 50, < 25.

A confirmed value is based on a consecutive lab value within 7 days. If that value is in the same or worse category the initial value is confirmed. If the consecutive value is in a better category, then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days, then the initial value is presumed confirmed. If there are multiple results on the same day, no matter from the same lab vendor or different lab vendors, then the worst value will be utilized in the analysis.

Laboratory data will be presented in by-patient listings.

4.10.5. Vital Signs, Physical Findings and Other Observations Related to Safety

4.10.5.1. Vital Signs

Vital signs will include heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure and pulse pressure. Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum) for vital sign values, weight, and BMI as well as the change and percent change from baseline at each analysis visits.

4.10.5.2. Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as AEs. All physical examination data will be provided in a by-patient listing. Per Study Protocol Amendment 2 (UK only), additionally, assessments of growth development and sexual maturity (i.e., Tanner Staging) for adolescent patients (12-17 years) will be provided in a by-patient listing.

4.10.5.3. 12-Lead Electrocardiograms (ECG)

Safety 12-lead ECG data will include Ventricular Rate, PR Interval, RR Interval, QRS Duration, QTc, QTcF (QT corrected using the Fridericia's formula), QTcB (QT corrected using the Bazett's formula), and Overall interpretation. QTcF and QTcB will be calculated based on the patient's reportable ECG data at each time point using the formula described below:

$QTcF = QT / (RR)^{1/3}$, where RR = 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR = 60/VR

For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum) of the results at each analysis visit, as well as the changes and percent changes from Baseline to each study visit, will be presented in summary tables; for the categorical responses to overall interpretation, the results and the associated findings at each visit will be summarized by counts and percentages. In the case when triplicate results are collected, for the continuous variables, average of triplicate results will be derived before generating the descriptive summary; for the categorical responses, the worst of triplicate results will be choosing for the descriptive summary.

All the ECG data collected will be listed.

4.10.6. Data Monitoring

4.10.6.1. Safety Data Monitoring

Ionis (or designee) is responsible for processing all reported AEs. All serious adverse events (SAEs), reported to Ionis (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis (or designee) will also prepare a safety notification letter and transmit it to study site.

4.10.6.2. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be established to monitor the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter.

4.11. Pharmacokinetics

Plasma concentrations of ISIS 721744 (measured as total full-length oligonucleotides or ISIS 721744-equivalent, i.e., ISIS 721744-eq, including fully conjugated, partially conjugated, and unconjugated ISIS 721744, along with the scheduled (nominal) and actual sampling times (i.e., time from subcutaneous [SC] dosing) will be listed for each evaluable patient by treatment, actual dose, cohort, gender, body weight, age, subject IM status, and study day. Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". Percent differences between nominal and actual dose, as well as between scheduled and actual sampling times will also be listed for all patients.

For all patients administered with ISIS 721744, ISIS 721744 plasma trough, 2 hours post-dose concentrations after the first and last dose and post-treatment concentrations will be summarized

using descriptive statistics by treatment, dose, cohort, study day, and scheduled time point, without and with age group stratification (12 to < 18-year-old and ≥ 18-year-old patients), without and with stratification by subject Anti-Drug Antibody (ADA) status overall (see Section 4.12.2). For the purpose of calculating typical summary descriptive statistics (n, mean, SEM/SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are below the LLOQ will be presented as BLQ, and the SD, SEM/SD, %CV, and geometric %CV will be reported as not applicable (NA). Other stratifications may also be performed if deemed warranted. Samples will be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times (percent difference between scheduled and actual sampling time greater than 30%), or large deviations between actual dose and nominal dose (percent difference between nominal and actual dose greater than 30%). Any samples excluded from the summary descriptive statistics, if deemed necessary, will be listed separately along with the reason for exclusion.

Population PK, PK/PD or exposure-response analysis may be performed using the PK and PD data from this study, and/or combined with other clinical study data and reported separately. If appliable, details of these analyses will be presented in a separate analysis plan.

4.12. Immunogenicity (IM) Analysis

Samples collected for IM assessment at baseline (Day 1 pre-dose), during treatment and post-treatment follow-up period including early termination samples will be analyzed for anti-ISIS 721744 antibodies (ADA).

4.12.1. Sample Level ADA Data

An evaluable sample will be designated 'Positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'Negative'. Sample ADA results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS 721744 antibodies) before, during, and after treatment with study drug (ISIS 721744 or placebo) (sample ADA status) will be listed by treatment, dose, cohort, and day of collection.

The sample ADA incidence (number) and incidence rate (percent) at each evaluated study time point will be determined and appropriately summarized by treatment, dose, and cohort as the total number of and percentage of evaluated subjects with sample ADA negative, positive, and unknown status. Furthermore, titer over time will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment, dose, and cohort. Summarization of ADA incidence, incidence rate and titer by age group (12 to < 18-year-old and ≥ 18-year-old patients) may also be reported.

4.12.2. Subject Level ADA Data

Subject ADA status overall (ADASTAT) will be defined as 'Positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods; 'Negative' status if all evaluated ADA sample results during the treatment

and post-treatment evaluation periods are ADA negative and they have at least one evaluable ADA result collected post study drug treatment. Otherwise, a study subject will be assigned 'Unknown' ADA status.

Furthermore, subjects with positive overall ADA status will be further classified into different ADA types (ADATYPE) based on their baseline ADA status and change in ADA titer post-treatment as described below :

- Treatment-Emergent ADA: sum of treatment-induced ADA and treatment-boosted ADA as described below:
  - Treatment-Induced ADA: ADA developed de novo (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA)
  - Treatment-Boosted ADA: pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 8-fold or more
- Treatment-Unaffected ADA: pre-existing ADA that were not affected (boosted) following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is 4-fold or less)
- ADATYPE would be not applicable (NA) if the subject overall ADA status is negative.

Other subject level IM parameters to be calculated/defined may include but not limited to:

- Subject ADA Status at Baseline (ADASTATB): "Positive" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed positive; "Negative" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed negative; "Unknown" if the subject has Week 1 Day 1 pre-dose sample (baseline) unevaluable.
- Onset of ADA (TFSTADA): i.e., the first day ADA positive sample observed, will be calculated by: the date of first sample has "positive" sample IM status - first dose date +1
- Last Positive ADA Study Day (TLSTADA): defined as the last positive ADA sample observed from the start of study drug treatment and will be calculated by: the date of last sample has "positive" sample IM status - first dose date +1
- Last IM Sampling Study Day (TLSTSAMP): defined as the last ADA sample collected from the start of study drug treatment and will be calculated by: the date of last sample collected - first dose date +1
- Peak titer (PEAKTIT): the highest titer observed for the subject
- Time to peak titer (TPEAKTIT): the time to reach peak titer will be calculated by: the date of first peak titer observed- first dose date +1

- Total number of ADA Positive Samples (NOPOSAMP): the total number of ADA samples being confirmed positive for the subject
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the subject

Lastly, subjects with positive ADA status may further be classified as being transient or persistent ADA response, if there are sufficient number of subjects with transient ADA status. Transient and persistent ADA definitions are defined below and based on :

Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA response:

- Treatment-induced ADA detected at 2 or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The subject level ADA prevalence, incidence, and positive ADA response being transient or persistent (if applicable) will be calculated as the number and the proportion (percent) of the study population during the study period by treatment, dose, and cohort. Subject level IM parameters (as described above) will be listed by treatment, dose, and cohort for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment, dose, and cohort. Summarization of subject level ADA response and IM parameters by age group (12 to < 18-year-old and ≥ 18-year-old patients) may also be reported.

4.12.3. Evaluation of IM Impact on PK, PD, Efficacy and Safety

The impact of IM on PK, PD, and safety will be evaluated by stratifying plasma trough and post-treatment ISIS 721744 concentrations, PD biomarker levels, selected clinical efficacy end points and safety measures by subject ADA status, summarized using typical descriptive statistics, and presented graphically and/or in tables. Efficacy and PD measures to be stratified by subject IM status may include Investigator-confirmed HAE attacks and plasma PKK levels . Safety measures to be stratified by subject IM status may include AEs, and lab tests for

hematology, liver and kidney functions. Other efficacy, PD and safety measures stratifications with subject IM status may also be conducted, if deemed appropriate.

Other stratifications (e.g., based on antibody titer, onset of ADA, etc.) of selected PK, PD, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

4.13. Exploratory Analyses

All exploratory analyses will be performed as a reference based on the FAS as defined in Section 4.5. By-patient listings will be provided too. Missing data will not be imputed.

For exploratory endpoints which are count data, in the case when Poisson regression models cannot be converged, e.g., when all patients within one treatment group have 0 event, Fisher's Exact Test will be used as the main analysis.

For exploratory endpoints which are responder data, in the case when Logistic regression models cannot be converged, e.g., when all patients within one treatment group are responders, Fisher's Exact Test will be used as the main analysis.

In the case of convergence problems with the repeated measures mixed model, Section 4.9.3.7 provides alternative model options.

4.13.1. Change and Percent Change from Baseline in Plasma Prekallikrein (PKK) Level

The change and percent change from baseline in plasma PKK levels will be summarized by visit and treatment group. The change and percent change from baseline in plasma PKK levels at each visit during the treatment period will be compared between ISIS 721744 80 mg every 4 weeks (or every 8 weeks) and pooled placebo using MMRM model based on the FAS. The response variable is the change or percent change from baseline at post-baseline visit up to Week 25.

The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997).

4.13.2. Change from Baseline in Generalized Anxiety Disorder (GAD-7) Questionnaire Total Score

A GAD-7 questionnaire will be administered to evaluate anxiety experienced by patients. The GAD-7 is a self-administered patient questionnaire and it is used as a screening tool and severity measure for generalized anxiety disorder (Spitzer *et al.* 2006).

The GAD-7 questionnaire includes 7 questions, and the response to each question is scored as: Not at all = 0, Several days =1, More than half the days = 2, Nearly every day = 3.

The total score is calculated by summing the score of each question and provides a possible score from 0-21. GAD-7 total score will be classified into severity stages (Spitzer *et al.* 2006) as shown below, which will be summarized for each visit.

Total Score Range	Symptom
0–4	Minimal Anxiety
5–9	Mild Anxiety
10–14	Moderate Anxiety
15–21	Severe Anxiety

The GAD-7 total score, the change and the percent change from baseline will be summarized by visit and treatment group. The change from baseline in GAD-7 total score will be compared between ISIS 721744 80 mg every 4 weeks (or every 8 weeks) and pooled placebo using the MMRM model based on the FAS. The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997).

4.13.3. EuroQoL-5-Dimensions Quality of Life Questionnaire (EQ-5D-5L) and Change from Baseline in Visual Analog Scale (EQ VAS) Score

EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal (Herdman *et al.* 2011). The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual analog scale (EQ VAS).

The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and the response to each dimension is scored in 5 levels as: No problems = 1, Slight problems = 2, Moderate problems = 3, Severe problems =4, Unable to/extreme problems = 5. Each state is referred to by a 5-digit code. For example, the health state, 12121, represents a patient who indicates no problems on mobility, usual activities, and anxiety/depression but slights problems on self-care and pain/discomfort.

EQ-5D health state index score reflects how good or bad a health state is according to the preferences of the general population of a country/region. To derive this index score, the response of each dimension from the EQ-5D-5L descriptive system will be first translated into a weight based on the value sets issued by EuroQoL group. Index value = 1 - sum of weights from these 5 dimensions' response.

The possible best value is 1 and the possible worst value varies by country. Validated weights for many countries are available from the EuroQol page of https://euroqol.org/support/analysis-tools/index-value-set-calculators/. If there is a missing response from a dimension, then the index value will not be calculated and be treated as missing. For countries without validated health state utility values yet, the suggestion from EuroQol group, currently, is using the United States EQ-5D-5L value set from (Pickard *et al.* 2019). The display of the index value is with 3 digits of decimal points.

The EQ VAS is used as a quantitative measure of health outcome as judged by the individual respondent. The EQ VAS records a self-rating of health status on a vertical VAS anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

The index score, its change and it's percent change from baseline as well as EQ VAS score, its change and it's percent change from baseline will be summarized by visit and treatment group. The change from baseline in index score and in EQ VAS will be compared between ISIS 721744 80 mg every 4 weeks (or every 8 weeks) and pooled placebo using the MMRM model based on the FAS. The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997). Health state index score and EQ VAS will be summarized in tables and listed in a by-patient listing.

4.13.4. Patient Global Impression of Change (PGIC) Scale at Week 25/Early Termination

The PGIC scales will also be administered throughout the study for purposes of PRO validation and its use as an anchor for estimation of minimal important difference (MID) of other PRO measures. PGIC is a single item rated on a 5-point Likert scale (Much better = 1, A little better = 2, No change = 3, A little worse = 4, Much worse = 5) designed for patients to rate their own perceptions of change in HAE-related health status.

The number and percentage of patients of each scale at Week 25 will be summarized by treatment group.

The PGIC scale will be dichotomized to category of "better" and "no change or worse". The binary category data be summarized by treatment group and be analyzed by using a logistic regression. The odds ratio, corresponding 95% CI, and p-value will be provided.

The analysis will be conducted in FAS.

4.13.5. Change from Baseline in Patient Global Impression of Severity (PGIS) Scale

The PGIS scales will also be administered throughout the study for purposes of PRO validation and its use as an anchor for estimation of MID of other PRO measures. PGIS is a 1-item questionnaire rated on a 5-point scale (None = 1, Mild = 2, Moderate = 3, Severe = 4, Very severe = 5) designed to assess patient's impression of disease severity.

The number and percentage of patients of each scale will be summarized by visit and treatment group.

The change from baseline in PGIS will be summarized by visit and treatment group and be analyzed using Wilcoxon Sum Rank test.

The change from baseline in PGIS will also be dichotomized to category of "better" (change from baseline < 0) and "no change or worse" (change from baseline ≥ 0). The binary category data be summarized by visit and treatment group and be analyzed by using a logistic regression with baseline as the covariate.

Both analyses will be conducted in FAS.

4.13.6. Change from Baseline in Work Productivity and Impairment (WPAI)

Pharmacoeconomics will be assessed by the WPAI questionnaire plus Classroom Impairment Questions (CIQ): specific health problem (SHP), US Version 2 (WPAI+CIQ:SHP). Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

Questions:

During the past seven days (not including today, i.e., the day of answering questions):

1 = currently employed (No; Yes)

2 = hours missed work due to HAE symptoms

3 = hours missed work due to other reasons

4 = hours actually worked

5 = degree HAE symptoms affected productivity while working (0–10) with 0 = had no effect on my work and 10 = completely prevented me from working

6 = currently attended classes/school (No; Yes)

7 = hours missed classes/school due to HAE symptoms

8 = hours actually attend class or school

9 = degree HAE symptoms affected productivity while in classes/school (0-10) with 0 = had no effect on my class work and 10 = completely prevented me from doing my class working

10 = degree health affected regular activities (0–10) with 0 = had no effect on my daily activities and 10 = completely prevented me from doing my daily activities

Weight of work/school for each subject and each visit per hours:

Weight of work (WW) = 0, if Q1 = No;

= (Q2+Q3+Q4)/(Q2+Q3+Q4+Q7+Q8), if Q1 = Yes and Q6 = Yes;

= 1, if Q1 = Yes and Q6 = No;

Weight of school (WS) = 0, if Q6 = No;

= (Q7+Q8)/(Q2+Q3+Q4+Q7+Q8), if Q1 = Yes and Q6 = Yes;

= 1, if Q1 = No and Q6 = Yes;

Weekly scores will be derived as following and multiply scores by 100 to express in percentages:

- Absenteeism Score is percent work/school time missed due to HAE symptoms: (Q2+Q7)/(Q2+Q3+Q4+Q7+Q8)
- Presenteeism Score is percent impairment while working/attending school due to HAE symptoms: Q5/10 × WW + Q9/10 x WS

- Overall Productivity Impairment Score is percent overall work/school impairment due to HAE symptoms:

  {Q2/(Q2+Q3+Q4)+[(1-(Q2/(Q2+Q3+Q4)))x(Q5/10)]}xWW +

  {Q7/(Q7+Q8)+[(1-(Q7/(Q7+Q8)))x(Q9/10)]}xWS

- Activity Impairment Score is percent activity impairment due to HAE symptoms: Q10/10

WPAI every-4-week mean score (WPAI4): Weekly WPAI score will be grouped into every-4-week intervals, incorporating WPAI+CIQ:SHP weekly scores from the 4 weeks immediately prior to/ at the assessment point. The mean of every-4-week WPAI score is to be calculated to get WPAI4. For example, WPAI4 at Week 5 is a mean of 4 consecutive weekly scores prior to Week 5 since Study Day 1. Similarly, each successive interval, i.e., WPAI4 at Week 9, Week 13, Week 17, Week 21 and Week 25, will start from the end of the prior interval, exclusively, and end 4 weeks later.

WPAI 4 of Absenteeism score, Presenteeism score, overall productivity impairment score and activity impairment score and the change from baseline will be summarized by visit and treatment group. Patients (or visits) with both Q1 = No and Q6 = No will be excluded from the summary of Absenteeism score, Presenteeism score and overall productivity impairment score.

All patients are expected to answer Q10 and have the activity impairment score. The change from baseline in WPAI4 of the activity impairment score will be compared between ISIS 721744 80 mg every 4 weeks (or every 8 weeks) and pooled placebo using the MMRM model based on the FAS. The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997).

4.13.7. Incidence of ER Visits, All-Cause Hospitalization, and Total Inpatient Days

The incidence of all-cause ER visits and ER visits due to HAE attack, all-cause hospitalization and total inpatient days during the treatment period will be summarized using descriptive statistics.

If supported by data, the incidence of all-cause ER visits, ER visits due to HAE attack and all-cause hospitalization may be compared between treatment group and pooled placebo group using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion on the FAS. The model will include the treatment group as the factor. The logarithm of time in month that each patient observed during the on-treatment period will be used as an offset variable.

The total inpatient days may be compared between treatment group and pooled-placebo group using an ANOVA model with the treatment group as the factors.

4.13.8. Change in each AE-QoL Questionnaire Domain Scores

Scoring of each AE-Qol domain is described in the Section 4.9.3.7.

The change and percent change from baseline in each AE-QoL domain score will be summarized by visit and treatment group.

The change from baseline in each AE-QoL domain score at Week 13 and Week 25 will be compared between ISIS 721744 80 mg every 4 weeks and pooled placebo using the MMRM model. The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value at Study Day 1. Missing baselines will be imputed first by the average of available baselines across all patients in the FAS. The analysis will be conducted in the FAS. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997) .

The comparison between ISIS 721744 every 8 weeks and pooled placebo will also be analyzed in the same way as above mentioned.

The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

4.13.9. Time-Normalized Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks (per Every-4-week) from Week 17 to Week 25

For exploring the dosing effect when administrated every 8 weeks with at least 3 doses of study drug, the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 17 to Week 25 will be analyzed using the same methods as described for the primary efficacy endpoint in Sections 4.9.2.1.

The analysis using Poisson regression model will be performed on a subset of FAS including patients in Cohort B who received ISIS 721744 and patients who received Placebo in both Cohort A and Cohort B.

For patients who discontinued the Treatment Period early and started OLE, and patients who discontinued the Treatment Period early and were lost to follow-up before Week 25, missing HAE count will be imputed by HAE count occurred during the last 56 days.

4.13.10. Investigator-Confirmed Hereditary Angioedema (HAE) Attacks that involves the larynx

For exploring the dosing effect on laryngeal attacks, the time-normalized Investigator-confirmed HAE attacks that involves the larynx (per every-4-week) will be summarized by treatment group and compared between treatment group and pooled placebo group using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion on the FAS. The model will include fixed effect for treatment group (categorical), baseline (the time-normalized run-in period attack rate, continuous), and the treatment-by-baseline interaction as covariates, and the logarithm of time in every-4-week that each patient was observed during the interested periods will be used as an offset variable.

Analyses on 2 interested periods will be performed, including from Week 1 to Week 25 and from Week 5 to Week 25. Number of patients and percentage per treatment group will also be summarized.

4.13.11. Angioedema Activity Score (AAS)

The AAS is a PRO measure developed to assess disease activity in patients with recurrent angioedema, which includes patients with HAE (Weller *et al.* 2013). The AAS consists of an opening question as well as 5 questions regarding the swelling episodes.

Opening question is "Have you had a swelling episode in the last 24 hours?" It may be used to count the number of angioedema affected days during the AAS documentation period but has no score.

5 questions regarding the swelling episodes will be summed up for AAS score calculation. A score between 0 and 3 points is assigned to every question as None = 0 and increase the point from 1 to 3 per severity for each question. The question scores are summed up to an AAS daily score. The daily AAS is summed up to AAS7 and AAS28. Calculation is described as the following: taking the first dose date/time as the start point, sum of daily AAS score during each period divided by the number of days contributed to that period multiplied by 7 days as AAS7 or multiplied by 28 days as AAS28. The minimum number of days for a valid AAS7 and AAS28 is 4 days per week and 3 weeks per 28 days, respectively. Accordingly, the minimum and maximum possible AAS scores are 0–15 for AAS daily score, 0–105 for AAS7, and 0–420 for AAS28.

AAS28 will be compared between ISIS 721744 80 mg every 4 weeks (or every 8 weeks) and pooled placebo using the MMRM model based on the FAS. The MMRM model will include effects of treatment, time, treatment-by-time interaction, and baseline value. The unstructured covariance model will be used to model the within patient errors, shared across treatment and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward and Roger 1997).

AAS scores will be listed in by-patient listings.

4.14. Other Analyses

Psychometric analyses will be conducted for selected PRO assessments. Details will be specified in a separate analysis plan.

4.15. Determination of Sample Size

The power and sample size estimations were calculated using simulations based on a generalized linear model for count data assuming a Poisson distribution. The primary endpoint is the time-normalized number of Investigator-confirmed HAE attacks (per every-4-week) from Week 1 to Week 25. Assuming an HAE attack rate of 13.26 attacks per 6-month period in the placebo group and an HAE attack rate of 1.38 attacks per 6-month period in the ISIS 721744 80 mg every 4 weeks group, the sample size of 54 patients (2:1 ratio [ISIS 721744 : placebo]) will provide at least 90% power for the primary endpoint, with a 0.05 significance level. A total of approximately 84 patients (42 in the ISIS 721744 every-4-weeks group, 21 in the pooled placebo group, and 21 in the ISIS 721744 every-8-weeks group) will be enrolled in this trial to account for potential early dropouts and to facilitate some general safety evaluations.

4.16. Changes in the Conduct of the Study or Planned Analysis

The FAS represents the practically feasible intent-to-treat (ITT) population as delineated in International Conference on Harmonization (ICH) Guideline E9. This SAP choose to use FAS for the primary analysis of efficacy.

Responder analyses will be performed by using logistic regression with baseline and the interaction of baseline and treatment groups as covariates, if specified in the SAP. Compare to the Chi-square requested in the protocol, adjustment for baseline related covariates will generally reduce the variability of estimation of treatment effects and thus lead to more powerful hypothesis testing.

Rather than checking the distribution difference between treatment groups as ordinal variables by using a proportional odds model, PGIC and PGIS will be dichotomized to “better” and “no change or worse” and be analyzed for treatment effect by using logistic regression model. Additionally, the change from baseline on PGIS at each visit will be checked for the mean difference as continuous variable by using Wilcoxon Rank Sum test.

5. REFERENCES

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APPENDIX A. SAS SAMPLE CODES

(1) Poisson Regression:

```
proc genmod data=adeff;
   class arm;
   model no_attks = arm baserate arm*baserate / dist=poisson link=log offset=logmon pscale;
   lsmeans arm/ diff cl exp ilink;
run;
```

where

arm is treatment arm (i.e., ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks and pooled placebo);

no attks is number of Investigator-confirmed HAE attacks during the treatment period;

baserate is time-normalized Investigator-confirmed HAE attack rate during the run-in period;

logmon is logarithm of time in months each patient was observed during the treatment period.

(2) Negative Binomial Regression:

```
proc genmod data=adeff;
   class arm;
   model no_attks = arm baserate arm*baserate/ dist=negbin link=log offset=logmon;
   lsmeans arm/ diff cl exp ilink;
run;
```

where

arm is treatment arm (i.e., ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks and pooled placebo);

no_attks is number of Investigator-confirmed HAE attacks during the treatment period;

baserate is time-normalized Investigator-confirmed HAE attack rate during the run-in period;

logmon is logarithm of time in every-4-weeks each patient was observed during the treatment period.

(3) Mixed Model with Repeated Measures (MMRM):

```
proc mixed /*scoring=4*/;
   class arm visit subject;
   model endpoint=arm baseline visit arm*visit arm*baseline/ ddfm=kr;
```

```
repeated visit / subject=subject type=UN;
lsmeans arm*visit / cl diff;
run;
```

where

arm is treatment arm (i.e., ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks and pooled placebo);

endpoint is change from baseline in AE-QoL total score/each domain score at Week 25;

baseline is baseline AE-QoL total score/each domain score;

visit is scheduled visit.

(4) Jump-to-Reference (J2R) for Recurrent Events:

Step 1a:

Draw a series of independent samples from the posterior distribution of model parameters using a Bayesian Poisson log-link model with an offset variable which holds the log of the exposure time for each patient.

```
proc genmod data = input_data;
class arm;
model no_attks = arm baserate arm*baserate /DIST= poisson LINK = log OFFSET = logmon ;
bayes outpost=bayes_out seed=721744 thin=n_thin nmc=n_draws nbi=n_bi;
run;
```

where

arm is treatment arm (i.e., ISIS 721744 80 mg every 4 weeks, ISIS 721744 80 mg every 8 weeks and pooled placebo);

no_attks is number of Investigator-confirmed HAE attacks during the treatment period;

baserate is time-normalized Investigator-confirmed HAE attack rate during the run-in period;

logmon is logarithm of time in every-4-weeks each patient was observed during the treatment period;

n_thin is the number of thinning parameters;

n_draws is the number of draws;

n_bi is the number of burn-in.

Step 1b:

According to the definition of J2R, the event rate in the active treatment arm is expected to shift to that of the reference arm. Post-withdrawal event rate in the reference arm is still under MAR.

Then calculate the unobserved event rate to sample the number unobserved events as the following:

rand('Poisson', exp(<unobserved event rate>)*<unobserved exposure period until the study end>

The imputed unobserved event numbers are added together with no_attks (i.e., observed event numbers) to be the final total event numbers for patients who withdraw early from the study.

Step 2:

Analyze each imputed dataset using the designated statistical methods in previous sections (e.g., Poisson regression, etc.). Sample codes refer to other corresponding sections.

Step 3:

Combine the result by using PROC MIANYLIZE.

proc mianalyze;

modeleffects estimate;

stderr std_err;

run;

where

estimate is the parameter estimate from Step 2;

std_err is the standard error for the parameter estimate from Step 2.

(5) Tipping-Point Analysis for Recurrent Events:

First three steps are similar with (4) J2R for Recurrent Events multiple imputation mentioned above, expect for Step 1b being different:

Step 1b:

The unobserved event rate for both reference arm and active treatment arm is added by a series of shift parameter (denoted as δ). The number of unobserved events for each discontinued patient is then sampled as the following:

rand('Poisson', exp(<unobserved event rate + δ >)*<unobserved exposure period until the study end>

Step 1b to Step 3 are repeated multiple times, each time with a different δ and thus multiple scenario results are generated.

APPENDIX B. EUROQOL-5-DIMENSIONS INDEX SCORE VALUESET FOR SAS BY COUNTRIES

- Germany

	Mobility	**Self-care**	**Usual Activities**	**Pain/ Discomfort**	**Anxiety/ Depression**
1	0	0	0	0	0
2	0.026	0.050	0.036	0.057	0.030
3	0.042	0.056	0.049	0.109	0.082
4	0.139	0.169	0.129	0.404	0.244
5	0.224	0.260	0.209	0.612	0.356

  - Index Score = 1 – total of (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)

- Netherlands

	Mobility	**Self-care**	**Usual Activities**	**Pain/ Discomfort**	**Anxiety/ Depression**
1	0	0	0	0	0
2	0.035	0.038	0.039	0.066	0.070
3	0.057	0.061	0.087	0.092	0.145
4	0.166	0.168	0.192	0.360	0.356
5	0.203	0.168	0.192	0.415	0.421

  - Index Score = 1 – 0.047 – total of (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)
  - If all 5 domains are 1, then index score is 1.

- Italy

	Mobility	**Self-care**	**Usual Activities**	**Pain/ Discomfort**	**Anxiety/ Depression**
1	0	0	0	0	0
2	0.051	0.046	0.050	0.047	0.044
3	0.064	0.056	0.064	0.088	0.109
4	0.244	0.216	0.225	0.353	0.318
5	0.329	0.257	0.255	0.408	0.322

  - Index Score = 1 – total of (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)

- United States

	Mobility	**Self-care**	**Usual Activities**	**Pain/ Discomfort**	**Anxiety/ Depression**
1	0	0	0	0	0
2	0.096	0.089	0.068	0.060	0.057
3	0.122	0.107	0.101	0.098	0.123
4	0.237	0.220	0.255	0.318	0.299
5	0.322	0.261	0.255	0.414	0.321

  - Index Score = 1 – total of (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)

- United Kingdom, Turkey, Spain, Poland, Israel, France, Denmark, Canada, Bulgaria, Belgium

Follow United States valuesets as there are no pre-defined valuesets for these countries.

Version:	3
Version Date:	12 Dec 2023
Title:	

APPROVALS:

[redacted] 13-Dec-2023 00:07:24 GMT+0000 [redacted] 13-Dec-2023 00:10:24 GMT+0000 [redacted] Pharmacokinetics & Clinical Pharmacology [redacted] 13-Dec-2023 00:19:19 GMT+0000 [redacted] 13-Dec-2023 00:42:47 GMT+0000

Approval Signatures

Document Name: Statistical Analysis Plan 12 Dec 2023 [redacted]_PK5

Document Number: VV-TMF-6021782

Parexel Version Number:

System Version Number: 2 .0

Document Approvals	
Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 13-Dec-2023 03:55:35 GMT+0000

Version:	4
Version Date:	13 Dec 2023
Title:	

APPROVALS:

[redacted] 13-Dec-2023 00:07:24 GMT+0000
[redacted] 13-Dec-2023 00:10:24 GMT+0000
[redacted] Pharmacokinetics & Clinical Pharmacology
[redacted] 13-Dec-2023 00:19:19 GMT+0000
[redacted] 13-Dec-2023 00:42:47 GMT+0000