An Open-Label Extension Study of ISIS 721744 in Patients With Hereditary Angioedema

NCT04307381

19 March 2024

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

1. STUDY INFORMATION

1.1. Protocol and Protocol Amendments

The protocol was amended 3 times. The latest version of the protocol (Protocol Amendment 3) is provided along with the change summary for the revision.

Protocol Version	Date	Document Provided
Original	17 January 2020	None
Protocol Amendment 1	09 February 2021	None
Protocol Amendment 2	13 January 2022	None
Protocol Amendment 3	17 February 2023	Protocol and change summary

IONIS PHARMACEUTICALS, INC.

ISIS 721744-CS3

An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema

Protocol Amendment 3 – 17 February 2023

EudraCT No: 2020-000197-14

Trial Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Telephone Number: 760-603-4665
Fax Number: 760-603-2625

Key Sponsor Contact:

PPD PhD
PPD PPD
2855 Gazelle Court
Carlsbad, CA 92010
Email: PPD
Phone: PPD
Mobile: PPD

Sponsor Medical Monitor:

PPD MD
PPD PPD
2855 Gazelle Court
Carlsbad, CA 92010
Email: PPD
Phone: PPD
Mobile: PPD

ISIS 721744-CS3

Protocol Amendment 3

EudraCT No: 2020-000197-14

Clinical Phase: 2

An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema

Protocol History

Original	17 January 2020
Amendment 1	9 February 2021
Amendment 2	13 January 2022

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

PPD MD
PPD

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-CS3
Protocol Title:	An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema
Amendment:	3
Date:	17 February 2023

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema," dated 17 February 2023, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

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-CS3

Protocol Title: An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema

Amendment Number: 3

Amendment Date: 17 February 2023

The following is a summary of rationale to support modifications made to Protocol ISIS 721744-CS3, dated 17 February 2023.

1. Inclusion of additional Extended Treatment Period (up to an additional 52 weeks, for a total Treatment Period of up to 209 weeks)
2. Revisions to Appendix A to support the additional Extended Treatment Period
3. Updated language for contracteptive use

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**
Throughout the protocol updated Weeks of Treatment and ET visits	up to an additional ~~104~~ **156** weeks Added Week 209 for ET Added Week 221 for Post-Treatment Period	To allow for extension of Treatment
Appendix A	Added Appendix A4 Year 4	Added Table for Procedures with additional 52 weeks (Year 4)
Appendix A**3**	Added optional dose to Week 157	An optional dose was added to Week 157 visit to allow for dosing of patients continuing into a fourth year of Treatment.

Protocol Section	**Description of Change (Additions in bold, deletions in strikethrough)**	**Rationale**
Protocol Synopsis Inclusion Criteria 4a	if engaged in sexual relations of childbearing potential, patient is using ~~highly effective~~ **an acceptable** contraceptive method from time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration	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 Synopsis Inclusion Criteria 4b	Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of childbearing potential, patient is utilizing ~~a highly effective~~ **an acceptable** contraceptive method	The reproductive toxicity study performed in mice (combined Seg I and II) indicated no ISIS 721744-related effects on fertility or embryo/fetal development
Section 6.3.1 Contraception Requirements	All male and woman/women of childbearing potential (WOCBP) patients must refrain from sperm/egg donation and either be abstinent[†] or use ~~highly effective~~ **acceptable** contraception from the time of signing the ICF until at least 24 weeks after their last dose of ISIS 721744. For male patients engaged in sexual relations with a WOCBP, if their female partner is using ~~highly effective~~ **acceptable** contraception from the time of the patient signing the informed consent until 24 weeks after the patient's last dose of study treatment, then it is not required for the male patient to also use an acceptable contraceptive method. For the purposes of this study, a WOCBP is defined as any female who has experienced menarche, and who does <u>not</u> meet 1 of the following conditions: • Post-menopausal: 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 <u>and</u> FSH levels in the post-menopausal range for the laboratory involved	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 6.3.1 Contraception Requirements (Continued)	• 6 weeks after surgical bilateral oophorectomy with or without hysterectomy • Post-hysterectomy For the purposes of the study, ~~highly effective~~ **acceptable** contraception is defined as follows: For male patients: • ~~Highly effective~~ **Acceptable** male contraception includes a vasectomy with negative semen analysis at Follow-up, **surgically sterile via bilateral orcidectony, abstinence†, condom with spermicide** or the non-pregnant female partner of childbearing potential uses ~~a highly effective~~ **an acceptable** contraceptive method (defined below) **from the time of the signing of the informed consent and as applicable assent form though 24 weeks after the last dose of donidalorsen** • Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to ISIS 721744 For female patients and female partners of male patients, ~~highly effective~~ **acceptable** contraception methods comprise: • Surgical sterilization (i.e., 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])** ~~hormonal contraception associated with inhibition of ovulation~~ 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 contraceptives in this study. Chronic estrogen use for gender reassignment is allowed as long as the dose is stable for at least 12 weeks prior to Screening and throughout the Treatment Period** **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.**	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 9.5.4 Contraception and Pregnancy	Male patients and female patients of childbearing potential must continue to use ~~highly effective~~ **acceptable** contraception with their partners, or refrain from sexual activity, as described in 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
Appendix C Immunogenicity, Pharmacokinetic and Pharmacodynamic Sampling Schedule	Extended Treatment ~~Period 1~~ Extended Treatment ~~Period 2~~	Removed Period 1 and 2 for clarity
Appendix B	[3] These laboratory analytes will not be assessed in the Extended Treatment Period (Year 2 and 3 and **Year 4** of the OLE) [4] These laboratory analytes will not be assessed in the Extended Treatment Period (Year 2 and 3 and **Year 4** of the OLE)	Updated with Year 4

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema (HAE).
Study Phase	2 (CS3-An Open-Label Extension Trial of ISIS 721744-CS2).
Indication	Hereditary Angioedema (HAE) Type I (HAE-1), Type II (HAE-2) and Type III (HAE with normal C1-inhibitor [C1-INH]).
Study Objectives	**Primary Objective:** To evaluate the safety of extended dosing , and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE **Secondary Objective:** To evaluate the efficacy of extended dosing , and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE **Additional/Exploratory Objectives:** To evaluate the effects of ISIS 721744 on plasma prekallikrein (PKK) levels, plasma proenzyme activation and cleaved high molecular weight kininogen (cHK) levels. To evaluate the effects of ISIS 721744 on the clinical and angioedema quality of life (AE-QoL) endpoints. To evaluate PK exposure over time.
Study Design	Multi-center open-label extension study with ISIS 721744.
Number of Patients	Approximately 24 patients will be enrolled.
Study Population	**Inclusion Criteria** 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Satisfactory completion of ISIS 721744-CS2 (index study) through Week 17 with an acceptable safety and tolerability profile, per Sponsor and Investigator judgement 3. Able and willing to participate in a 64-week study 4. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 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 follicle-stimulating hormone (FSH) levels in the post-menopausal range for the laboratory involved), abstinent*, or, if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method from time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration

PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Inclusion Criteria (Continued)** b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration * Abstinence 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 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 bradykinin receptor (BK)2-receptor antagonist) to treat angioedema attacks **Exclusion Criteria** 1. Have any new condition or worsening of an existing condition or change or anticipated change in medication or other reason, which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
Treatment Groups	Dose Treatment Period 1 (Fixed Dosing Period): All patients will receive a subcutaneous (SC) injection of ISIS 721744 (80 mg) every 4 weeks for at least 12 weeks. Dose Treatment Period 2 (Flexible Dosing Period): During the Treatment Period 2, if the patient is attack-free for ≥ 12 weeks after entering this OLE study, the Investigator can ***initiate*** a switch to 80 mg ISIS 721744 every 8 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks. For patients who are not attack free for ≥ 12 weeks the Investigator can ***initiate*** a switch to 100 mg ISIS 721744 every 4 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks. After completion of the 52-week Treatment Period , there is an option to participate in an Extended Treatment Period (up to an additional 156 weeks). There is a 12-week Follow-up Period after Year 1, Year 2, Year 3 or Year 4, or early termination from, the Treatment Period. During the course of the study, the use of acute medication (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.

PROTOCOL SYNOPSIS (CONTINUED)

ISIS 721744 Dosage and Administration	During the Treatment Period, ISIS 7217744 will be administered as a single 80 mg SC injection every 4 weeks or every 8 weeks or a single 100 mg SC injection every 4 weeks.
Rationale for Dose and Schedule Selection	The dose level of 80 mg every 28 days was selected based on the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from the ISIS 721744-CS1 study in healthy volunteers and is supported by sub-chronic and chronic toxicity studies in rodents and monkeys of up to 6 and 9 months dosing duration, respectively. The NOAEL in the 9-month monkey study provides an approximate 21-fold safety margin over an 80 mg monthly dose in humans. 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. The estimated half-life ($t_{½}$) was approximately 4 to 5 weeks, supporting the once every 28-day dosing regimen. The every 8 weeks schedule is an exploratory objective to evaluate a reduced frequency of administration of ISIS 721744 treatment. The rationale for 100 mg dosing is in case the patients do not respond to 80 mg because of the severity of the disease and the persistence of the attacks. Preclinical studies show that there is a large therapeutic index for both the 80-mg dose, 21 fold, and the 100-mg dose, 17 fold.
Adjustment of Dose and/or Treatment Schedule	The total duration of the trial is 64 weeks with 52 weeks for the treatment phase and 12 weeks of follow-up. There is an option to participate in an Extended Treatment Period (up to an additional 156 weeks). The 12-week Follow-up Period will be conducted after the patient completes treatment. All patients will begin treatment with ISIS 721744 (80 mg) every 4 weeks for at least 12 weeks. At the end of this time, the patient and the Investigator (in consultation with the Sponsor Medical Monitor) can decide which option to choose: Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks Option 2: For patients who are attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 80 mg every 8 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks. Option 3: For patients who are not attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 100 mg ISIS 721744 every 4 weeks. This switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.

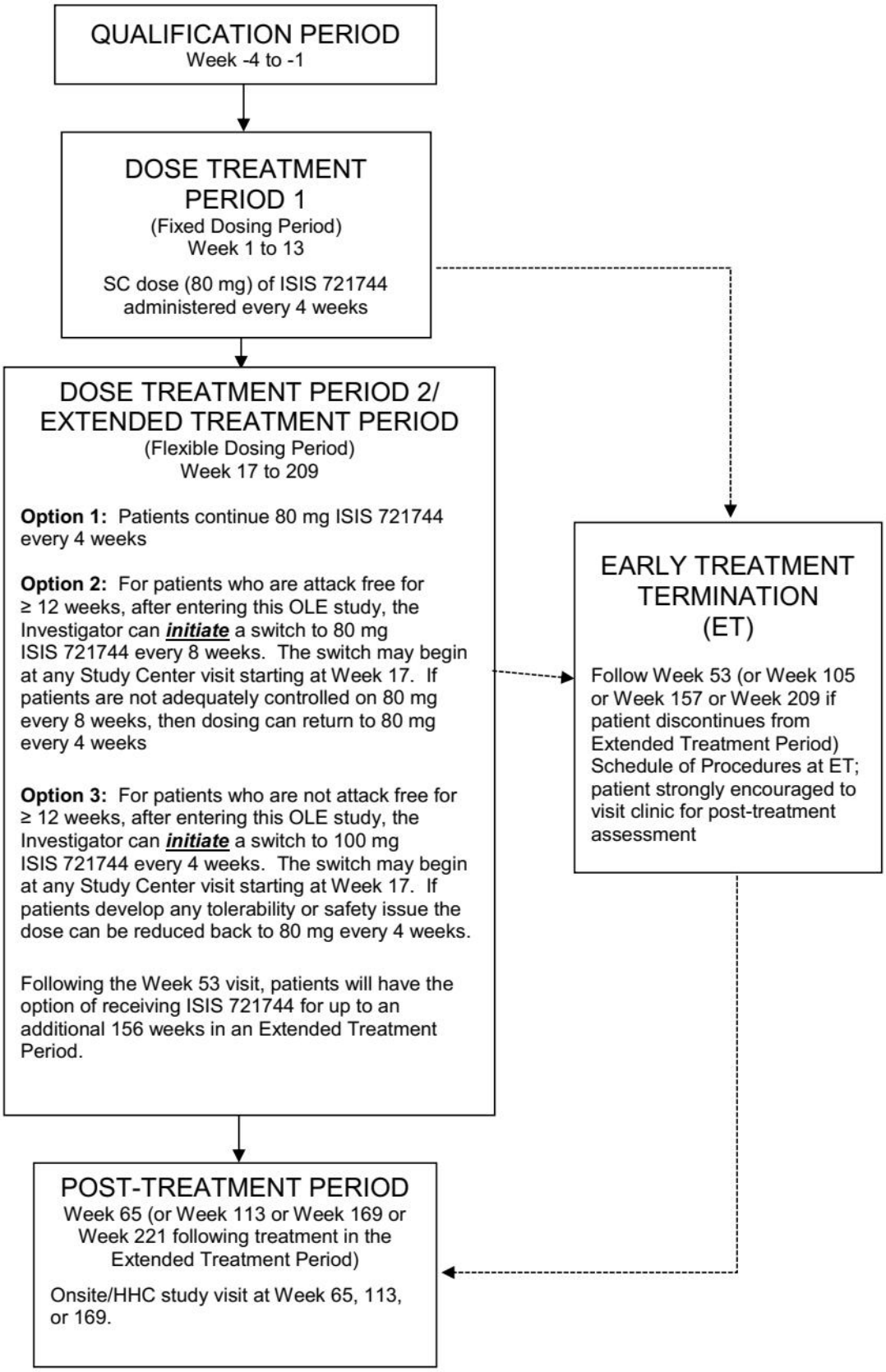
PROTOCOL SYNOPSIS (CONTINUED)

Study Visit Schedule and Procedures	After providing written informed consent, all patients will undergo qualification assessments to confirm eligibility for ISIS 721744-CS3. Patient eligibility for the study should be determined within 30 days prior to study entry. In order to enroll into this study, patients will have successfully completed the qualification procedures and in the opinion of the Investigator the patient should continue treatment. A Qualification Period longer than 30 days may be considered after discussion with the Sponsor Medical Monitor, but the intention is to minimize the treatment pause between the 2 studies. As is operationally feasible, the first dose in this study (ISIS 721744-CS3) should ideally be administered 28 ± 2 days after the last dose in ISIS 721744-CS2. The first dose of ISIS 721744 for CS3 will be administered at the Study Center on Day 1. Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member, home healthcare [HHC] nurse), may be allowed after dosing instructions and training are provided by qualified site personnel and HHC nurse is available to complete all pre-dosing procedures. ISIS 721744 will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm. Study visits (or HHC (if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A) will be performed during Treatment Period 1 at Week 1 (Administration 1), Week 5 (Administration 2), Week 9 (Administration 3), and Week 13 (Administration 4). Study visits (or HHC (if available), Appendix A) will continue to be performed every 4 weeks during Treatment Period 2 and the Extended Treatment Period. The schedule for ISIS 721744 administration will also continue every 4 weeks for Options 1 and 3 but, per guidelines for Option 2, ISIS 721744 administration will change to every 8 weeks. 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 (assessed by the AAS and 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. In addition, at study visit time points, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site. Additionally, blood will be collected during the Treatment and Post-Treatment Periods to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK analyses. Additional assessments will be performed throughout the study as indicated in the Schedule of Procedures table in Appendix A.

PROTOCOL SYNOPSIS (CONTINUED)

Study Visit Schedule and Procedures (Continued)	Following the Week 53 visit, patients will have the option of receiving ISIS 721744 for up to an additional 156 weeks. During this Extended Treatment Period patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack. The AAS questionnaire will only be completed by patients if an HAE attack occurs. Procedures, assessments, and confirmation of Study Drug administration to be conducted via telephone contact by qualified site personnel on non study visit/HHC days.
Study Endpoints	Primary Endpoint: • Incidence and severity of treatment-emergent adverse events (TEAE) Secondary Endpoints: • The time-normalized HAE attacks (monthly) by treatment • Plasma PKK levels, plasma proenzyme activation and cHK levels • Consumption of on-demand medications • AE-QoL questionnaire score Safety Endpoints: • Laboratory tests • Electrocardiograms (ECGs) • Use of concomitant medications • Vital signs
Pharmacokinetic Evaluations	PK exposure over time and potential exposure-response analysis using relevant exposure parameters and biomarkers.
Statistical Considerations	The sample size is dictated by the number of patients enrolled in the prior study (ISIS 721744-CS2). One or more interim analyses may be performed to support ISIS 721744 drug development. Details of the analyses will be provided in the Statistical Analysis Plan (SAP).
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AAS	Angioedema Activity Score
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE(s)	adverse event(s)
AE-QoL	angioedema quality of life
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
BK	bradykinin
BUN	blood urea nitrogen
C	centrigrade
C1-INH	C1-inhibitor
C4	complement factor C4
C5a	complement factor C5a (activated complement split product)
cHK	cleaved high molecular weight kininogen
CRNMB	clinically relevant non-major bleeding
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	Early Termination
FSH	follicle-stimulating hormone
$GalNAc_3$	*N*-acetyl galactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema
HAE-1	hereditary angioedema type I
HAE-2	hereditary angioedema type II
HAE-nC1-INH	hereditary angioedema with normal C1-inhibitor
HHC	home healthcare
HK	high molecular weight kininogen
hs-CRP	C-reactive protein measured by high sensitivity assay
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M

INR	international normalized ratio
IRB	Institutional Review Board
ISIS 721744	antisense inhibitor of prekallikrein
ITT	Intent-to-Treat
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
mRNA	messenger ribonucleic acid
NCS	not clinically significant
OLE	open-label extention
PD	pharmacodynamic(s)
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PKa	plasma kallikrein
PKK	prekallikrein
PP	Per-Protocol
PT	prothrombin time
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
Study Day 1	defined as the first day ISIS 721744 is administered to the patient
Study Drug	ISIS 721744
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman/women of childbearing potential

1. OBJECTIVES AND ENDPOINTS

The objective of the study is to evaluate the safety and efficacy of extended dosing , and alternative dosing and/or dose frequency with antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE).

1.1. Objectives

1.1.1. Primary Objective

To evaluate the safety of extended dosing , and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE.

1.1.2. Secondary Objective

To evaluate the efficacy of extended dosing , and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE.

1.1.3. Additional/Exploratory Objectives

To evaluate the effects of ISIS 721744 on plasma prekallikrein (PKK) levels, plasma proenzyme activation and cleaved high molecular weight kininogen (cHK) levels.

To evaluate the effects of ISIS 721744 on the clinical and angioedema quality of life (AE-QoL) endpoints.

To evaluate PK exposure over time.

1.2. Study Endpoints

1.2.1. Primary Endpoint

- Incidence and severity of treatment-emergent adverse events (TEAE)

1.2.2. Secondary Endpoints

- The time-normalized HAE attacks (monthly) by treatment
- Plasma PKK levels, plasma proenzyme activation and cHK levels
- Consumption of on-demand medications
- AE-QoL questionnaire score

1.2.3. Safety Endpoints

Safety endpoints which will include:

- Laboratory tests
- Electrocardiograms (ECGs)
- Use of concomitant medications
- Vital signs

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 into 3 sub-types. 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 blood levels of C1-INH protein (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 further categorized into 4 sub-types, 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) production (derived from the proteolytic cleavage of high molecular weight kininogen [HK] into cHK and 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 plasma kallikrein (pKK) 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 recently Food and Drug Administration-approved monoclonal antibody directed against PKa. Plasma kallikrein circulates in blood as a zymogen (i.e., PKK) which is bound to one of its main substrates, HK. Prekallikrein is cleaved upon contact activation, forming the active protease PKa. Plasma kallikrein cleaves HK in turn, thereby releasing BK and the split product 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 second-generation, ligand-conjugated antisense oligonucleotide (ASO) drug designed to reduce the production of PKK mRNA. Antisense technology is characterized by its high specificity in inhibiting a single-gene product, thereby diminishing the potential for off-target drug effects. Furthermore, since ligand-conjugated ASOs require infrequent administration, ~once every month or even less often, the availability of a plasma PKK ASO inhibitor could be of additional value to the arsenal of prophylactic drugs for the prevention of

HAE attacks. The long (half-life) $t_{½}$ of second-generation antisense drugs and the lower frequency of administration afforded by ligand conjugation might provide additional benefit to patients.

The Phase 1 clinical data show that ISIS 721744 reduces plasma PKK levels effectively in a dose-dependent manner without safety concerns.

2.3. ISIS 721744

2.3.1. Mechanism of Action

ISIS 721744 is an *N*-acetyl galactosamine ($GalNAc_3$)-conjugated, second-generation ASO drug targeted to the human PKK protein messenger ribonucleic acid (mRNA). It is complementary to a 20 nucleotide sequence in the translated regions (Exon 9) of the PKK mRNA and, following cleavage of the $GalNAc_3$ moiety, binds to the PKK mRNA target sequence by Watson and Crick base pairing. The hybridization (binding) of ISIS 721744 to the cognate PKK mRNA results in the activation of the ubiquitous endonuclease RNase H1, that recognizes the mRNA/ASO duplex and specifically hydrolyzes the mRNA strand resulting in degradation of the PKK mRNA and thus preventing production of the PKK protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Palmer and Henrich 1996; Wang et al. 2002). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2. Chemistry

Chemically, ISIS 721744 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The nucleotide sequence of ISIS 721744 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 9 of the PKK protein mRNA. Structurally, the oligonucleotide has 4 regions. Two (2) of them, 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 2′-MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) 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 (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. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of ribonucleic acid (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 enzyme (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. A fourth region, comprised of a triantennary cluster of $GalNAc_3$ sugars, is linked to the 5′ end of

ISIS 721744 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high-affinity ligand for the asialoglycoprotein receptor, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 721744 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the $GalNAc_3$ 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 deoxyribonucleic acid (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 potency and therapeutic index of $GalNAc_3$-conjugated ASOs.

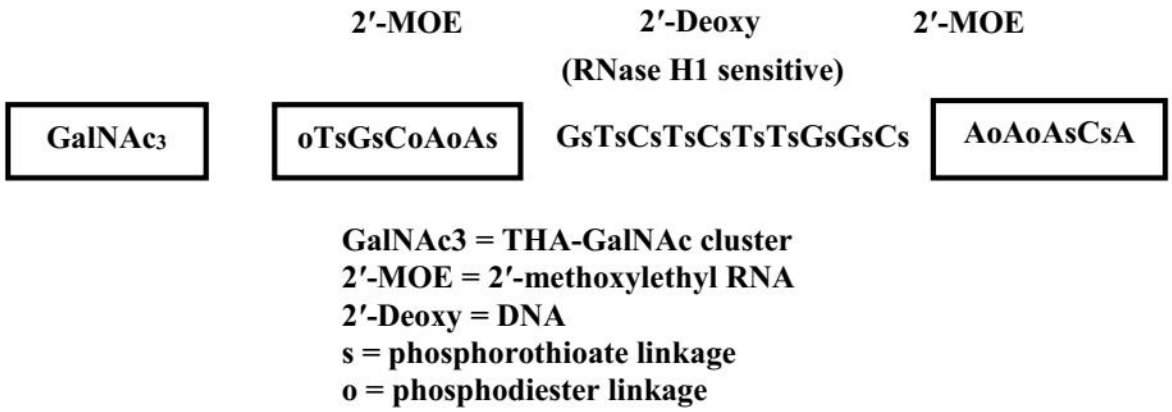


Figure 1: Design of $GalNAc_3$-Conjugated Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence of ISIS 721744 is shown.

2.3.3. Preclinical Experience

Please refer to the Investigator's Brochure for a detailed description of the preclinical pharmacology, nonclinical toxicology and PK studies conducted with ISIS 721744.

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

Detailed information concerning the clinical studies conducted with ISIS 721744 can be found in the Investigator's Brochure. A summary is included below.

The safety and tolerability of ISIS 721744 was evaluated in the clinical setting in a double-blind, multiple-dose, dose-escalation Phase 1 safety study (ISIS 721744-CS1) in a total of 32 healthy volunteers. 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. ISIS 721744 was well-tolerated at doses up to 80 mg administered as a single-dose every 4 weeks. There were no SAEs and all reported AEs were mild in severity. There were no dose-dependent clinically meaningful trends in laboratory assessments.

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 index study, ISIS 721744-CS2, is a randomized, double-blind, placebo-controlled multicenter study of ISIS 721744 or placebo. In this study, 18 patients with HAE-1 and HAE-2 and approximately 6 patients with HAE-nC1-INH will be dosed with 80 mg of ISIS 721744 every 28 days. This dose level was selected based on the safety, tolerability and PK/ pharmacodynamic (PD) data from the ISIS 721744-CS1 study in healthy volunteers. Patients will receive the Study Drug for 12 weeks with a follow-up treatment time of 4 to 12 weeks, depending upon whether they enroll in the open-label extension study. The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. The study will also evaluate PKK levels and AE-QoL.

2.4. Rationale for Dose and Schedule of Administration

The dose level of 80 mg every 28 days was selected based on the safety, tolerability, PK, and PD data from the ISIS 721744-CS1 study in healthy volunteers. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered 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]). The estimated $t_{½}$ from the Phase 1 PK data was approximately 4 to 5 weeks, supporting the once-every-28-day dosing regimen. This open-label extention (OLE) study includes the option to dose 80 mg ISIS 721744 every 8 weeks for patients who are attack free for ≥ 12 weeks after entering the OLE or to increase the dose of ISIS 721744 to 100 mg every 4 weeks for patients who are not attack free for ≥ 12 weeks after entering the OLE. Preclinical studies show that there is a large therapeutic index for both the 80-mg dose, 21 fold, and the 100-mg dose, 17 fold.

2.5. Benefit-Risk Assessment

2.5.1. Benefit Assessment

The benefits of treatment of ISIS 721744 are currently unknown. Due to its mechanism of action, ISIS 721744 has the potential to be efficacious for the treatment of patients with HAE.

2.5.2. Risk Assessment

The known potential risks to study participants associated with ISIS 721744 are elaborated on in the "Guidance to Investigator" section of the Investigator's Brochure.

There are no anticipated risks associated with reducing plasma PKK levels; however, a potential theoretical risk associated with PKK inhibition would be prolongation of activated partial thromboplastin time (aPTT). This risk is informed by 80 cases of PKK deficiency that have been described in the literature (Girolami et al. 2010). In these individuals, there is a discrepancy between an observed *in vitro* defect and an absence of bleeding. Thus, it is believed that most cases go undetected or, if detected, go unreported. Occasional bleeding or thrombosis has been reported in a few PKK deficient patients but these instances were due to the presence of associated risk factors. Diagnosis is based on the prolongation of partial thromboplastin time and normal prothrombin time (PT) and thrombin time. In these individuals, platelet and vascular tests are normal and the long partial thromboplastin time has shown to be fully corrected by the addition of normal plasma or normal serum.

In monkeys, doses of ISIS 721744 of up to 30 mg/kg/wk for 13 weeks were well-tolerated with the exception of thrombocytopenia observed in 1 female at 12 mg/kg/wk and 1 male at 30 mg/kg/wk. The monkey dose of 6 mg/kg/wk provides an approximate 20-fold margin relative to a human dose of 80 mg every 4 weeks and therefore there is sufficient therapeutic margin to assure the safe clinical use of ISIS 721744 at the proposed clinical dose and regimen.

One (1) subject in the ISIS 721744-CS1 study had a confirmed platelet nadir count between $100 \times 10^3/\mu L$ and the lower limit of normal (LLN) ($140 \times 10^3/\mu L$). The subject received ISIS 721744 at 20 mg and had a platelet count of $139 \times 10^3/\mu L$ on Study Day 99; all other reported values for this subject were within the reference range.

Platelet counts will be monitored closely throughout the clinical study.

More complete details can be found in the Investigator's Brochure.

2.5.3. 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-CS3. 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 COVID19-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 is an open-label extension study of ISIS 721744 to evaluate the safety and efficacy of extended dosing and alternative dosing and/or dose frequency in patients with HAE.

3.2. Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3. Number of Patients

Approximately 24 patients will be enrolled.

3.4. Overall Study Duration and Follow-up

The study will consist of a Qualification Period, a Treatment Period, and a Post-Treatment Period. The Treatment Period will be comprised of Treatment Period 1 (Fixed Dosing Period), Treatment Period 2 (Flexible Dosing Period), and an Extended Treatment Period (flexible dosing period Year 2 and Year 3 and Year 4). 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.

The length of each patient's participation in the study is approximately 68 weeks, which includes an up to 4-week Qualification Period, a 52-week Treatment Period, and a 12-week Post-Treatment Period. Following the Week 53 Treatment Period visit, patients will have the option of receiving ISIS 721744 in an Extended Treatment Period for up to an additional 156 weeks. Patients participating in the Extended Treatment Period will enter the 12-week Post-Treatment Period after completion of, or early termination from, the Extended Treatment Period. During the Treatment Period, ISIS 721744 will be administered as a single 80-mg SC injection every 4 weeks or every 8 weeks or a single 100-mg SC injection every 4 weeks as outlined in Appendix A.

3.4.1. Qualification Period

Patient eligibility for the study should be determined within 30 days prior to study entry. In order to enroll into this study, patients will have successfully completed the qualification procedures and in the opinion of the Investigator the patient should continue treatment. A Qualification Period longer than 30 days may be considered after discussion with the Sponsor Medical Monitor, but the intention is to minimize the treatment pause between the 2 studies.

Please refer to Section 6.1.1 and Appendix A for further detail regarding Qualification procedures.

3.4.2. Treatment Period

Eligible patients will report to the Study Center for the first administration of ISIS 721744 on Study Day 1 (Week 1 Visit) and will continue to receive 80 mg ISIS 721744 once every 4 weeks

during the 12-week Treatment Period 1. Following completion of Treatment Period 1 and continuing through the Extended Treatment Period, patients (based on the Investigator and Sponsor Medical Monitor recommendation) have 3 different dosing options:

- Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks
- Option 2: For patients who are attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 80 mg ISIS 721744 every 8 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks then dosing can return to 80 mg every 4 weeks
- Option 3: For patients who are not attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 100 mg ISIS 721744 every 4 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.

Following the Week 53 visit, patients will have the option of receiving ISIS 721744 for up to an additional 156 weeks in an Extended Treatment Period.

3.4.3. Post-Treatment Period

Patients are to return to the Study Center or use HHC for post-treatment follow-up visit at Study Week 65, Week 113, or Week 169 or Week 221 depending on whether the patient chooses to continue receiving ISIS 721744 for up to an additional 156 weeks in the Extended 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.

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.

4. PATIENT ENROLLMENT

4.1. Qualification

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, informed consent form (ICF), and all other patient information and/or recruitment material.

Patients or their legally acceptable representatives must sign the consent form before any study specific procedures or evaluations related to this open-label study are performed. Patient eligibility for the study should be determined within 30 days prior to study entry. In order to enroll into this study, patients will have successfully completed qualification procedures and in the opinion of the Investigator the patient should continue treatment. A Qualification Period longer than 30 days may be considered after discussion with the Sponsor Medical Monitor, but

the intention is to minimize the treatment pause between the 2 studies. As is operationally feasible, the first dose in this study (ISIS 721744-CS3) should ideally be administered 28 ± 2 days after the last dose in ISIS 721744-CS2. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 721744-CS2 index study. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2. Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Section 5.1 and Section 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using web based Interactive Response Technology (IRT).

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

4.4. Unblinding of Treatment Assignment

All study patients will receive ISIS 721744 in an unblinded manner.

5. PATIENT ELIGIBILITY

5.1. Inclusion Criteria

Patients must meet all of the following criteria at Qualification Period to be eligible:

1. Patients must provide written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements for the duration of the study.
2. Satisfactory completion of ISIS 721744-CS2 (index study) through Week 17 with an acceptable safety and tolerability profile, per Sponsor and Investigator judgement.
3. Able and willing to participate in a 64-week study.
4. Satisfy 1 of the following:
    a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 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 follicle-stimulating hormone (FSH) levels in the post-menopausal range for the laboratory involved), abstinent*, or, if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method from time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until 24 weeks after the last dose of ISIS 721744 administration

* Abstinence 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

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

5.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for the study:

1. Have any new condition or worsening of an existing condition or change or anticipated change in medication, which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

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 and the Sponsor Medical Monitor.

The length of each patient's participation from Qualification Period to the last study visit is up to approximately 68 weeks. For patients who choose to continue in the Extended Treatment Period, participation will last up to approximately 172 weeks.

6.1.1. Qualification Period

Written informed consent for the study will be obtained prior to the performance of any study-related procedures, including qualification procedures.

Safety labs may be retested for determination of patient eligibility at the Investigator's discretion. The Sponsor Medical Monitor will be available for consultation, if needed.

After providing written informed consent, all patients will undergo qualification assessments to confirm eligibility for ISIS 721744-CS3. Patient eligibility for the study should be determined within 30 days prior to study entry. In order to enroll into this study, patients will have successfully completed the qualification procedures and in the opinion of the Investigator the patient should continue treatment. A Qualification Period longer than 30 days may be considered after discussion with the Sponsor Medical Monitor, but the intention is to minimize

the treatment pause between the 2 studies. As is operationally feasible, the first dose in this study (ISIS 721744-CS3) should ideally be administered 28 ± 2 days after the last dose in ISIS 721744-CS2.

Safety clinical laboratory parameters and assessments from ISIS 721744-CS2 may be used for determination of eligibility (as Qualification for ISIS 721744-CS3) if they were obtained within the Qualification Period (i.e., 30 days prior to enrollment in the study or longer if approved by the Sponsor Medical Monitor).

During the course of the study, the use of acute 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.

6.1.2. Treatment Period

The first dose of ISIS 721744 will be administered at the Study Center on Day 1. Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member, home healthcare [HHC] nurse), may be allowed after dosing instructions and training are provided by qualified site personnel and HHC nurse is available to complete all pre-dosing procedures. ISIS 721744 will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm. Study visits will be performed during Treatment Period 1 at Week 1 (Administration 1), Week 5 (Administration 2), Week 9 (Administration 3), and Week 13 (Administration 4). Following completion of Treatment Period 1 and continuing through the Extended Treatment Period, the patient and the Investigator (in consultation with the Sponsor Medical Monitor) can decide which dosing option to choose:

- Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks
- Option 2: For patients who are attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 80 mg ISIS 721744 every 8 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks, then dosing can return to 80 mg every 4 weeks
- Option 3: For patients who are not attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 100 mg ISIS 721744 every 4 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.

During Treatment Period 2 and the Extended Treatment Period, study visits will continue to be performed every 4 weeks. The schedule for ISIS 721744 administration will also continue every 4 weeks for Options 1 and 3 but, per guidelines for Option 2, ISIS 721744 administration will change to every 8 weeks.

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 Period, the following data will be collected: angioedema activity score (AAS) and number of HAE attacks (assessed by the AAS and 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. In addition, at study visit time points, site personnel will inquire for any new HAE attack information that was not provided through patient contact with the site.

Additionally, assessments and procedures (i.e., blood draws) will be conducted at Study Center visits during the Treatment Period as outlined in the Schedule of Procedures. Visits can be conducted at the Study Center or by Home Healthcare (if available) as defined in Appendix A. Blood will be collected during the Treatment Period to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, complement factor C4 (C4) split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK analyses. Additional assessments will be performed throughout the study as indicated in the Schedule of Procedures table in Appendix A.

Following the Week 53 visit, patients will have the option of receiving ISIS 721744 for up to an additional 156 weeks in an Extended Treatment Period. During this Extended Treatment Period patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack. The AAS questionnaire will only be completed by patients if an HAE attack occurs. Procedures, assessments, and confirmation of Study Drug administration to be conducted via telephone contact by qualified site personnel on non-study visit/HHC days.

During the course of the study, the use of acute 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. With the exception of Qualification and Day 1 visits, a ± 3 day excursion from the scheduled visit date is permitted for all visits.

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.

6.1.2.1. Day 1 Visit Conducted on Post-Treatment Study Visit Week 17 ISIS 721744-CS2

For patients that will roll-over to ISIS 721744-CS3 it is critical to complete all procedures from Post-Treatment Study Visit Week 17 ISIS 721744-CS2 because that visit includes procedures for the ISIS 721744-CS2 primary endpoint analysis. Study Day 1 of ISIS 721744-CS3 can be conducted on the same day as ISIS 721744-CS2 Post-Treatment Study Visit Week 17. In this case, complete all ISIS 721744-CS2 procedures first prior to Study Drug administration.

6.1.3. Post-Treatment Period

Each patient will be followed for safety assessments for up to 12 weeks after completion of, or early termination from, the Treatment Period. Patients are to return to the Study Center or use HHC for post-treatment follow-up visit at Study Week 65, Week 113, or Week 169 or Week 221 depending on whether the patient chooses to continue receiving ISIS 721744 for up to an additional 156 weeks in the Extended Treatment Period for safety and clinical laboratory evaluations and for blood sampling for PK/PD analyses.

During the Post-Treatment Period, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and 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 Post-Treatment Period, site personnel will contact the patient once a month in order to inquire about any attack that may have occurred. In addition, at the Week 65, Week 113, or Week 169 study visit, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site.

Blood samples will also be collected regularly throughout the study for safety and PK analyses. Additionally, blood will be collected to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Additional assessments will be performed throughout the Post-Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

Patients who withdraw early from the study during the Treatment Period will be required to complete their end-of-study evaluations following procedures listed for the Week 53/ET, Week 105/ET, or Week 157/ET Visit, or Week 209/ET visit unless consent is withdrawn; see Appendix A.

6.2. Study 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 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).

6.2.2. Collection of Hereditary Angioedema Attack Details

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. In addition, at study visit time points, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site.

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

- Date/time of symptom onset
- Description of symptoms
- 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, emergency room 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

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 an at least 24-hour symptom-free period between attacks.

6.2.3. Patient-Reported Outcomes

6.2.3.1. Angioedema Quality of Life Questionnaire

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. 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.

Quality of life will be assessed by the AE-QoL questionnaire during the Treatment and Post-Treatment Periods as indicated in the Schedule of Procedures table in Appendix A.

6.2.3.2. Angioedema Activity Score

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 symptom-related factors from 0 to 3, resulting in a total daily score of 0 to 15. Daily AAS can be summed to provide scores every 7 days, every 4 weeks, and every 12 weeks (Weller et al. 2013).

Patients will record their HAE attacks using the AAS questionnaire during the Qualification Period. Enrolled patients will continue to record HAE attacks using the AAS questionnaire throughout the Treatment and Post-Treatment Periods. During Treatment Period 1 and Treatment Period 2, the AAS questionnaire will be completed by patients on a daily basis

(minimum of 4 daily assessments per week). During the Extended Treatment Period and Post-Treatment Period the AAS questionnaire will only be completed by patients if an HAE attack occurs.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male and woman/women of childbearing potential (WOCBP) patients must refrain from sperm/egg donation and either be abstinent[†] or use acceptable contraception from the time of signing the ICF until at least 24 weeks after their last dose of ISIS 721744.

For male patients engaged in sexual relations with a WOCBP, if their female partner is using acceptable contraception from the time of the patient signing the informed consent until 24 weeks after the patient's last dose of study treatment, then it is not required for the male patient to also use an acceptable contraceptive method.

For the purposes of this study, a WOCBP is defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Post-menopausal: 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 post-menopausal 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 childbearing potential uses an acceptable contraceptive method (defined below) from the time of the signing of the informed consent and as applicable assent form though 24 weeks after the last dose of donidalorsen
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to ISIS 721744

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

- Surgical sterilization (i.e., 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 contraceptives in this study. Chronic estrogen use for gender reassignment is allowed as long as the dose is stable for at least 12 weeks prior to Screening and throughout the Treatment Period

†**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, or post-ovulation methods), declaration of abstinence for the duration of the study, or 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 manmade 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
- **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.If a patient has a reaction from a vaccination, ensure the reaction has resolved prior to next administration of Study Drug.

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) characteristics are listed in Table 1.

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

During the Treatment Period, Study Drug (ISIS 721744) will be administered as a single-SC injection.

Table 1: Study Drug Characteristics

Study Drug	**ISIS 721744**
Strength	100 mg/mL
Volume/Formulation	0.8 mL solution per vial
Route of Administration	SC

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 721744) 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) 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) will be administered as a single-SC injection once every 4 weeks or every 8 weeks. Vials of Study Drug (ISIS 721744) 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) preparation and administration.

8.2. Other Protocol-Required Drugs

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. During the course of the study, the use of acute 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

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

For the purposes of safety monitoring, Baseline is defined as described in Section 10.4 Definition of Baseline.

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.

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 retest results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator 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

below (refer to 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.

In the event of an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement that is > 3 × upper limit of normal (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 × ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase, 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:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Perform serology for viral hepatitis (hepatitis A virus immunoglobulin M ([IgM], hepatitis B surface antigen, hepatitis C virus antibody, cytomegalovirus IgM, and Epstein-Barr Virus antibody panel)
- Perform serology for autoimmune hepatitis (e.g., antinuclear antibody)

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography or magnetic resonance imaging scans, may be performed at the discretion of the Investigator, 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.

8.5.2. Safety Monitoring Rules for Platelet Count Results

Please refer also to Table 2.

Platelet count will be monitored during the Treatment and Post-Treatment Periods per the Schedule of Procedures. The Investigator should review all platelet count results within 48 hours of receipt. Any unreportable platelet count result must be rechecked ideally within 7 days and determined not to have met a stopping rule before dosing can continue. If a patient's platelet count falls to 100,000/mm^3 or less, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75,000/mm^3, the platelet monitoring rule defined in stopping rules (Section 8.6.2) should be followed.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted in consultation with the Sponsor Medical Monitor.

8.5.3. Safety Monitoring Rules for Renal Function Test Results

If a patient's results meet Criteria 1 or 2 below, the Investigator should confirm the results and initiate weekly monitoring if confirmed. If the event of a persistent elevation is observed over 2 consecutive weeks, then go to Section 8.6.3.

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 8.6)
2. Proteinuria, urine protein/creatinine ratio > 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

8.5.4. Safety Monitoring for Minor Bleeding Events

If a bleeding event occurs, including minor bleeding events such as excess bruising, petechiae, or gingival bleeding on brushing teeth, the Investigator should notify the Sponsor Medical Monitor and additional testing of coagulation parameters (aPTT, PT, and INR) and platelet count should be performed.

8.6. Stopping Rules

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) 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 × 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 × baseline value or 3 × 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. Stopping Rules for Platelet Count Results

Please refer also to Table 2.

In the event of any platelet count < 25,000/mm^3, dosing of the patient with ISIS 721744 will be stopped permanently. Platelet count should be monitored daily until 3 successive values > 25,000/mm^3. Then, monitor twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Administration of steroids is strongly recommended for patients whose platelet count is < 25,000/mm^3. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days. (**Note:** Patient may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count ≥ 25,000/mm^3 to < 50,000/mm^3, dosing of the patient with ISIS 721744 will be stopped permanently. Platelet count should be monitored twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring and/or the administration of steroids if additional risk factors for bleeding are present (see Table 2).

In the event of a platelet count ≥ 50,000/mm^3 to < 75,000/mm^3, and in the absence of major bleeding (MB) or clinically relevant non-major bleeding (CRNB, defined below), dosing with ISIS 721744 should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. Platelet count must be measured twice weekly until 3 successive values > 75,000/mm^3, then weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Any unreportable platelet count result must be rechecked, ideally within 7 days, and determined not to have met a stopping rule before dosing can continue.

Definition of Major Bleeding Events (Schulman and Kearon 2005).

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of ≥ 2.0 g/dL (1.24 mmol/L) within 24 hours

Definition of Clinically Relevant Non-Major Bleeding Events

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for MB but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient.

Definition of Minor Bleeding Events

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

If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in Table 2.

Table 2: Actions in Patients with Confirmed Low Platelet Count

Platelet count (K/mm^3)	Dosing	Monitoring frequency
> 100	Dosing every 4 weeks should be continued.	At least every 4 weeks.
≥ 75 to ≤ 100	Dosing every 4 weeks should be continued.	Every week.
≥ 50 to < 75	Pause dosing. When platelet count returns to > 100K/mm^3, restart dosing only if approved by the Sponsor Medical Monitor.	Twice weekly until 3 successive values > 75K/mm^3, then weekly until 3 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
≥ 25 to < 50	Permanently discontinue ISIS 721744. Consider corticosteroids if additional risk factors for bleeding are present.‡	Twice weekly until 3 successive values > 75K/mm^3, then weekly until 3 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
< 25	Permanently discontinue ISIS 721744. Corticosteroids strongly recommended.*	Daily until 3 successive values > 25K/mm^3, then twice weekly until 3 successive values > 75K/mm^3, then weekly until 3 successive values > 100K/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present.‡

‡ Additional risk factors for bleeding include age > 60 years, receiving anticoagulant or antiplatelet medicinal products, and/or prior history of MB events.

* It is strongly recommended that, unless corticosteroids are contraindicated, the patient receives glucocorticoid therapy to reverse the platelet decline as recovery in platelet count may be accelerated by administration of high-dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**Note:** patient may require continuation with oral steroids after methylprednisolone).

8.6.3. 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) 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. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hours)

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

8.7. Adjustment of Dose and/or Treatment Schedule

Adjustment of dose and/or schedule is permitted in accordance with the Schedule of Procedures (Appendix A).

8.8. Discontinuation of Study Drug

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
- The patient withdraws from treatment (but does not withdraw consent)
- The patient experiences an AE that necessitates permanent discontinuation of ISIS 721744
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1, 8.6.2, or 8.6.3

The reason for discontinuation of ISIS 721744 must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who discontinue ISIS 721744 will remain in the study and attend the ET visit (Week 53, Week 105, or Week 157 or Week 209 visit assessments) unless consent is withdrawn. Any patient who discontinues early from the Treatment or Post-Treatment Periods should be strongly encouraged to complete the follow-up study visit, procedures, and observations (see Appendix A).

8.9. Withdrawal of Patients from the Study Procedures

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

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

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

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator 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 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 ET study procedures (Week 53, Week 105, or Week 157 or Week 209 visit assessments) and observations at the time of withdrawal (see Appendix A).

For patients withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the ET study procedures and observations at the time of withdrawal (see Appendix A).

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 (AEs) 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 Qualification Period and the end of the Post-Treatment Period.

Allowed Concomitant Therapy

During the course of the study, the use of acute 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. Vaccines are allowed. It is recommended that there be an interval of at least 7 days (or longer in the case of prolonged adverse effects) between the administration of the vaccine and Study Drug.

Disallowed Concomitant Therapy

1. Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens. Any use of Lanadelumab (Takhzyro) will not be permitted

   NOTE: The use of acute medications (plasma-derived or recombinant C1-INH concentrate or BK2-receptor antagonist) to treat angioedema attacks is allowed as medically indicated.

2. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy)
3. Any oligonucleotides (including small interfering RNA) other than ISIS 721744. This exclusion does not apply to vaccines
4. Plasmapheresis
5. Any other investigational drug or device

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 Qualification and the end of the Post-Treatment Period.

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 Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Council for Harmonisation (ICH) guidelines E2A and ICH Good Clinical Practice (GCP). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards/IECs will be notified of any SAE according to applicable regulations.

In addition to the Investigator'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) is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision, it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

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 in a blinded fashion.

9.3. Definitions

9.3.1. Adverse Event

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

An AE 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 ISIS 721744
- 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 Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction

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, adverse drug reactions (ADRs) are defined as follows:

- All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs

The phrase “responses to a medicinal product” means that a causal relationship between the medicinal product and the AE 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

A serious adverse event (SAE) is any AE that, in the view of either the Investigator 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 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 emergency room 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 AE (e.g., rated as mild, moderate, or severe; or according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]); 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 AE recorded on the eCRF.

9.3.4. Adverse Events of Special Interest

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

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) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator 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

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to ISIS 721744) 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 65, Week 113, or Week 169 visit. Serious adverse events should be reported using electronic SAE submission (via eDC- SAE eCRF) 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 follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree that the patient's condition is unlikely to resolve, the Investigator 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 65, Week 113, or Week 169 visit. The Investigator 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 opinion of the following should be documented on the eCRF:

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 721744) 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), 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) 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) 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 believes no relationship exists between the event and Study Drug (ISIS 721744)

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests and AEs at the injection site will be graded based on criteria from the CTCAE Version 5.0, November 2017 (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

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) will not be allowed during the study.

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

- **None:** No changes made to Study Drug (ISIS 721744) administration and dose
- **Not Applicable:** AE reported during the Qualification Period prior to Study Drug (ISIS 721744) administration or during the Post-Treatment Period
- **Permanently Discontinued:** Study Drug (ISIS 721744) 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 dose

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 eCRF. 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 1 of the following:

- **AE Persists:** Patient terminates from the study 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 1 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 Follow-up

During the Study Period, the Investigator 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. Every effort should be made to follow all SAEs considered to be related to ISIS 721744 or related to study procedures until a final outcome can be reported.

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

Investigators 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 the male study patient until pregnancy outcome is available.

Sponsor Follow-up

For SAEs 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, or autopsy reports) in order to perform an independent medical assessment of the reported 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, 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 until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator 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 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 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 between the patient's consent 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) 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) 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 ISIS 721744 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 ISIS 721744. However, the patient will be encouraged to complete the Post-Treatment Period (12 weeks after the ET visit) 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 Statistical Analysis Plan (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 Sections 1.1 and 1.2, respectively.

10.1. Stratification and Subsets

There is no stratification factor for this study.

There is no subgroup analysis planned. Details of the prespecified subgroup analyses will be provided in the SAP. Details of the prespecified subgroup analyses will be provided in the SAP. Details of the prespecified subgroup analyses will be provided in the SAP.

10.2. Sample Size

The sample size is dictated by the number of patients enrolled in the prior study (ISIS 721744-CS2).

10.3. Populations

The Safety Population will include all enrolled patients who receive at least 1 dose ISIS 721744.

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

The PK Population will include all patients who are enrolled and receive at least 1 dose of ISIS 721744 and have at least 1 evaluable PK sample.

10.4. Definition of Baseline

For patients who received the placebo in ISIS 721744-CS2 study, the baseline will be defined as the following:

- For platelets, Baseline will be defined as the average of all non-missing pre-dose assessments within 4 weeks prior to the first dose in this OLE study
- For other assessments, Baseline will be defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in the OLE study. If there is only 1 pre-dose measurement available in this OLE study, then it will be assigned as Baseline

For patients who received active treatment in ISIS 721744-CS2 study, Baseline will be the ISIS 721744-CS2 baseline.

10.5. Interim Analysis

One (1) or more interim analyses may be performed to support ISIS 721744 drug development. Details of the analyses will be provided in the SAP.

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 data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

The efficacy endpoints will be assessed on the ITT and PP populations. The safety endpoints will be assessed on the Safety Population. The PK analyses will be conducted in the PK population.

10.6.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group in ISIS 721744-CS2 study and overall, and by HAE type (HAE-1/HAE-2 vs. HAE-nC1-INH). Patient disposition will be summarized by treatment group in ISIS 721744-CS2 study and overall, and by HAE type. All patients enrolled will be included in a summary of patient disposition.

10.6.2. Safety Analysis

The Safety Population will be used for all safety analyses.

Treatment duration and amount of ISIS 721744 received will be summarized by treatment group in ISIS 721744-CS2 study and overall, and by HAE type.

Patient incidence rates of TEAEs, all TEAEs potentially related to ISIS 721744, all treatment-emergent serious AEs, and all TEAEs potentially related to ISIS 721744 will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA™) system organ class, MedDRA™ preferred term, and treatment group in ISIS 721744-CS2 study and overall, and by HAE type. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

Laboratory tests to ensure patient safety, including chemistry panel, complete blood count with differential, coagulation panel, and complement, will be summarized by study visit for each treatment group in ISIS 721744-CS2 study and overall, and by HAE type. These safety variables will also be presented as change and percent change from Baseline over time after ISIS 721744 administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group in ISIS 721744-CS2 study and overall, and by HAE type. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group in ISIS 721744-CS2 study and overall, and by HAE type.

10.6.3. Efficacy Analysis

The ITT Population will be used for all efficacy analyses. The PP Population will be used for a sensitivity analysis to assess robustness of the efficacy analysis results.

The time-normalized number of HAE attacks will be summarized using the descriptive statistics.

The change and percent change from Baseline in plasma PKK levels, plasma proenzyme activation, cHK levels, and AE-QoL questionnaire score will be summarized by visit using the descriptive statistics. Consumption of on-demand medications will also be summarized.

10.6.4. Pharmacokinetic Analysis

The plasma pharmacokinetic (PK) of ISIS 721744 will be assessed following SC administration. Plasma ISIS 721744 concentrations at trough during the Treatment Period and concentrations observed during the Post-Treatment Evaluation Period will be listed by dose, study day, time point, and summarized using descriptive statistics.

$t_{½}$ and other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

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 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 data from this study, and/or combined with other ISIS 721744 clinical PK/PD data later in the development timeline.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent

The written informed consent 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 is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug (ISIS 721744) are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent 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 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 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 ISIS 721744. 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 ISIS 721744. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The Investigator 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 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 must ensure that the patient's confidentiality is maintained. On the case report forms 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.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator 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 is obligated to inform and obtain the consent 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 must be obtained for all protocol amendments and amendments to the informed consent 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 **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 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 Electronic Data Capture (eDC) application will be used for this study.

The Investigator 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 case report form 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 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 case report forms, informed consents, 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, ISIS 721744 Product Accountability Record, Return of ISIS 721744 Product for Destruction, final ISIS 721744 product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms 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. Should the Investigator 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., case report forms and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case report forms 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 case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, 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 case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, 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 studies 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 ICF.

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A1. Schedule of Procedures - Year 1

	Qual[1]	Treatment Period 1 Fixed Dosing Period				Treatment Period 2 Flexible Dosing Period										Post-Treatment Period
Study Week	**-4 to 1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**65**
Study Day	**-30 to -1**	**1[2]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**308**	**337**	**365**	**449**
Visit Windows (days)	**0**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed Consent	X															
Inclusion/Exclusion	X															
Study Visit	X	X	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X	X[11]	X[11]	X[11]	X	X[11]
Concomitant Medications & Concurrent Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination/ Body Assessment	X	X	X		X			X			X				X	X
12-lead ECG		X			X			X			X				X	X
Inflammatory Panel[5]		X			X			X			X				X	X
Complement[5]		X			X			X			X				X	X
Coagulation[5]	X	X	X		X			X			X				X	X
Chemistry, Hematology[5, 6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration (ISIS 721744)[7]		X	X	X	X	Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks. Option 2: For patients who are attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 80 mg ISIS 721744 every 8 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients are not adequately controlled on 80 mg every 8 weeks then dosing can return to 80 mg ISIS 721744 every 4 weeks. Option 3: For patients who are not attack free for ≥ 12 weeks, after entering this OLE study, the Investigator can ***initiate*** a switch to 100 mg ISIS 721744 every 4 weeks. The switch may begin at any Study Center visit starting at Week 17. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.										
AE-QoL		X			X			X			X				X	X
Angioedema Activity Score[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAE Attack Assessement[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[5]	X	X	X	X	X		X		X		X		X		X	X
Immunogenicity Testing		See Appendix C														
PK Blood Sampling		See Appendix C														
PD Blood Sampling		See Appendix C														
Archived Serum Samples[10]		X	X	X	X		X		X		X		X		X	X

Appendix A1. Schedule of Procedures (Continued)

[1] Patient eligibility for the study should be determined within 30 days prior to study entry. A Qualification Period longer than 30 days may be considered after discussion with the Sponsor Medical Monitor, but the intention is to minimize the treatment pause between the 2 studies (see Protocol Section 6.1.1). Safety clinical laboratory parameters and assessments from ISIS 721744-CS2 may be used for determination of eligibility (as Qualification for ISIS 721744-CS3) if they were obtained within the Qualification Period (i.e., 30 days prior to enrollment in the study or longer if approved by the Sponsor Medical Monitor)

[2] Study Day 1 can be conducted on the same day as ISIS 721744-CS2 Study Visit Week 17 (All procedures are to be completed prior to Study Drug administration). As is operationally feasible, the first dose in this study (ISIS 721744-CS3) should ideally be administered 28 ± 2 days after the last dose in ISIS 721744-CS2

[3] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature

[4] Females of childbearing potential only

[5] For a complete list of laboratory tests refer to Appendix B

[6] 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)

[7] Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member, HHC nurse), may be allowed after dosing instructions and training are provided by qualified site personnel and HHC nurse is available to complete all pre-dosing procedures

[8] The AAS questionnaire will be completed by patients daily (minimum of 4 daily assessments per week) during Treamtent Period 1 and Treatment Period 2. During the Post-Treatment Period, the AAS will only be completed by patients if an HAE attack occurs

[9] During the study patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack

[10] For follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.)

[11] Assessments and procedures to be conducted by either a HHC nurse (if available), or the Study Center as arranged by the Study Center personnel

Appendix A2. Schedule of Procedures – Extended Treatment Period Year 2

	Extended Treatment Period (*Flexible Dosing*)													**Post-Treatment Period**
Study Week	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**105/ET**	**113**
Study Day	**393[11]**	**421[11]**	**449[11]**	**477[11]**	**505[11]**	**533[11]**	**561[11]**	**589[11]**	**617[11]**	**645[11]**	**673[11]**	**701[11]**	**729**	**785[11]**
Visit Windows (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Study Visit[1]			X			X			X				X	X
Concomitant Medications & Concurrent Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight & Vital Signs[2]			X			X			X				X	X
Urine Pregnancy Test[3, 4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination/ Body Assessment													X	
12-lead ECG													X	
Complement[5]						X							X	
Plasma PKK	See Appendix C													
Chemistry, Hematology, Coagulation[5, 6]			X			X			X				X	X
Study Drug Administration (ISIS 721744)[7, 8]	Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks. Option 2: Patients continue 80 mg ISIS 721744 every 8 weeks. If patients are not adequately controlled on 80 mg every 8 weeks then dosing can return to 80 mg ISIS 721744 every 4 weeks. Option 3: Patients continue 100 mg ISIS 721744 every 4 weeks. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.													
Immunogenicity & PK	See Appendix C													
AE-QoL						X							X	
AAS[9] and HAE Attack Assessement[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[5]			X			X			X				X	X

Appendix A2. Schedule of Procedures (Continued)

[1] Procedures, assessments, and confirmation of Study Drug administration to be conducted via telephone contact by qualified site personnel on non-study visit/HHC days
[2] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature
[3] Females of childbearing potential only
[4] Patient to take a home pregnancy test (Ionis to supply) and provide a picture of the stick to the site. Except on site/HHC visit days
[5] For a complete list of laboratory tests refer to Appendix B
[6] 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)
[7] Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member), may be allowed after dosing instructions and training are provided by qualified site personnel. A Home Healthcare professional must be available to complete all pre-dosing procedures prior to Study Drug administration
[8] If the patient is not continuing for another year then no dose will be given at Week 105
[9] The AAS questionnaire will only be completed by patients if an HAE attack occurs
[10] During the study patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack
[11] Assessments and procedures to be conducted by either a HHC nurse (if available), or the Study Center as arranged by the Study Center personnel

Appendix A3. Schedule of Procedures – Extended Treatment Period Year 3

	Extended Treatment Period (*Flexible Dosing*)													**Post-Treatment Period**
Study Week	**109**	**113**	**117**	**121**	**125**	**129**	**133**	**137**	**141**	**145**	**149**	**153**	**157/ET**	**169**
Study Day	**757[11]**	**785[11]**	**813[11]**	**841[11]**	**869[11]**	**897[11]**	**925[11]**	**953[11]**	**981[11]**	**1009[11]**	**1037[11]**	**1065[11]**	**1093**	**1177[11]**
Visit Windows (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Study Visit[1]			X			X			X				X	X
Concomitant Medications & Concurrent Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight & Vital Signs[2]			X			X			X				X	X
Urine Pregnancy Test[3, 4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination/ Body Assessment													X	
12-lead ECG													X	
Complement[5]						X							X	
Plasma PKK	See Appendix C													
Chemistry, Hematology, Coagulation[5, 6]			X			X			X				X	X
Study Drug Administration (ISIS 721744)[7, 8]	Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks. Option 2: Patients continue 80 mg ISIS 721744 every 8 weeks. If patients are not adequately controlled on 80 mg every 8 weeks then dosing can return to 80 mg ISIS 721744 every 4 weeks. Option 3: Patients continue 100 mg ISIS 721744 every 4 weeks. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.													
Immunogenicity & PK	See Appendix C													
AE-QoL						X							X	
AAS[9] and HAE Attack Assessement[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[5]			X			X			X				X	X

Appendix A3. Schedule of Procedures (Continued)

[1] Procedures, assessments, and confirmation of Study Drug administration to be conducted via telephone contact by qualified site personnel on non-study visit/HHC days
[2] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature
[3] Females of childbearing potential only
[4] Patient to take a home pregnancy test (Ionis to supply) and provide a picture of the stick to the site. Except on site/HHC visit days
[5] For a complete list of laboratory tests refer to Appendix B
[6] 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)
[7] Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member), may be allowed after dosing instructions and training are provided by qualified site personnel. A Home Healthcare professional must be available to complete all pre-dosing procedures prior to Study Drug administration
[8] If the patient is not continuing for another year then no dose will be given at Week 157
[9] The AAS questionnaire will only be completed by patients if an HAE attack occurs
[10] During the study patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack
[11] Assessments and procedures to be conducted by either a HHC nurse (if available), or the Study Center as arranged by the Study Center

Appendix A4. Schedule of Procedures – Extended Treatment Period Year 4

	Extended Treatment Period (*Flexible Dosing*)													**Post-Treatment Period**
Study Week	**161**	**165**	**169**	**173**	**177**	**181**	**185**	**189**	**193**	**197**	**201**	**205**	**209/ET**	**221**
Study Day	**1121**	**1149**	**1177**	**1205**	**1233**	**1261**	**1289**	**1317**	**1345**	**1373**	**1401**	**1429**	**1457**	**1541**
Dose Windows (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Study Visit[1]			X			X			X				X	X
Concomitant Medications & Concurrent Procedures	Throughout													
Adverse Events (AEs)	Throughout													
Body Weight & Vital Signs[2]			X			X			X				X	X
Urine Pregnancy Test[3, 4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination/ Body Assessment													X	
12-lead ECG													X	
Complement[5]													X	
Chemistry, Hematology, Coagulation[5, 6]			X			X			X				X	X
Study Drug Administration (ISIS 721744)[7,]	Option 1: Patients continue 80 mg ISIS 721744 every 4 weeks. Option 2: Patients continue 80 mg ISIS 721744 every 8 weeks. If patients are not adequately controlled on 80 mg every 8 weeks then dosing can return to 80 mg ISIS 721744 every 4 weeks. Option 3: Patients continue 100 mg ISIS 721744 every 4 weeks. If patients develop any tolerability or safety issue the dose can be reduced back to 80 mg every 4 weeks.													
AAS[8] and HAE Attack Assessement[9]	Throughout													
Urinalysis[5]			X			X			X				X	X

Appendix A4. Schedule of Procedures (Continued)

[1] Procedures, assessments, and confirmation of Study Drug administration to be conducted via telephone contact by qualified site personnel on non-study visit
[2] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature
[3] Females of childbearing potential only
[4] Patient to take a home pregnancy test (Ionis to supply) and provide a picture of the stick to the site. Except on site visit days
[5] For a complete list of laboratory tests refer to Appendix B
[6] 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)
[7] Self administration of ISIS 721744, or administration by other qualified individuals (e.g., family member), may be allowed after dosing instructions and training are provided by qualified site personnel
[8] The AAS questionnaire will only be completed by patients if an HAE attack occurs
[9] During the study patients will be instructed to report details of any HAE attack, including on-demand treatment, to the study site within 72 hours of the onset of the attack

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.

Chemistry Panel	**Coagulation**	**Hematology**	**Inflammatory**
• 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 • Alkaline phosphatase • Creatine kinase • GGT • eGFR (calculation)	• aPTT (sec)[3] • PT (sec)[3] • INR[3] • Plasmin-antiplasmin complexes[3] • D-dimer **Complement** • C5a • Bb • C4 split products • C4 **Pharmacodynamics Panel[4]** • Plasma prekallikrein (PKK) • Plasma proenzyme activation[3] • Cleaved high molecular weight kininogen (cHK)[3]	• Red blood cells • Hemoglobin • Hematocrit • MCV, MCH, MCHC • Platelets • White blood cells (WBC) • WBC Differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes **Pharmacokinetics[1, 4]** • ISIS 721744 concentration in plasma **Immunogenicity[4]** • Anti-ISIS 721744 antibodies	• hs-CRP[3] **Urinalysis** • Color • Appearance • Specific gravity • pH • Protein/creatinine ratio • Protein • Blood • Ketones • Urobilinogen • Glucose • Bilirubin • Leukocyte esterase • Nitrate • Microscopic examination[2]

[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] These laboratory analytes **will not** be assessed in the Extended Treatment Period (Year 2 and 3 and Year 4 of the OLE)

[4] These laboratory analytes **will not** be assessed in the Extended Treatment Period (Year 2 and 3 and Year 4 of the OLE)

APPENDIX C. IMMUNOGENICITY, PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING SCHEDULE

Appendix C. Immunogenicity, Pharmacokinetic and Pharmacodynamic 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 Treatment and Post-Treatment Periods 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, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation), or to assess other actions of ISIS 721744 with plasma constituents.

Treatment Period 1 and Treatment Period 2

	Treatment Period 1				Treatment Period 2										Post-Treatment Period
Study Week	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**65**
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose		Pre-dose		Pre-dose		Pre-dose		Pre-dose		Pre-dose	Anytime

Extended Treatment Period Year 2

	Extended Treatment													Post-Treatment Period
Study Week	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**	**105**	**113**
Time Point			Pre-dose			Pre-dose			Pre-dose				Pre-dose	Anytime

Extended Treatment Period Year 3

	Extended Treatment													Post-Treatment Period
Study Week	**109**	**113**	**117**	**121**	**125**	**129**	**133**	**137**	**141**	**145**	**149**	**153**	**157**	**169**
Time Point			Pre-dose			Pre-dose			Pre-dose				Pre-dose	Anytime

If administration of ISIS 721744 dose or frequency is adjusted at any visit starting at Week 17, then Immunogenicity, PK, and PD assessments will be collected on the day of the switch prior to the dose, and then in accordance with the Appendix C schedule.

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 and adverse events at the injection site are based on the CTCAE Version 5.0, November 2017 with modifications outlined in the footnotes below.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased'	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs -	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*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

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

Protocol

Version:	1
Version Date:	21 Feb 2023
Title:	Amendment 3: An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema

APPROVALS:

PPD
PPD , 21-Feb-2023 22:26:33 GMT+0000

1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 3.0 (14 Mar 2024), is provided.

Statistical Analysis Plan

ISIS 721744-CS3

An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema (HAE)

Date: 14 March 2024

Version: Final 3.0

STATISTICAL ANALYSIS PLAN SIGNATURE

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court Carlsbad, CA 92010

Compound Name:	721744
Protocol:	ISIS 721744-CS3
Study Title:	An Open-Label Extension Study of ISIS 721744 in Patients with Hereditary Angioedema (HAE)
Issue Date:	14 March 2024

Signature: See electronic signature and date attached at end of document
PPD
PPD
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Signature: See electronic signature and date attached at end of document
PPD
PPD
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Signature: See electronic signature and date attached at end of document
PPD
PPD
Ionis Pharmaceuticals, Inc.

Signature: See electronic signature and date attached at end of document
PPD, MD
PPD
2855 Gazelle Court
Carlsbad, CA 92010

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Changes
1.0	30 Mar 2022	New Document
2.0	22 Feb 2023	• Added Abbreviations • Section 3.1.1.6, modified study day window for visits 53, 65, and 77. • Section 3.1.5, added Year 2 Interim Analysis • Section 3.3.3, specified "HAE" for acute therapy • Section 3.3.8, added a summary for AE-QoL responders
3.0	xx Mar 2024	• Section 3.1.1.4 , clarified the definition of each dosing period • Section 3.1.5 , clarified the interim Analysis as part of the NDA submission • Section 3.7 , clarified the data handling on cHK levels.

ABBREVIATIONS

Abbreviations	Definition
AAS	Angioedema Activity Score
AE(s)	adverse event(s)
AE-QoL	angioedema quality of life
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLQ	below limit of quantification
BUN	blood urea nitrogen
C1-INH	C1-inhibitor
C4	complement factor C4
C5a	complement factor C5a (activated complement split product)
cHK	cleaved high molecular weight kininogen
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
FSH	follicle-stimulating hormone
GCP	Good clinical practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema
HAE-1	hereditary angioedema type I
HAE-2	hereditary angioedema type II
HAE-nC1-INH	hereditary angioedema with normal C1-inhibitor
hs-CRP	C-reactive protein measured by high sensitivity assay
IA	interim analysis
ICH	International Council for Harmonisation
INR	international normalized ratio
ISIS 721744	antisense inhibitor of prekallikrein
ITT	Intent-to-Treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NDA	New Drug Application
OLE	open-label extension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKK	prekallikrein
PP	Per-Protocol
PT	prothrombin time

Abbreviations	Definition
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SE	standard error
Study Day 1	defined as the first day ISIS 721744 is administered to the patient
Study Drug	ISIS 721744
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be viewed as flexible. The statistical analysis to some degree is iterative since so much of the planning is based on statistical and other assumptions, which require verification.

1.1. Study Overview

This is an open-label extension (OLE) study of ISIS 721744 to evaluate the safety and efficacy of extended dosing and alternative dosing and/or dose frequency in patients with hereditary angioedema (HAE). Approximately 24 patients will be enrolled.

The study will consist of a Qualification Period, a Treatment Period and a Post-Treatment Period. The Treatment Period will be comprised of Treatment Period 1 (Fixed Dosing Period), Treatment Period 2 (Flexible Dosing Period Year 1), and an optional Extended Treatment Period (Flexible Dosing Period Year 2 and Year 3). Please refer to the Schedule of Procedures in Protocol 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.

The length of each patient's participation in the study is approximately 68 weeks, which includes an up to 4-week Qualification Period, a 52-week Treatment Period, and a 12-week Post-Treatment Period. Following the Week 53 Treatment Period visit, patients will have the option of receiving ISIS 721744 in an Extended Treatment Period for up to an additional 104 weeks. Patients participating in the Extended Treatment Period will enter the 12-week Post-Treatment Period after completion of, or early termination from, the Extended Treatment Period. During the Treatment Period, ISIS 721744 will be administered as a single 80 mg subcutaneous (SC) injection every 4 weeks or every 8 weeks or a single 100 mg SC injection every 4 weeks as outlined in Protocol Appendix A.

1.2. Objectives

1.2.1. Primary Objective

To evaluate the safety of extended dosing, and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE.

1.2.2. Secondary Objectives

To evaluate the efficacy of extended dosing, and alternative dosing and/or dose frequency with ISIS 721744 in patients with HAE.

1.2.3. Additional/Exploratory Objectives

- To evaluate the effects of ISIS 721744 on plasma PKK levels, plasma proenzyme activation and cleaved high molecular weight kininogen (cHK) levels.
- To evaluate the effects of ISIS 721744 on the clinical and angioedema quality of life (AE-QoL) endpoints.
- To evaluate PK exposure over time.

1.3. Endpoints

1.3.1. Primary Endpoints

Incidence and severity of treatment-emergent adverse events (TEAE).

1.3.2. Secondary Endpoints

Secondary endpoints include the following:

- The time-normalized HAE attacks (monthly) by treatment
- Plasma PKK levels and cHK levels
- Consumption of on-demand medications
- AE-QoL questionnaire score

1.3.3. Safety Endpoints

In addition to incidence and severity of TEAE, the safety endpoints will also include the following:

- Laboratory tests
- Electrocardiograms (ECGs)
- Use of concomitant medications
- Vital signs

2. PROCEDURES

2.1. General Overview of Procedures

Ionis Pharmaceuticals, Inc. will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Laboratory data will be transferred electronically to Ionis Pharmaceuticals, Inc.

2.2. Randomization & Treatment Allocation

Patients won't be randomized. All patients will receive open-label SC injections of ISIS 721744.

2.3. Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4. Data Monitoring

2.4.1. Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (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 Pharmaceuticals, Inc. (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 Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to study site.

2.5. Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

2.5.1. Case Report Form Data

BioClinica (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. (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 Pharmaceuticals, Inc. 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.

2.5.2. Laboratory Data

Ionis Pharmaceuticals, Inc. (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).

2.5.3. Plasma PKK, Plasma Proenzyme Activation, and Cleaved High Molecular Weight Kininogen (cHK) Data

PPD is contracted and responsible for analyzing plasma PKK. Carroucell is contracted and responsible for analyzing plasma proenzyme activation. University of California San Diego is contracted and responsible for analyzing cHK. Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma PKK, plasma proenzyme activation, and cHK data. Final data, which has been approved by Quality Assurance, will be stored in a version-controlled repository.

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

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

3. ANALYTICAL PLAN

3.1. General Overview of Analyses

3.1.1. Statistical Methods

Descriptive summary statistics including number of patients, mean, median, standard deviation, 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.

Only central lab data will be used in by visit summaries and figures. Local lab data will only be used for baseline derivation and abnormality summary as specified in Section 3.4.3. Local lab data will be displayed in a separate listing apart from central lab data.

The summary tables for ISIS 721744-CS3 data will be presented by the index study ISIS 721744-CS2 treatment group and overall for HAE-1/HAE-2, as well as overall for HAE-nC1-INH. Data will be summarized for each of the following periods (as defined in Section 3.1.1.4):

- During the entire on-treatment period DY1 within ISIS 721744-CS3
- During the entire on-treatment period WK5 within ISIS 721744-CS3
- During the Fixed Dosing Period DY1 within ISIS 721744-CS3
- During the Fixed Dosing Period WK5 within ISIS 721744-CS3

The data within the flexible dosing period will be summarized by dose options (i.e., ISIS 721744 80 mg every 4 weeks as option 1, ISIS 721744 80 mg every 8 weeks as option 2, ISIS 721744 100 mg every 4 weeks as option 3). Data will be summarized for each of the following periods (as defined in Section 3.1.1.4):

- During the Flexible Dosing Period Year 1 within ISIS 721744-CS3
- During the Flexible Dosing Period Year 1+2 within ISIS 721744-CS3
- During the Flexible Dosing Period within ISIS 721744-CS3

For patients who switch between option 1 and option 3, each option interval starts from the first dose of the current option to the second before the first dose of the next option, except the last interval starts from the first dose of the current option until the end of on-treatment period (as defined in Section 3.1.1.4).

For patients who switch between option 1 and option 2, the option 1 interval starts from the first dose of the current interval to the last dose of the current interval + 28 days. The option 2 interval starts from the day that patients skip the dose (i.e., 1 second after the end of the option 1 interval) to the second before the first day of switching back to option 1, or to the end of on-treatment period (as defined in Section 3.1.1.4) if the patients do not switch back to option 1.

The summary tables for ISIS 721744-CS2 and ISIS 721744-CS3 integrated data will be presented by HAE type, HAE-1/HAE-2 and HAE-nC1-INH. Data will be summarized for each of the following periods (as defined in Section 3.1.1.4):

- During Integrated Treatment Period DY1
- During Integrated Treatment Period WK5

PK parameters will be summarized using number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, geometric %CV, median, minimum, and maximum.

3.1.1.1. General Presentation Considerations

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 standard deviation 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 any summary statistic.

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 text and the data displays.

Percentages will be presented to one decimal place and not be presented for zero counts. Percentages will be calculated using n as the denominator.

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

3.1.1.2. Study Day Definition

For analysis of OLE study only, Study Day will be calculated relative to the date of first dose in ISIS 721744-CS3, i.e., CS3 Study Day = Assessment Date - Date of CS3 first dose + 1.
CS3 Study Day 1 is the first dose date in the OLE study. If the assessment date is prior to the

first dose date of CS3, Study Day will be calculated as CS3 Study Day = Assessment Date - Date of CS3 first dose.

For ISIS 721744-CS2 and ISIS 721744-CS3 integrated analysis, Study Day will be calculated relative to the date of first dose in ISIS 721744-CS2, i.e., CS2 Study Day = Assessment Date – Date of CS2 first dose + 1. CS2 Study Day 1 is the first dose date in the index study. If the assessment date is prior to the first dose date of CS2, Study Day will be calculated as CS2 Study Day = Assessment - Date of CS2 first dose.

3.1.1.3. Baseline Definition

The CS2-on-treatment baseline will be used in the analysis for HAE attack rate. It is defined as the HAE attack rate from Week 1 to the end of on-treatment period of the index study.

The OLE baseline will be used for all analyses. It is defined as the following:

- For HAE attacks, the OLE baseline is defined as the HAE attack rate within 8 weeks, (including the attacks that occurred during the index study) prior to the first dose of the OLE study. It will be calculated for each patient as the number of HAE attacks occurring during the 8-week period divided by 56 days multiplied by 28 days.
- For platelets, the OLE baseline is defined as the average of all non-missing pre-dose assessments within 4 weeks (including the assessments in the index study) prior to the first dose of the OLE study.
- For Angioedema Activity Score (AAS) 4-week sum score (AAS28), the OLE baseline is calculated for each subject by summing up all AAS measurements occurred prior to the first dose of the OLE study up to study day -28, divided by the number of days the subject contributed to this period multiplied by 28 days.
- For other assessments, the OLE baseline is defined as the average of the Day 1 pre-dose assessment and the last measurement (including the assessments in the index study) prior to the first dose of the OLE study. If there is only 1 pre-dose measurement available, this measurement will be assigned as the OLE Baseline.

The CS2-run-in baseline is defined as the baseline being defined in the index study. It may be used as an additional baseline when integrating data from the index study.

3.1.1.4. On-treatment and Post-treatment Periods of the OLE study

The on-treatment period spans the time during which the study treatment is administered until 28 days after the last dose of medication for patients who are dosed every 4 weeks, or 56 days after the last dose of medication of the study for patients who are dosed every 8 weeks. When date and time are both collected in the database, datetime will be used in defining an analysis period. Otherwise, only date part will be used.

- OLE Study Day 1 is defined as the date of first study medication administered in the OLE study.
- OLE Study Week 5 is defined as 28 days after the OLE Study Day 1.

- On-treatment period DY1 is defined as from OLE Study Day 1 to 28 days after the last dose of medication of the study, or the last date of lost to follow-up, whichever happens first.
- On-treatment period WK5 is defined as from OLE Study Week 5 to 28 days after the last dose of medication of the study for patients who are dosed every 4 weeks, or 56 days after the last dose of medication of the study for patients who are dosed every 8 weeks, or the last date of lost to follow-up, whichever happens first.
- Fixed Dosing Period DY1 is defined as from OLE study Day 1 to the earliest date of the following: the day before the Week 17 dose for patients who are dosed at Week 17, or 28 days after the 4th dose for patients who skip dosing at Week 17, or 28 days after the last dose date if the patient terminates treatment before the 4th dose, or the last date of lost to follow-up, whichever happens first.
- Fixed Dosing Period WK5 is defined as from OLE study Week 5 to the earliest date of the following: the day before the Week 17 dose for patients who are dosed at Week 17, or 28 days after the 4th dose for patients who skip dosing at Week 17, or 28 days after the last dose date if the patient terminates treatment before the 4th dose, or the last date of lost to follow-up, whichever happens first.
- Flexible Dosing Period is defined as from the first date of the 5th dose for patients who are dosed at Week 17 or 28 days after the 4th dose for patients who skip dosing at Week 17, to the end of the On-treatment period.
- Flexible Dosing Period Year 1 is defined as from the first date of the 5th dose for patients who are dosed at Week 17 or 28 days after the 4th dose for patients who skip dosing at Week 17, to 28 days after the dose on or before the one-yearend, or 28 days after the last dose date if the patient terminates treatment before the one-yearend, or the last date of lost to follow-up, whichever happens first. The one-yearend is defined as the visit date of Study Week 53. This analysis period will be used in the Year 1 Interim Analysis (IA).
- Flexible Dosing Period Year 1+2 is defined similarly as mentioned above. The two-yearend is defined as the visit date of Study Week 105. This analysis period will be used in the Year 2 IA.
- Flexible Dosing Period Year 1+2+3 is defined as from the first date of the 5th dose for patients who are dosed at Week 17 or 28 days after the 4th dose for patients who skip dosing at Week 17, to the data cutoff point for Year 1+2+3, which is based on the final patient's first Year 4 visit (Week 161/Day 1121). This analysis period may be used in a Year 3 IA.

The post-treatment period of the OLE study starts on the day after the on-treatment period and ends on the day of the patient's last contact date.

3.1.1.5. Period for Integrated Analyses Including both the Index and the OLE Study

For patients who received ISIS 721744 in the index study, an integrated analysis of HAE attack rate will also be done by including data in the index study and the OLE study.

- Integrated Treatment Period DY1 is defined as from first study medication administered in the index study to the end of the on-treatment period of the OLE study, or last date of lost to follow-up, whichever happens first.
- Integrated Treatment Period WK5 is defined as from 28 days after the index Study Day 1, to the end of the on-treatment period of the OLE study, or last date of lost to follow-up, whichever happens first.

3.1.1.6. Analytical Visits

PD (PKK, and plasma proenzyme activation) and AE-QoL data 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 week can be integrated to best represent the patient's status during that period of the study. 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.

Assessments	Mapped Visit (Week)	Target Day	Study Day Window
PKK and plasma proenzyme activation (in which PPA will only be performed during Year 1)	5	29	2-43
	9	57	44-71
	13	85	72-113
	21	141	114-169
	29	197	170-225
	37	253	226-281
	45	308	282-337
	53	365	338-407
	65	449	408-491
	77	533	492-575
	89	617	576-673
	105	729	674-771
	117	813	772-855
	129	897	856-939
	141	981	940-1037
	157	1093	1038-1135

Assessments	Mapped Visit (Week)	Target Day	Study Day Window
AE-QoL	13	85	2-127
	25	169	128-211
	37	253	212-309
	53	365	310-407
	77	533	492-631
	105	729	632-813
	129	897	814-995
	157	1093	996-1180

Other data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged. Results with visit labels as "Unscheduled" will not be included in the by-visit summary tables and figures except for determining baseline and laboratory abnormality summaries but will be presented in data listings.

3.1.2. Subject Population Analyzed

The following analysis populations will be used for the analysis of data as described within each analysis population.

Safety Population

The Safety Population will include all enrolled patients who receive at least 1 dose in the OLE study.

Intent-to-Treat (ITT) Population

The ITT Population will include all enrolled patients in the OLE study.

Per Protocol Population

The Per-Protocol (PP) Population will include all patients in the ITT Population who are treated according to the protocol with no major protocol deviations that could compromise the interpretation of efficacy. Major protocol deviations that could compromise the interpretation of efficacy will be determined prior to the database lock.

PK Population

The PK Population will include all patients who are enrolled and receive at least 1 dose of Study Drug (ISIS 721744) and have at least 1 evaluable PK sample.

3.1.3. 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 listed and summarized by deviation category.

Protocol deviations will be classified to major or minor based on the study protocol deviation process plan. Protocol deviations will be provided in the data listings. Additional table may be provided to summarize the 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 subject number identifier and by investigational site, and a description of how the individual's participation was altered will be provided.

3.1.4. Sample Size Consideration

The sample size is dictated by the number of patients enrolled in the index study (ISIS 721744-CS2).

3.1.5. Planned Interim Analysis (IA)

One (1) or more interim analyses may be performed to support ISIS 721744 drug development and New Drug Application (NDA) submission.

The sponsor recognizes the importance of confidentiality of interim results before the index study is unblinded. To minimize any potential risk to the integrity of the study, the first interim analysis will be conducted only after the database of the index study is locked and unblinded.

Once all patients have been enrolled in this OLE study and have completed one year of study drug administration, a Year 1 interim analysis (IA) is planned to be performed.

For Year 1 IA, data cutoff point will be 28 days after the last dose of one year treatment. Summaries of pre-defined efficacy and PD endpoints, including HAE attack rate related endpoints and plasma PKK level, safety endpoints including AEs and clinical laboratory assessments as well as subject disposition and demographics will be included in the Year 1 IA.

A Year 2 IA is planned to be performed after all patients completing two years of study drug administration. This IA will include the same summaries as the Year 1 IA. The data cutoff point will be 28 days after the last dose of 2-year treatment. Summaries for the Flexible Dosing Period Year 1+2 will be included in the Year 2 IA. Summaries for the Flexible Dosing Period Year 1, which has been provided in the Year 1 IA, will not be repeated.

A Year 3 IA is planned to be performed to support the NDA submission. The data cutoff point will be based on the final patient's first Year 4 visit (Week 161/Day 1121). Summaries for all data collected by this fixed data cutoff point be included in the Year 3 IA. Summaries for the Flexible Dosing Period Year 1 and Year 1+2, which have been provided in the Year 1 and Year 2 IAs, will not be repeated.

3.1.6. Incomplete or Missing Data

Missing values will not be imputed unless otherwise specified.

For HAE attack, all patients who discontinued the treatment period early and were lost to follow-up, will have the time-adjusted attack rate included in the analysis.

All analyses and summaries by visits will be performed based on analytical visits defined in Section 3.1.1.6.

3.1.7. 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 Qualification, 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 as 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 an 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. 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 two 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.

3.2. Demographic and Baseline Characteristics and Patient Disposition

Demographic and baseline characteristics will be summarized descriptively by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH, and for each analysis population.

Demographic and baseline characteristics to be presented include age, age category (18 to 39, 40 to 64, ≥ 65 years), gender, race, ethnicity, height, weight, and BMI.

For race summary, if multiple races are recorded in database, ‘Multiple Race’ will be used in the summary table but details records in the listing.

A separate table will be created for HAE history collected in the index study and will include family history of HAE, age at onset of angioedema symptoms, HAE type, type of attack(s) experienced, lanadelumab use, reason for discontinuation of lanadelumab, number of attacks in the last 12 months.

Baseline HAE attack rate (attacks/4 weeks) and baseline HAE attack rate group (1 to < 2 , 2 to < 3, ≥ 3 attacks/4 weeks) will also be summarized, including CS2-run-in Baseline; CS2 on-treatment Baseline; OLE baseline, which are defined in Section 3.1.1.3.

AEs that occurred during the index study will be reported as medical history in the OLE study.

Medical history in the OLE study will be provided in the data listings.

Subject enrollment and disposition will be summarized for all enrolled patients by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH.

The summaries will include: the number of patients enrolled/dosed, the number of patients in each analysis population, the number of patients completing treatment, the primary reason for terminating treatment, the number of patients completing post-treatment follow-up, and the primary reason for terminating post-treatment follow-up. Additionally, the number and percentage of subjects who terminated from treatment and study due to COVID-19 related impact will also be summarized.

3.3. Efficacy Analyses

All efficacy analyses for the OLE study will be performed on the ITT population and Per-protocol population. All efficacy analyses integrating ISIS 721744-CS2 (index study) and the OLE study will be performed on the ITT population.

3.3.1. Time-normalized Number of Investigator-confirmed HAE Attacks

The investigator-confirmed HAE attack rates as well as the changes and the percent changes from baseline during the on-treatment period and Fixed Dosing Period will be summarized using the descriptive statistics by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. The investigator-confirmed HAE attack rate will be calculated for each patient as the number of HAE attacks occurring during the on-treatment period divided by number of days the patient contributed to the period multiplied by 28 days.

For on-treatment period and Fixed Dosing Period, 3 sets of analysis will be performed. For the first set of analysis, the CS2-on-treatment baseline will be used to derive change and percent change from baseline, regardless of which study drug the patients took in the index study. For the second set of analysis, patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline to derive change and percent change from baseline. For the third set of analysis, all patients will use CS2-run-in baseline.

Summaries for all analysis periods during the Flexible Dosing Period will only be summarized by dose options, using CS2-run-in baseline for patients who took active drug in the index study and OLE baseline for patients who took placebo in the index study. The analysis will be repeated using CS2-run-in baseline for all patients. This analysis will also be repeated using the fixed dosing period HAE attack rate as the baseline.

Listing(s) of individual patient attack rate during the on-treatment period, Fixed Dosing Period, Flexible Dosing Period, and for each dose option will also be generated.

For patients who received ISIS 721744 in the index study, an integrated analysis of HAE attack rates will also be done by including data in the index study. CS2-run-in baseline will be used for derivation of change and percent change from baseline. The time-normalized investigator-confirmed HAE attack rate for each patient will be calculated as the number of HAE attacks occurring from first dose of the index study to the end of treatment period in the OLE study divided by number of days in the period multiplied by 28 days. The data will be presented by HAE type (HAE-1/HAE-2 and HAE-nC1-INH). Additionally, data will be summarized during the integrated treatment period DY1 and WK5 respectively as specified in Section 3.1.1.4.

3.3.2. Time-normalized Number of Moderate or Severe Investigator-confirmed HAE Attacks

The endpoint will be summarized using the same method as described in Section 3.3.1 for investigator-confirmed HAE attack rates.

3.3.3. Time-normalized Number of Investigator-confirmed HAE Attacks Requiring Acute HAE Therapy

The endpoint will be summarized using the same method as described in Section 3.3.1 for investigator-confirmed HAE attack rates. HAE attacks requiring acute HAE 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)

3.3.4. Response Rate Analysis

The number and percentage of patients who achieve 50%, 70%, 90% reduction from baseline in the HAE attack rate during the OLE study by the end of on-treatment period WK5 will be tabulated based on the ITT population. Data within the on-treatment period WK5 will be summarized by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH.

When summarizing under on-treatment period WK5, patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of reduction from baseline.

For patients who received ISIS 721744 in the index study, an integrated analysis of responders will also be performed based on the ITT population. CS2-run-in baseline will be used for derivation of reduction from baseline. Data during Integrated Treatment Period starting from WK5 will be summarized by HAE type (HAE-1/HAE-2 and HAE-nC1-INH).

Patients who discontinued treatment early will have their termination reasons reviewed by the clinical team. Patients whose termination reasons are classified as lack of efficacy or clinically significant AEs that are considered as at least possibly study drug related by PI and clinical team review will be considered as non-responders.

3.3.5. HAE Attack Free Analysis

The number and percentage of Investigator-confirmed HAE attack free patients by the end of on-treatment period WK5 will be tabulated. Data within the on-treatment period WK5 will be summarized by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH.

When summarizing under on-treatment period WK5, patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation.

For patients who received ISIS 721744 in the index study, an integrated analysis of Investigator-confirmed HAE attack free patients will also be performed based on ITT population. CS2-run-in baseline will be used for derivation. Data during Integrated Treatment Period starting from WK5 will be summarized by HAE type (HAE-1/HAE-2 and HAE-nC1-INH).

Additional endpoints for Investigator-confirmed HAE attack free patients as listed below will be summarized in the same way as above:

- Percentage of total days that patients are Investigator-confirmed HAE attack free
- Percentage of total months that patients are Investigator-confirmed HAE attack free
- Duration in days of the longest Investigator-confirmed HAE attack free interval
- Percent of patients that are Investigator-confirmed HAE attack free for 6 or 12 months
- Mean/median longest Investigator-confirmed HAE attack free interval

3.3.6. Change and Percent Change in Plasma Prekallikrein (PKK) Levels, and Plasma Proenzyme Activation

Plasma prekallikrein (PKK) levels and plasma proenzyme activation as well as the change and percent changes from baseline over time within the on-treatment period DY1 will be summarized using descriptive statistics by visit, the index study treatment group and overall for HAE-1/ HAE-2, overall for HAE-nC1-INH. Data within the Flexible Dosing Period will be summarized by dose options as specified in Section 3.1.1.

When summarizing under on-treatment period DY1 and any analysis period during the Flexible Dosing Period, patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

For patients who received ISIS 721744 in the index study, integrated summaries of plasma proenzyme activation and plasma PKK levels as well as the changes and percent changes from baseline from index study to the end of treatment period in the OLE study will be generated.

CS2-run-in baseline will be used for derivation. The summaries will be based on the visits defined in the individual study and presented by HAE type (HAE-1/HAE-2 and HAE-nC1-INH).

3.3.7. Consumption of On-demand Medication

The number and percentage of patients who used on-demand medication during the on-treatment period, Fixed Dosing Period, and Flexible Dosing Period will be tabulated. Data within the on-treatment period DY1/WK 5 and within Fixed Dosing Period starting from Day 1/Week 5 will be summarized by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. Data within the Flexible Dosing Period will be summarized by dose options as specified in Section 3.1.1.

On-demand medications include the following concomitant medications:

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

3.3.8. AE-QoL score

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. The first answer option gets 0 points, the second option 1 point, the third option 2 points, etc. The AE-QoL domain scores and total score are calculated by using the following formula:

(Sum of all completed items) / (maximum sum 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.

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

The AE-QoL total score and domain scores as well as change and percent change from baseline within the on-treatment period DY1 will be summarized using the descriptive statistics by visit, the index study treatment group overall for HAE-1/HAE-2, and overall for HAE-nC1-INH. Data within the Flexible Dosing Period will be summarized by dose options as specified in Section 3.1.1.

In addition, a responder summary will be performed for the AE-QoL total score. A clinical response is defined as at least 6-point improvement from baseline in AE-QoL total score, i.e., Post-baseline – Baseline ≤ -6. Number and percentage of responder at Week 53, Week 105, and Week 157 will be summarized by treatment group. The percentage will be calculated based on the number of patients with available data at each visit.

When summarizing under on-treatment period DY1 and any analysis period during the Flexible Dosing Period, patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

For patients who received ISIS 721744 in the index study, integrated summaries of AE-QoL total score and domain scores as well as change and percent change from baseline from index study to the end of treatment period in the OLE study will be generated. CS2-run-in baseline will be used for derivation. The summaries will be based on the visits defined in the individual study.

3.4. Safety Analyses

Safety analyses will be performed on the safety population.

3.4.1. Exposure

When summarizing under on-treatment period, duration of Study Drug exposure in days, total number of injections, number of injections for each dose option, and amount of Study Drug will be listed and summarized by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. When summarizing under flexible dosing periods, treatment duration, total number of injections and amount of Study Drug will be summarized by dose option.

Duration of Study Drug exposure (days): Duration will be derived as the difference between the date of the last dose of study drug and the date of the first dose plus 28 days.

3.4.2. Adverse Events

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of ISIS 721744 in the OLE study and subsequently worsens, or is not present prior to receiving the first dose of ISIS 721744 but subsequently appears.

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. These linked events will be identified based on "Formlink" dataset and compared pairwise, and consider 2 cases, where the AE severity (mild/moderate/severe) are compared between the 2 records in the pair.

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.

When counting the total number of treatment-emergent events, events linked together through change in severity will still be counted as separate events.

When summarizing treatment-emergent adverse events (TEAEs) by study period, the start date of a TEAE will be used to determine which period it occurs in. If a TEAE starts in Fixed Dosing Period, the TEAE will be counted under Fixed Dosing Period. The same goes for Flexible Dosing Period Year 1/Year 1+2/Year 1+2+3.

When summarizing TEAEs in Flexible Dosing Period, a TEAE may span over multiple dosing option periods:

- If an TEAE starts in one dosing option (e.g., option 1) but ends in another dosing option (e.g. option 2), the AE will be counted under the dosing option it starts in (e.g., option 1);
- If an TEAE starts in one dosing option (e.g., option 1) but ends in another dosing option (e.g., option 2), then the same AE starts again in the same option (e.g., option 2), the AEs should be counted once both under the options they start in (e.g., option 1, option2);
- If an TEAE starts in one dosing option (e.g., option 1) but ends in another dosing option (e.g., option 2), then the same AE starts again after the patient switch back the dosing option again (e.g., option 1), the AEs should be treated as 2 separate AEs and both should be counted under the dosing option they start in (e.g., option 1).

All TEAEs identified based on the rules above will be summarized in the event number analysis. All TEAEs and TEAEs that occurred during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. On the other hand, TEAEs that occurred during the Flexible Dosing Period will be summarized by dose option. These apply to the summaries listed in later paragraph as well.

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 Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class for:

- An overview of all TEAEs including maximum severity, potentially related to ISIS 721744, SAEs, TEAEs leading to withdrawal from ISIS 721744, TEAEs leading to death, and AESIs (adverse event of special interests) will be summarized.
- Any treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as "Related", "Possible", or missing relationship to study drug
- Any treatment emergent adverse events 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. Adverse events with missing severity will categorized as "Missing" for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

AEs that lead to study discontinuation or investigational drug discontinuation will be listed. Non-treatment emergent adverse event will be flagged in the data listing.

Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe adverse events with the preferred terms (PTs) 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 due to AE at the injection site will be summarized separately. All LCRIS and LCRIS occurred during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. On the other hand, LCRIS that occurred during the Flexible Dosing Period will be summarized by dose option.

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 all injections leading to LCRIS and such injections during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. On the other hand, percentage of

injections leading to LCRIS that occurred during the Flexible Dosing Period will be summarized by dose option.

Percentage of injections leading to LCRIS at the injection site 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 also be listed.

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 preferred term and by treatment group. All flu-like reactions that occurred during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/ HAE-2, overall for HAE-nC1-INH. On the other hand, flu-like reactions that occurred during the Flexible Dosing Period will be summarized by dose option.

Percentage of injections leading to flu-like reactions will be summarized by treatment group and by Part using the descriptive statistics. Percentage of all injections leading to flu-like reactions and such injections that occurred during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. On the other hand, percentage of injections leading to flu-like reactions that occurred during the Flexible Dosing Period will be summarized by dose option.

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.

Bleeding Adverse Events

Bleeding AEs will be identified based on the Haemorrhages (SMQ) Export from MedDRA and summarized by MedDRA system organ class and preferred term. All bleeding AEs that occurred during the Fixed Dosing Period DY1 will be summarized separately by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. On the other hand, bleeding AEs that occurred during the Flexible Dosing Period will be summarized by dose option.

3.4.3. Laboratory Measurements

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, uric acid, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, ALT, AST, alkaline phosphatase, creatinine kinase, GGT

- Hematology: red blood cells, hemoglobin, hematocrit, platelets, MCV, MCH, MCHC, white blood cells, and WBC differential (percentage and absolute count) (basophils, eosinophils, lymphocytes, monocytes and neutrophils)
- Coagulation: aPTT (sec): PT (sec), INR, Plasmin-antiplasmin complexes, D-dimer
- Complement: Bb, C5a, C4 split products
- Inflammatory: Hs-CRP
- Urinalysis (other): color, appearance, specific gravity, pH, P/C ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrate, microscopic examination. The data will only be displayed in subject 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 subject 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, Q1, Q3, minimum, and maximum) by visit, the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH. Patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

For ALT and AST, the number and percent of patients falling in each of the following categories based on results after the first dose of the OLE study will be tabulated by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH:

- ALT/AST > 3 x ULN
- ALT/AST > 5 x ULN

For platelet, the number and percentage of patients falling in each of the following categories based on results after the first dose of the OLE study will be tabulated by treatment group for 100,000/mm^3 to < 140,000/mm^3, 75,000 to < 100,000/mm^3, 50,000 to < 75,000/mm^3, 25,000 to < 50,000/mm^3, 0 to < 25,000/mm^3.

The abnormality summaries for ALT, AST and platelet will be repeated using confirmed values. 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.

3.4.4. Vital Signs, Weight, and BMI

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, Q1, Q3, minimum, and maximum) for vital sign values, weight, and BMI as well as the change and percent change from baseline at each study visits. Patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

3.4.5. Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as adverse events. All physical examination data will be provided in a data listing.

3.4.6. 12-Lead Electrocardiograms (ECG)

The ECG data will include Ventricular Rate, PR 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, 25^{th} percentile, 75^{th} percentile, minimum and maximum) of the results at each study 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. Patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

All the safety ECG data collected will be listed.

3.4.7. Prior and Concomitant Medications

Prior medications include medications started prior to the first dose of ISIS 721744 in the OLE study regardless of whether continued while on treatment or not. Concomitant medications include medications that patients are exposed to on or after the first dose of ISIS 721744 in the OLE study.

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 the date of first dose of ISIS 721744
- If month and day are missing and year is:
  - earlier than the year of the first dose of ISIS 721744 then assign December 31
  - otherwise, assign January 1
- If only day is missing and month-year is:
  - earlier than the month-year of the first dose of ISIS 721744 then assign the last day of the month
  - otherwise, assign 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.

Prior and concomitant medications will be coded using WHO Drug dictionary and summarized by ATC class, preferred name and by index study treatment group and overall for HAE-1/ HAE-2, overall for HAE-nC1-INH.

3.4.8. Angioedema Activity Score

The AAS consists of 5 questions as well as an opening question. A score between 0 and 3 is assigned to every answer field. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28). Accordingly, the minimum and maximum possible AAS scores are 0-15 (AAS day sum score), 0-105 (AAS7), and 0-420 (AAS28). Missing scores will be imputed using the LOCF method.

The opening question may be used to count the number of angioedema affected days during the AAS documentation period but has no score.

The AAS scores will be listed. The AAS 4-week sum score as well as change and percent change from baseline will also be summarized by the index study treatment group and overall for HAE-1/HAE-2, overall for HAE-nC1-INH over time. Patients who took active drug in the index study will use CS2-run-in baseline and patients who took placebo in the index study will use OLE baseline for derivation of change and percent change from baseline.

3.5. Pharmacokinetic Analysis

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 SC dosing) will be listed for each evaluable patient by treatment, actual dose, cohort, dosing option when applicable (option 1, 2 or 3), 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 concentrations will be summarized using descriptive statistics by treatment, dose, cohort, dosing option when applicable (option 1, 2 or 3), study day, and scheduled time point, without and with stratification by subject ADA status overall. For the purpose of calculating typical summary descriptive statistics (n, mean, SD, SE, %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, SE, %CV, and geometric %CV will be reported as not applicable. Other stratifications (for example fixed and flexible dosing period) 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 and PK/PD analysis may be performed using the PK and PD data from this study, and/or combined with other clinical study data and reported separately.

3.6. Immunogenicity (IM) Analysis

Samples collected for IM assessment during treatment and post-treatment follow-up period including early termination samples will be analyzed for anti-ISIS 721744 antibodies (ADA). The IM data analysis may be presented from the combined dataset of the ISIS 721744 CS2 and ISIS 721744 CS3 studies.

3.6.1. 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 [CS2]) (sample ADA status) will be listed by treatment, dose, dosing option when applicable (option 1, 2 or 3), 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, dosing option when applicable (option 1, 2 or 3) 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, dosing option when applicable (option 1, 2 or 3) and cohort. These results may be presented stratified by CS2 and CS3 study and combined CS2+CS3 study as deemed appropriate.

3.6.2. 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 (from CS2 or CS3) as described below (Shankar *et al.* 2014):

- 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. For patients on donidalorsen treatment in the index study (ISIS 721744 CS2), the baseline IM value in the CS3 study will be inputted from their baseline values in the ISIS 721744 CS2 study.
- 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. This may be from the CS2 study, if applicable.

- 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. This may be from the CS2 study, if applicable.
- 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. This may be presented as without and with CS2 and CS3 stratification as well as their combined results.
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the subject. This may be presented as without and with CS2 and CS3 stratification as well as their combined results.

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. Data from CS2 and CS3 may be combined for the presentation of these results as well. Transient and persistent ADA definitions are defined below and based on (Shankar *et al.* 2014):

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 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 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, dosing option when applicable (option 1, 2 or 3) and cohort. Subject level IM parameters (as described above) will be listed by treatment, dose, dosing option when applicable (option 1, 2 or 3) and cohort for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment, dose, dosing option when applicable (option 1, 2 or 3) and cohort. Other stratifications and summarization may also be conducted (for example fixed vs. flexible dosing period) if deemed appropriate.

3.6.3. 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 overall, 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.

3.7. Changes in the Conduct of the Study or Planned Analysis

Cleaved high molecular weight kininogen (cHK) levels was defined as one of the secondary endpoints in the protocol. The Sponsor engaged the services of a third-party laboratory (UCSD) to conduct the assay. However, challenges arose during the study regarding the quality of sample analysis conducted at the lab. Given that this assay is non-commercial and has limitations on who can perform the analysis, the Sponsor has opted not to proceed with this endpoint.

REFERENCES

Shankar, G., Arkin, S., Cocea, L., … Yim, S. (2014). Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *Aaps j*, **16**, 658–73.

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