A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{Rx}, an Antisense Inhibitor Administered Subcutaneously to Hypertensive Subjects With Controlled Blood Pressure

NCT03714776

14-November-2019

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

Official Title:	A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure
NCT Number:	NCT03714776
Document Date:	Protocol Amendment 1: 29 March 2019

1. STUDY INFORMATION

1.1. Protocol and Protocol Amendments

The protocol was amended once. The latest version of the protocol (Protocol Amendment 1) is provided along with the change summary for the revision.

Protocol Version	Date	Document Provided
Original	22 August 2018	None
Protocol Amendment 1	29 March 2019	Protocol and change summary
Note to File	26 November 2018	757456-CS2 Day 3 and Day 8 Visit Window Clarification

IONIS PHARMACEUTICALS, INC.

ISIS 757456-CS2

A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-LRX, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure

Protocol Amendment 1 – 29 March 2019

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

ISIS 757456-CS2

Protocol Amendment 1

Clinical Phase: 2

A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure

Protocol History:

Original Protocol: 22 August 2018

Trial Sponsor: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Phone: 760-931-9200
Fax: [redacted]

Key Sponsor Contact: [redacted]
[redacted]
2855 Gazelle Court
Carlsbad, CA 92010
Phone: [redacted]
Fax: [redacted]

Date: 29 March 2019

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 757456-CS2

Protocol Title: A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure

Amendment: Amendment 1

Date: 29 March 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure," dated 29 March 2019, and agree to conduct the study as described herein.

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

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 757456-CS2
Protocol Title: A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-LRx, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure
Amendment Number: 1
Amendment Date: 29 March 2019

The following modifications to Protocol ISIS 757456-CS2, have been made.

The main purpose of this amendment is to incorporate FDA suggestions and further detail safety monitoring and stopping rules for platelets, renal parameters, potassium and blood pressure. Additionally, the inclusion criteria for BMI, age and beta blocker use have been updated to better access the mild hypertension population.

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 major changes to the protocol (deletions from *Was* are underlined; additions in the *Now is* are in bold font):

Protocol Section	Description of Change	Rationale
Synopsis: Inclusion Criteria in Study Population Section 5 1 Inclusion Criteria	Was: 2 Males or females aged 18-65 inclusive and weighing ≥ 50 kg at the time of informed consent Now Is: 2 Males or females aged 18-72 inclusive and weighing ≥ 50 kg at the time of informed consent	Updated to access the mild hypertension population
Synopsis: Inclusion Criteria in Study Population Section 5 1 Inclusion Criteria	Was: 5 BMI ≤ 32 0 kg/m^2 Now Is: 5 BMI ≤ 35 0 kg/m^2	Updated to access the mild hypertension population

Protocol Section	Description of Change	Rationale
Synopsis: Inclusion Criteria in Study Population Section 5 1 Inclusion Criteria	Was: 9 At Screening, the subject must have been on a stable regimen of antihypertensive medications … in the following categories: a beta blocker (≤ 25 mg per day), a calcium channel blocker or non-potassium sparing diuretic medication Now Is: 9 At Screening, the subject must have been on a stable regimen of antihypertensive medications … in the following categories: a beta blocker **i. acebutolol (≤ 400 mg q.d.)** **ii. atenolol (≤ 50 mg q.d.)** **iii. betaxolol (≤ 10 mg q.d.)** **iv. bisoprolol (≤ 5 mg q.d.)** **v. carvedilol (≤ 25 mg b.i.d.)** **vi. labetalol (≤ 200 mg b.i.d.)** **vii. metoprolol (≤ 100 mg q.d.)** **viii. nadolol (≤ 40 mg q.d.)** **ix. nebivolol (≤ 10 mg q.d.)** **x. propranolol (≤ 120 mg q.d.)** **xi. pindolol (≤ 5 mg b.i.d.),** b calcium channel blocker or c diuretic	Beta blocker usage at screening was updated to better access the mild hypertension population
Synopsis: Inclusion Criteria in Study Population Section 5 1 Inclusion Criteria	Now Is: **16. Agree to abstain from smoking, exercise and caffeine use 30 minutes prior to blood pressure measurements.**	Included per FDA suggestion
Synopsis: Exclusion Criteria in Study Population Section 5 2 Exclusion Criteria	Was: 3 Subject has secondary hypertension Now Is: 3 Subject has **a history of** secondary hypertension	Clarification added so that investigators are not expected to rule out secondary hypertension at screening
Synopsis: Exclusion Criteria in Study Population Section 5 2 Exclusion Criteria Section 8 10 1 2 Disallowed Concomitant Therapy	Was: 5 The use of the following at time of screening and during the course of the study:… c Oral anticoagulants (e g , warfarin, rivaroxaban, apixaban) Now Is: 5 The use of the following at time of screening and during the course of the study:… c Oral **or subcutaneous** anticoagulants (e g , warfarin, rivaroxaban, apixaban, **heparin, lovenox**)	Included per FDA suggestion

Protocol Section	Description of Change	Rationale
Synopsis: Exclusion Criteria in Study Population Section 5 2 Exclusion Criteria	Was: 9 Malignancy within 5 years, … no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor Now Is: 9 Malignancy within 5 years, … no recurrence within 5 years may also be eligible if **reviewed** by the Sponsor Medical Monitor	Clarification that Sponsor Medical Monitor will be reviewing potential patients
Synopsis: Exclusion Criteria in Study Population Section 5 2 Exclusion Criteria	Was: 10 History of bleeding diathesis or coagulopathy Now Is: 10 History of bleeding diathesis, coagulopathy, **immune thrombocytopenic purpura (ITP), thrombotic cytopenic purpura (TTP), or any qualitative or quantitative platelet defect**	Included per FDA suggestion
Section 6 1 1 Screening	Was: Safety labs may be re-tested for determination of subject eligibility after consultation with the Sponsor Medical Monitor Now Is: Safety labs may be re-tested up **to 2 additional times** for determination of subject eligibility after consultation with the Sponsor Medical Monitor	Guidance provided for amount of re-testing allowed at screening
Section 6 1 1 1 Seated Blood Pressure Measuring Instructions at Each Visit	Was: Observer Instructions: • Place the cuff on the subject's upper arm at the level of the heart and centered at the midpoint of the humerus • Leave patient alone for 5 minutes in a quiet setting • After 5 mins, return and take 3 readings, with 60 seconds between readings Now Is: Observer Instructions: • Place the cuff on the subject's upper arm at the level of the heart and centered at the midpoint of the humerus • Leave patient alone for 5 minutes in a quiet setting • After 5 mins, return and take 3 readings, with 60 seconds between readings • **Document the average of the 3 readings**	Instruction provided to ensure the average BP is documented

Protocol Section	Description of Change	Rationale
Section 6 1 1 2 Orthostatic Blood Pressure Assessment Table 2 Orthostatic Hypotension Assessment	Was: … The patient will then change to a standing position and the BP and pulse rate measurements will be repeated within 3 minutes of standing … During the study, orthostatic hypotension will be defined as a confirmed (sequence must be repeated to confirm) decrease in SBP of ≥ 20 mmHg and/or a decrease in DBP of ≥ 10 mmHg within 3 minutes of standing Now Is: … The patient will then change to a standing position and the BP and pulse rate measurements will be repeated **after standing greater than one minute, but less than or equal** to 3 minutes … During the study, orthostatic hypotension will be defined as a confirmed (sequence must be repeated to confirm) decrease in SBP of ≥ 20 mmHg and/or a decrease in DBP of ≥ 10 mmHg **after standing greater than one minute, but less than equal to** 3 minutes	Included per FDA suggestion
Section 6 1 1 3 At Home Blood Pressure and Heart Rate Monitoring	Was: Three (3) at home BP measurements should be taken every 7 calendar days on non-sequential days no more than 2 calendar days apart (e g , Monday, Thursday, Saturday) During the assessments, subjects will first rest in a quiet setting for 5 minutes and then evaluate BP in triplicate each time, with 60 seconds between each measurement and then record the average value Now Is: Three (3) at home BP **and HR** measurements should be taken every 7 calendar days on non-sequential days no more than 2 calendar days apart (e g , Monday, Thursday, Saturday) During the assessments, subjects will first rest in a quiet setting for 5 minutes and then evaluate BP **and HR** in triplicate each time, with 60 seconds between each measurement and then record the average value	Clarification that HR is required at each BP timepoint
Section 6 1 4 Treatment Period	Was: The subjects' BP will be taken pre-dose on Study Day 1 for a final seated BP to confirm eligibility according to Section 5 1 Inclusion Criteria #10 Now Is: Removed	Removed for consistency throughout the protocol as meeting Inclusion Criteria is required at Day – 7 not Day 1

Protocol Section	Description of Change	Rationale
Section 6 2 Laboratory Assessments	Was: 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) Now Is: 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) **Due to time constraints, a local lab draw is recommended if a repeat blood specimen is necessary to continue dosing at any time after Study Day 1 to Study Day 8. If there is a suspicion of EDTA mediated platelet clumping, a repeat platelet count should be collected in a sodium citrate tube as soon as possible.**	The inclusion of a local lab draw, in this situation, is recommended to better adhere to the study visit schedule since awaiting central lab results may incur a delay The use of a sodium citrate tube, if there is a suspicion of EDTA mediated platelet clumping, was added per FDA suggestion
Section 6 3 2 Other Requirements	Was: All subjects will be required to fast for 8 to 10 hrs before visits requiring fasted blood sampling Now Is: All subjects will be required to fast for **at least 8 hours** before visits requiring fasted blood sampling	Clarification added
Section 8 5 2 Safety Monitoring Rules for Potassium	Was: In the event of a potassium measurement ≥ 5 5 mmol/L at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed An ECG evaluation should be performed if the value is confirmed and signs of hyperkalemia should be assessed (delayed conduction, heart block, arrhythmias) If new signs consistent with hyperkalemia are present, proceed to stopping rules The patient will start oral hydration with 1-liter fluids not containing potassium to induce diuresis The frequency of monitoring, additional lab tests, and continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee Now Is: In the event of a potassium measurement ≥ 5 5 mmol/L at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed **If the initial potassium measurement is confirmed to be ≥ 5.5 mmol/L study drug is to be held.** An ECG evaluation should be performed if the value is confirmed and signs of hyperkalemia should be assessed (delayed conduction, heart block, arrhythmias) If new signs consistent with hyperkalemia are present, proceed to stopping rules The patient will start oral hydration with 1-liter fluids not containing potassium to induce diuresis **Measure potassium frequently until documented to be < 5.5 mmol/L. Dosing with study drug may continue after a confirmed potassium measurement <5.5 mmol/L with Investigator and Sponsor Medical Monitor or designee consultation.**	Included per FDA suggestion

Protocol Section	Description of Change	Rationale
Section 8 5 3 Safety Monitoring Rules for Blood Pressure	Was: In the event of a SBP ≤ 100 mmHg a second measurement must be done within a 30-minute period If the subject then experiences an additional SBP measurement ≤ 100 mmHg in a consecutive day (confirmed by triplicate measurement at the Study Center), or if the subject is symptomatic (i e , dizziness, light-headedness, clammy skin, fatigue, blurry vis on), the dose will be withheld… In the Post-Treatment Period, should a subject's BPM exceed 140 mmHg (systolic) or 90 mmHg (diastolic) a second measurement must be done within a 30-minute period If the subject's BP is > 140 mmHg (systolic) or > 90 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 24 hours at the Study Center … Now Is: In the event of a SBP ≤ 100 mmHg a second measurement must be done within a 30-minute period **If the subject's SBP is ≤ 100 mmHg within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home.** If the subject then experiences an additional SBP measurement ≤ 100 mmHg (confirmed by triplicate measurement at the Study Center), or if the subject is symptomatic (i e , dizziness, light-headedness, clammy skin, fatigue, blurry vision), the dose will be withheld…**The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.** **Prior to Study Day 64 in the Post-Treatment Period or in the Washout Period, should a subject's BPM exceed 170 mmHg (systolic) or 110 mmHg (diastolic) a second measurement must be done within a 30-minute period. If the subject's BP is > 170 mmHg (systolic) or > 110 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home. If the subject then experiences an additional BP measurement > 170 mmHg (systolic) or > 110 mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), they will then be withdrawn from further blinded, randomized treatment. The subject's pre-study antihypertensive medication(s) may be added back per Investigator and Sponsor Medical Monitor judgement. The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.** **On or after Study Day 64** in the Post-Treatment Period, should a subject's BPM exceed 140 mmHg (systolic) or 90 mmHg (diastolic) a second measurement must be done within a 30-minute period If the subject's BP is > 140 mmHg (systolic) or > 90 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within **48** hours at the Study Center, **regardless of whether the initial BP measurements were taken in clinic or at home. …**	Blood Pressure Monitoring Rules have been amended for the following reasons: A monitoring BP rule will always need to be confirmed in the clinic within 48 hours Screen failures are not required to follow Post-Treatment Period procedures The study drug has a long half-life and maximum angiotensinogen lowering is expected after 4 weeks of dosing based on Phase 1 data therefore the monitoring rules for the Treatment Period were extended into the Post-Treatment Period prior to Study Day 64 These updates allow time for the study medication to start working in uncontrolled hypertensive patients The threshold of the monitoring rules after Day 64 in the Post-Treatment Period were not amended

Protocol Section	Description of Change	Rationale
Section 8 6 2 Stopping Rules for Renal Function Test Results	Was: In the event of laboratory results for either of the following criteria, dosing of a subject with Study Drug (ISIS 757456 or placebo) will be stopped permanently: … 2 Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1 0 g /24 hour) The follow-up schedule for any events meeting either of these stopping criteria will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee Now Is: In the event of laboratory results for either of the following criteria, dosing of a subject with Study Drug (ISIS 757456 or placebo) will be stopped permanently: … **2. Confirmed 30% decline in eGFR from Baseline eGFR values** **3. Confirmed proteinuria (UPCR ≥ 500 mg/g)** The follow-up schedule for any events meeting either of these stopping criteria will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee **At the discretion of the Investigator, a decision to hold or permanently stop study drug may be based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities.**	Included per FDA suggestion
Section 8 6 3 Stopping Rule for Platelet Count Results	Table 6 Platelet Monitoring Summary added in place of Section 8 6 3 text Summary of Major Updates: • Permanently Discontinue Study Drug at < 50,000/mm^3 • Pause Study Drug if platelets are < 75,000/mm^3 to 50,000/mm^3 • Patients must be hospitalized and a hematologist consultation must be expedited if platelet counts are < 10,000/mm^3 Refer to Table 6 for complete updates	Amended per FDA suggestion and reformatted for clarification
Section 8 6 4 Stopping Rule for Potassium	Was: …Measure potassium frequently until documented to be < 5 5 mmol/L If there are ECG changes consistent with hyperkalemia or muscle weakness the subject should be admitted to the hospital and oral K+ binding resins (e g , Kayexalate, Valtassa) and or potassium wasting diuretics (loop diuretic, thiazides) should be considered… Now Is: …Measure potassium frequently until documented to be < 5 5 mmol/L If there are ECG changes consistent with hyperkalemia or muscle weakness the subject should be admitted to the hospital…	Instructions suggested during hospital admission have been removed

Protocol Section	Description of Change	Rationale
Section 8 6 5 Stopping Rule for Blood Pressure	Was: 1 In the event of a SBP ≤ 90 mmHg with symptoms of hypotension (i e , dizziness, light-headedness, clammy skin, fatigue, blurry vision) for more than 24 hrs, as measured by home BPM, at any point in the study, the patient should have the SBP confirmed by the Study Center If confirmed and the patient remains symptomatic, dosing of a subject with Study Drug will be interrupted If patient is still symptomatic after instituting IV hydration (see Section 8 5 3 Safety Monitoring Rules for Blood Pressure), the patient should be admitted to the hospital and a continuous hydration with normal saline should be instituted until asymptomatic and orthostasis resolves Timing for re-institution should be assessed depending on the reversibility of initiating factors (decreased oral intake, cold/flu, other illness)…The subject will continue to be followed up per protocol in the study 2 During the WO or Treatment Period, should a subject experience a BP measurement > 170 mmHg (systolic) or > 100 mmHg (diastolic) a second measurement must be done within a 30-minute period If the subject's BP is >170 mmHg (systolic) or > 100 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 24 hours at the Study Center If the subject then experiences a BP measurement > 170 mmHg (systolic) or > 100 mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), they will then be withdrawn from further blinded, randomized treatment… Now Is: 1 In the event of a SBP ≤ 90 mmHg with symptoms of hypotension (i e , dizziness, light-headedness, clammy skin, fatigue, blurry vision), as measured by home BPM, at any point in the study, the patient should **contact the Study Center immediately and** have the SBP confirmed by the Study Center If confirmed and the patient remains symptomatic, dosing of a subject with Study Drug will be interrupted If patient is still symptomatic after instituting IV hydration (see Section 8 5 3 Safety Monitoring Rules for Blood Pressure), the patient should be admitted to the hospital Timing for re-institution should be assessed depending on the reversibility of initiating factors (decreased oral intake, cold/flu, other illness)… The subject will continue to be followed per protocol in the study **Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.**	Clarifications added to specify actions to be taken based on "at-home" BP assessments and "at Study Center" BP assessments The diastolic stopping rule threshold during the Treatment period was increased to 110 mmHg from 100 mmHg in consideration of the uncontrolled hypertensive population

Protocol Section	Description of Change	Rationale
Section 8 6 5 Stopping Rule for Blood Pressure *Continued*	Now Is: *Continued* 2 During the Treatment Period, should a subject experience a BP measurement > 170 mmHg (systolic) or > **110** mmHg (diastolic) a second measurement must be done within a 30-minute period If the subject's BP is >170 mmHg (systolic) or > **110** mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within **48** hours at the Study Center, **regardless of whether the initial BP measurements were taken in clinic or at home** If the subject then experiences a BP measurement > 170 mmHg (systolic) or > **110** mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), they will then be withdrawn from further blinded, randomized treatment…	Clarifications added to specify actions to be taken based on "at-home" BP assessments and "at Study Center" BP assessments The diastolic stopping rule threshold during the Treatment period was increased to 110 mmHg from 100 mmHg in consideration of the uncontrolled hypertensive population
Section 8 10 1 2 Disallowed Concomitant Therapy	Was: The following are disallowed concomitant therapies: • Medications for the treatment of HTN (e g , clonidine, guanfacine, guanabenz, alpha methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors) (unless required for safety reasons to control BP) … Now Is: The following are disallowed concomitant therapies: • Medications for the treatment of HTN (e g , clonidine, guanfacine, guanabenz, alpha methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors) (unless required for safety reasons to control **BP in the Post-Treatment Period)** …	Clarification that blood pressure medications are not disallowed in specific instances of the Post-Treatment Period
Section 9 4 3 2 Severity	Was: The severity of AEs and SAEs relating to laboratory test and adverse events at the injection site will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 0, November 2017 (refer to Appendix D) … Now Is: The severity of AEs and SAEs relating to laboratory test and adverse events at the injection site **may** be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 0, November 2017 (refer to Appendix D) **and the Investigator should classify events and laboratory findings as mild, moderate, or severe based on the clinical significance of the event and laboratory finding in the study subject.** …	Added per FDA suggestion
Appendix A Schedule of Procedures	Visit windows for Week -3, Week -2, Week -1 and Study Day 1 visits were updated	Clarification of Visit Windows
Appendix A Schedule of Procedures Appendix B List of Laboratory Analytes	Renal urine biomarkers added: • NGAL • NAG • KIM-1	Added per FDA suggestion, all samples will be collected; however, NGAL and NAG may be analyzed
Appendix B List of Laboratory Analytes	A/C Ratio (UACR) added	Added per FDA suggestion

PROTOCOL SYNOPSIS

Protocol Title	A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure
Study Phase	Phase 2
Indication	Hypertension
Primary Objectives	To evaluate the effect of ISIS 757456 subcutaneous (SC) injection on plasma angiotensinogen concentration
Secondary Objectives	To evaluate the effect of ISIS 757456 on in-clinic systolic blood pressure over time in Treatment and Post-Treatment Periods
Safety Objectives	To evaluate the safety and tolerability of ISIS 757456 vs placebo
Exploratory Objectives	• To evaluate the effect of ISIS 757456 on at-home blood pressure over time in the Treatment and Post-Treatment Periods • To evaluate the exploratory effects of ISIS 757456 administered subcutaneously {e g , angiotensin II, renin [Plasma renin activity (PRA); active renin mass concentration (ARC)], plasma aldosterone} • To evaluate the pharmacokinetics (PK) of ISIS 757456 (as total Full Length ASO, including fully conjugated, partially conjugated, and unconjugated ISIS 757456) administered subcutaneously in subjects with hypertension • To evaluate potential PK/PD correlation with relevant biomarkers
Study Design	Double-blind, placebo-controlled, multi-center study
Number of Subjects	Approximately 30 subjects will be enrolled
Study Population	**Inclusion Criteria** 1 Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2 Males or females aged 18-72 inclusive and weighing ≥ 50 kg at the time of informed consent 3 Satisfy the following: a Females: must be non-pregnant and non-lactating, and either: i surgically sterile (e g , tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or, ii 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 postmenopausal range for the laboratory involved) b Males: Surgically sterile (i e , bilateral orchidectomy) or abstinent*, if engaged in sexual relations with a woman of child-bearing potential (WOCBP), the subject or subject's non-pregnant female partner must be using a highly effective contraceptive method (refer to Section 6 3 1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 757456 or placebo)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Inclusion Criteria *Continued***
	* True abstinence (i e , refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable 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
	4 Willing to refrain from strenuous exercise/activity (e g , heavy lifting, weight training, intense aerobics classes, etc) for at least 24 hrs prior to study visits
	5 BMI ≤ 35 0 kg/m^2
	6 Brachial circumference is ≥ 22 and ≤ 37 cm (8 7 and 14 6 inches)
	7 Subject must have been diagnosed with essential hypertension for a minimum of 3 months prior to screening
	8 At Screening, the subject must have a plasma AGT concentration ≥ 20 µg/mL
	9 At Screening, the subject must have been on a stable regimen of antihypertensive medications (a total of 2) for at least 1 month prior to screening, using either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), as well as a single other antihypertensive medication in the following categories: a beta blocker i acebutolol (≤ 400 mg q d) ii atenolol (≤ 50 mg q d) iii betaxolol (≤ 10 mg q d) iv bisoprolol (≤ 5 mg q d) v carvedilol (≤ 25 mg b i d) vi labetalol (≤ 200 mg b i d) vii metoprolol (≤ 100 mg q d) viii nadolol (≤ 40 mg q d) ix nebivolol (≤ 10 mg q d) x propranolol (≤ 120 mg q d) xi pindolol (≤ 5 mg b i d) b calcium channel blocker or, c diuretic
	10 At Screening, the average office seated BP must be within ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic The average is to be derived from 3 assessments taken within 10 minutes Up to 2 additional tests allowed in order to qualify
	11 On Study Day -7, the average office seated systolic blood pressure (SBP) must be within the following ranges with > 140 - ≤ 165 mmHg The average is to be derived from 3 assessments taken within 10 minutes Up to 2 additional tests allowed for eligibility purposes
	12 In the opinion of the Investigator, the subject could be safely withdrawn from antihypertensive therapy for at least 12 weeks
	13 Agree to conduct at home BP and HR monitoring (in triplicate using study provided device) thrice weekly and document the average of the triplicate measurements assessed on a day in the patient diary
	14 Agree to abstain from alcoholic beverages for at least 24 hours prior to clinic visits
	15 Agree to maintain adequate hydration and current diet regimen
	16 Agree to abstain from smoking, exercise and caffeine use 30 minutes prior to blood pressure measurements

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria** 1 Clinically-significant abnormalities in medical history (e g , previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening, type I diabetes mellitus) or physical examination 2 Unwilling to discontinue antihypertensive mediations during WO and Treatment Period of study 3 Subject has a history of secondary hypertension 4 Subject with borderline orthostatic hypotension (assessed at Screening), when they assume a standing position (within 3 minutes of standing up), defined as: a A decrease in SBP of ≥ 17 mmHg or b A decrease in diastolic blood pressure (DBP) of ≥ 7 mmHg 5 The use of the following at time of screening and during the course of the study: a Other medications for the treatment of hypertension (e g , clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors) b Medications that also may cause hyperkalemia (e g , cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins) c Oral or subcutaneous anticoagulants (e g , warfarin, rivaroxaban, apixaban, heparin, lovenox) d Organic nitrate preparations (e g , nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol) e Sildenafil, tadalafil, vardenafil 6 Treatment with another Study Drug, biological agent, or device within 1 month of screening, or 5 half-lives of study agent, whichever is longer 7 Previous treatment with an oligonucleotide or other RNA therapeutic (including siRNA) within 4 months of screening if single-dose received, or within 12 months of screening if multiple doses received 8 Known history of or positive test for human immunodeficiency virus, hepatitis C, or chronic hepatitis B 9 Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if reviewed by the Sponsor Medical Monitor 10 History of bleeding diathesis, coagulopathy, immune thrombocytopenic purpura (ITP), thrombotic cytopenic purpura (TTP), or any qualitative or quantitative platelet defect 11 Recent history of or current drug or alcohol abuse that could impact study compliance

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria *Continued***
	12 Unstable/underlying cardiovascular disease defined as: a Any history of congestive heart failure (NYHA class II-IV) b Any history of previous stroke, transient ischemic attack, unstable or stable angina pectoris, or myocardial infarction prior to screening c 12-lead ECG demonstrating a QT interval (corrected using Fridericia's formula [QTcF]) > 450 msec in males and > 470 msec in females at Screening, or a history or evidence of long QT syndrome d Any clinically-significant active atrial or ventricular arrhythmias e Any history of coronary bypass or percutaneous coronary intervention
	13 Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
	14 Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that patient is euthyroid
	15 Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion a Urine protein/creatinine (P/C) ratio ≥ 0 3 mg/mg In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24 hr b Positive test (including trace) for blood on urinalysis In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field c Alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase (ALP), serum creatinine, blood urea nitrogen (BUN) > 1 5 x upper limit of normal (ULN) d Platelet count < lower limit of normal (LLN) e Serum potassium > 4 85 mmol/L f Estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1 73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration formula
	16 Clinically-significant abnormalities upon physical examination which in the Investigator's opinion should exclude the subject from study participation
	17 Subject works night time shifts (e g , 11 PM to 7 AM)
	18 Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
	19 Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study
	20 Unwilling to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator

PROTOCOL SYNOPSIS *Continued*

Treatment Groups	Approximately 30 subjects will be stratified based on a screening plasma angiotensinogen (AGT) concentration (≤ 30 µg/mL vs > 30 µg/mL) and randomized 2:1 (80 mg ISIS 757456:placebo)
Study Drug Dosage and Administration	ISIS 757456 (100 mg/mL) and placebo will be supplied in vials of 0 8 mL solution in a 2 mL stoppered glass vial Study Drug (ISIS 757456 or placebo) injection volumes will be 0 8 mL All Study Drug injections will be subcutaneously administered in the clinic once-weekly and as a loading dose on Study Day 3 Refer to Section 8 1 for additional details
[redacted]	[redacted]
Study Visit Schedule and Procedures	Detailed information regarding the study procedures are outlined in Section 6, Appendix A and Appendix C Blood and urine samples will be collected regularly throughout the study for safety, pharmacokinetic, and pharmacodynamic analyses Appendix B shows a list of analytes required for the study The safety of ISIS 757456 will be monitored in an ongoing fashion throughout the trial **Screening: Weeks -6 to Week -4** Laboratory and other study procedures will be performed to assess eligibility during the Screening Period **Run-In Period: Week -3** After the 3-week Screening Period subjects will have a 1-week Run-In Period with home-based BPM Compliance with antihypertensive medications will be assessed **Washout: Week -2 to Week -1** After the 1-week run-in, all antihypertensive medications will be withdrawn Antihypertensive medications should be washed out for a period of 2 weeks prior to dosing on Study Day 1

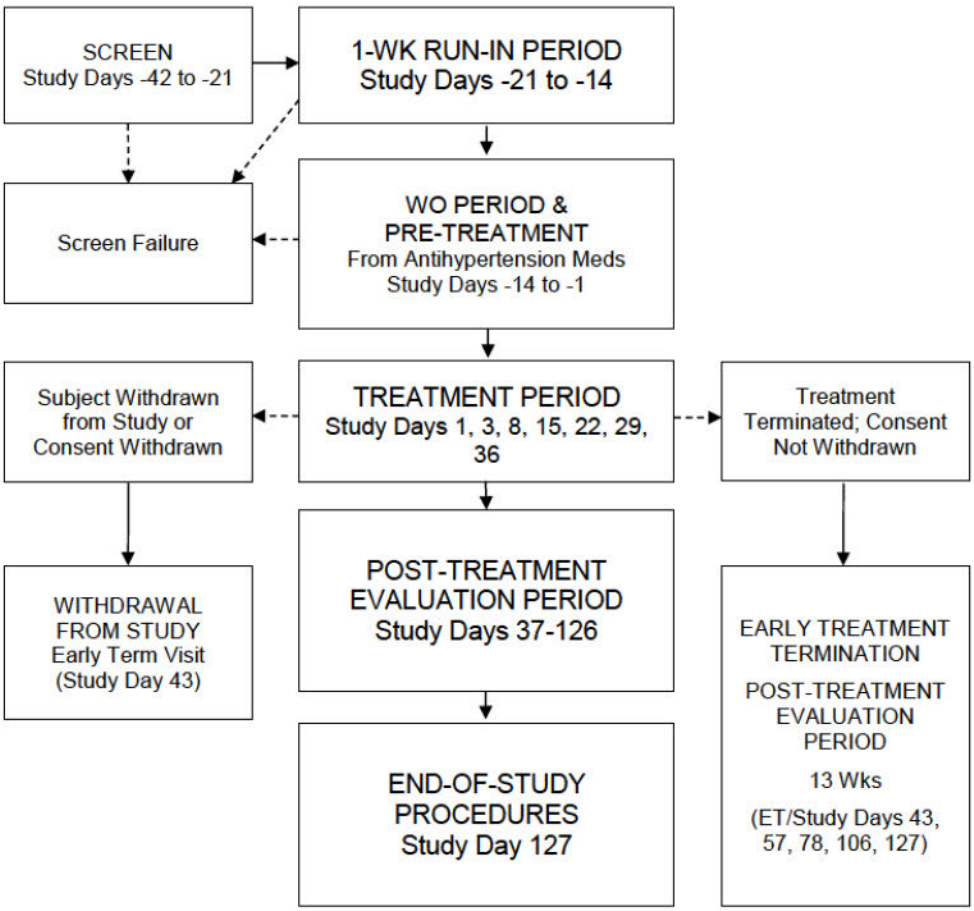
PROTOCOL SYNOPSIS ***Continued***

Study Visit Schedule and Procedures ***Continued***	**Treatment: Week 1 to Week 6** After the WO Period, eligible subjects will be stratified based on screening plasma angiotensinogen (AGT) concentration (≤ 30 µg/mL vs > 30 µg/mL) and randomized 2:1 to 80 mg ISIS 757456 or placebo Subjects will receive SC doses of Study Drug on Study Days 1, 3, 8, 15, 22, 29, and 36 Subjects will remain off antihypertensive medications for approximately 3 months throughout the study Subjects that discontinue treatment may remain in the study and will attend the Study Day 43 visit **Post-Treatment: Week 7 to Week 19** Subjects are to return to the Study Center for follow-up visits on Study Days 43, 50, 64, 78, 106 and 127 The final study visit will be Study Day 127 (Week 19)
Primary Endpoint	Percent change in plasma angiotensinogen from Baseline to Study Day 43 (Week 7) compared to placebo
Secondary Endpoints	Change on in-clinic SBP from Baseline to each scheduled, post-Baseline visit Change and percent change in plasma angiotensinogen from Baseline to each scheduled, post-baseline visit
Safety Endpoints	Incidence and severity of treatment-emergent adverse events (TEAE) (including hypotension and orthostatic hypotension), use of concomitant medications, laboratory assessments, ECG, and vital signs
Exploratory Endpoints	• Change of the weekly average of at-home BP from Baseline to each scheduled, post-Baseline visit • Change and percent change of angiotensin II, renin (Plasma renin activity [PRA]; active renin mass concentration [ARC]), plasma aldosterone from Baseline to each scheduled, post-Baseline visit • Percentage of subjects reaching the goals of in-clinic SBP ≤ 140 mmHg, DBP ≤ 90 mmHg, and both over time • Percentage of subjects and time to requiring antihypertensive therapy during the study • Assessments of urinary analytes (e g , cortisol, aldosterone, angiotensin II, albumin, creatinine, protein and sodium) from Baseline to each scheduled, post-Baseline visit may be performed • PK parameters including but not limited to C_{max} (maximum observed ISIS 757456 plasma concentration), T_{max} (time to maximal plasma concentration) and AUC (area under the plasma concentration time profile for ISIS 757456) • Potential exposure-response analysis using relevant exposure parameters and biomarkers including, but not limited to C_{trough} and plasma AGT may be performed

PROTOCOL SYNOPSIS ***Continued***

Statistical Considerations	[redacted] Approximately 30 subjects will be stratified based on screening plasma angiotensinogen (AGT) concentration (≤ 30 µg/mL vs > 30 µg/mL) and randomized in a 2:1 ratio to receive either 80 mg ISIS 757456 or placebo The primary efficacy analysis will be the comparison of percent change from Baseline to Study Week 7 (Study Day 43) in angiotensinogen between ISIS 757456 80-mg group and placebo group All planned analyses will compare ISIS 757456 to placebo An interim analysis may be conducted after at least 50% of the subjects have been enrolled
Sponsor	Ionis Pharmaceuticals, Inc

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
A/C	albumin/creatinine
ACE	angiotensin-converting enzyme
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
AGT	angiotensinogen
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blockers
ARF	acute renal failure
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AUC	area under the curve
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
b.i.d.	twice per day
BMI	body mass index
BP	blood pressure
BPM	blood pressure monitoring
BUN	blood urea nitrogen
C_{max}	maximum concentration
CKD	chronic kidney disease
CMV	cytomegalovirus
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report Form

ED_{50}	50% effective dose
eGFR	estimated glomerular filtration rate
FSH	follicle stimulating hormone
GalNAc	*N*-acetyl galactosamine
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HepB	hepatitis B
HIV	human immunodeficiency virus
HR	heart rate
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
HTN	hypertension
ICH	International Conference on Harmonization
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous(ly)
KIM-1	kidney injury molecule 1
LLN	lower limit of normal
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
min	minute
mm	millimeter
mmHg	millimeter mercury
MRI	magnetic resonance imaging

mRNA	messenger ribonucleic acid
NAG	*N*-acetyl-β D-glucosaminidase
NCS	not clinically-significant
NGAL	neutrophil gelatinase-associated lipocalin
NOAEL	No Adverse Effect Level
NYHA	New York Heart Association
on study	The subject is 'on study' from signing of the informed consent until their last study visit
P/C	protein/creatinine
PD	pharmacodynamic(s)
PH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PPS	per protocol population
pRBC	packed red blood cells
PT	prothrombin time
RAAS	renin-angiotensin-aldosterone system
RHTN	resistant hypertension
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
q.d.	daily
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 757456 or placebo
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to maximal concentration
UACR	urine albumin-creatinine ratio
ULN	upper limit of normal

UPCR	urine protein-creatinine ratio
WBC	white blood cell
WO	washout
WOCBP	woman of child-bearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objectives

- To evaluate the effect of ISIS 757456 subcutaneous (SC) injection on plasma angiotensinogen concentration

1.1.2. Secondary Objectives

- To evaluate the effect of ISIS 757456 on in-clinic systolic blood pressure over time in Treatment and Post-Treatment Periods

1.1.3. Safety Objectives

- To evaluate the safety and tolerability of ISIS 757456 vs. placebo

1.1.4. Exploratory Objectives

- To evaluate the effect of ISIS 757456 on at-home blood pressure over time in the Treatment and Post-Treatment Periods
- To evaluate the exploratory effects of ISIS 757456 administered subcutaneously {e.g., angiotensin II, renin [Plasma renin activity (PRA); active renin mass concentration (ARC)], plasma aldosterone}
- To evaluate the pharmacokinetics (PK) of ISIS 757456 (as total Full Length ASO, including fully conjugated, partially conjugated, and unconjugated ISIS 757456) administered subcutaneously in subjects with hypertension
- To evaluate potential PK/PD correlation with relevant biomarkers

1.2. Study Endpoints

1.2.1. Primary Endpoints

- Percent change in plasma angiotensinogen from Baseline to Study Day 43 (Week 7) compared to placebo

1.2.2. Secondary Endpoints

- Change on in-clinic SBP from Baseline to each scheduled, post-Baseline visit
- Change and percent change in plasma angiotensinogen from Baseline to each scheduled, post-baseline visit

1.2.3. Safety Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAE) (including hypotension and orthostatic hypotension), use of concomitant medications, laboratory assessments, ECG, and vital signs

1.2.4. Exploratory Endpoint

- Change of the weekly average of at-home BP from Baseline to each scheduled, post-baseline visit
- Change and percent change of angiotensin II, renin (Plasma renin activity [PRA]; active renin mass concentration [ARC]), and plasma aldosterone from Baseline to each scheduled, post-baseline visit
- Percentage of subjects reaching the goals of in-clinic SBP $\leq$ 140 mmHg, DBP $\leq$ 90 mmHg, and both over time
- Percentage of subjects and time to requiring antihypertensive therapy during the study
- Assessments of urinary analytes (e.g., cortisol, aldosterone, angiotensin II, albumin, creatinine, protein and sodium) from Baseline to each scheduled, post-baseline visit may be performed
- PK parameters including but not limited to C_{max} (maximum observed ISIS 757456 plasma concentration), T_{max} (time to maximal plasma concentration) and AUC (area under the plasma concentration time profile for ISIS 757456)
- Potential exposure-response analysis using relevant exposure parameters and biomarkers including, but not limited to C_{trough} and plasma AGT may be performed

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Resistant hypertension (RHTN) is defined as failure to achieve blood pressure (BP) goal of < 140/90 in patients adherent to adequate doses of $\geq$ 3 medications (1 of which is diuretic) (Judd and Calhoun 2014). Some patients have pseudo-resistance hypertension (HTN) and they are not compliant with their medications or they have white coat HTN.

In US alone, 70 million adults have HTN, of which 12-15% have RHTN. Among these patients 33% of them have uncontrolled RHTN (Judd and Calhoun 2014). In an analysis of National Health and Nutrition Examination Survey database, these patients are more likely to be black, with diabetes, with chronic kidney disease (CKD) Stage 3, with proteinuria and congestive heart failure compared to patients with HTN and without resistant HTN.

2.2. Therapeutic Rationale

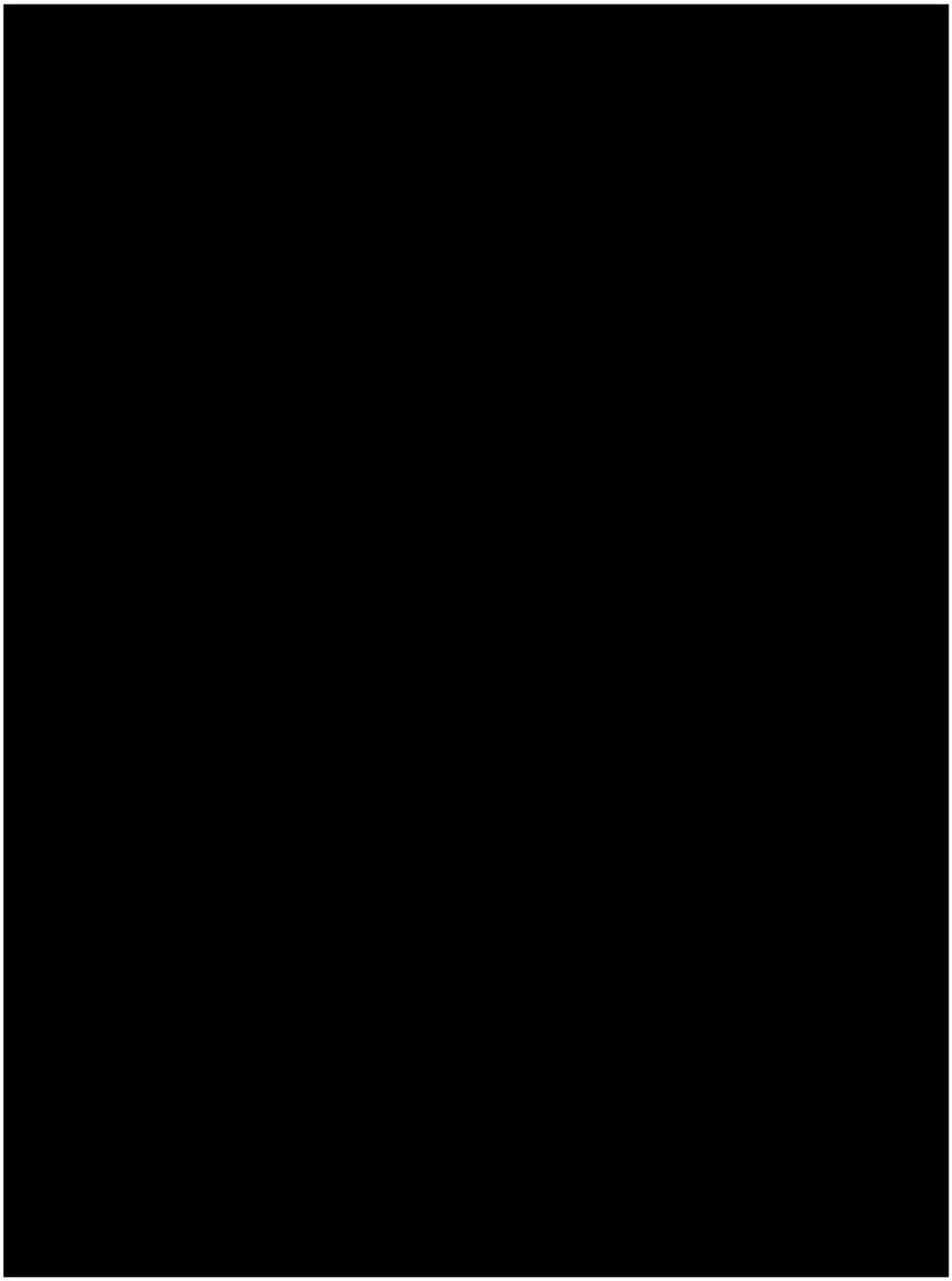
Renin-angiotensin-aldosterone system (RAAS) inhibition is well established as a mode of improving HTN (Te Riet et al. 2015) and complications of HTN. While ACEi, angiotensin receptor blockers (ARB) and renin inhibitors are widely used, escape mechanisms are common and lead to incomplete RAAS blockade. Efforts to provide better RAAS blockade using 2 or more agents in this pathway have been complicated by hyperkalemia, hypotension, and acute renal failure (ARF). The effect of this ASO occurs upstream of all the known targets for RAAS inhibitors used in clinical practice, and therefore will potentially reduce escape mechanisms. The hyperkalemia and ARF of RAAS blockade could be secondary to renal specific reduction of

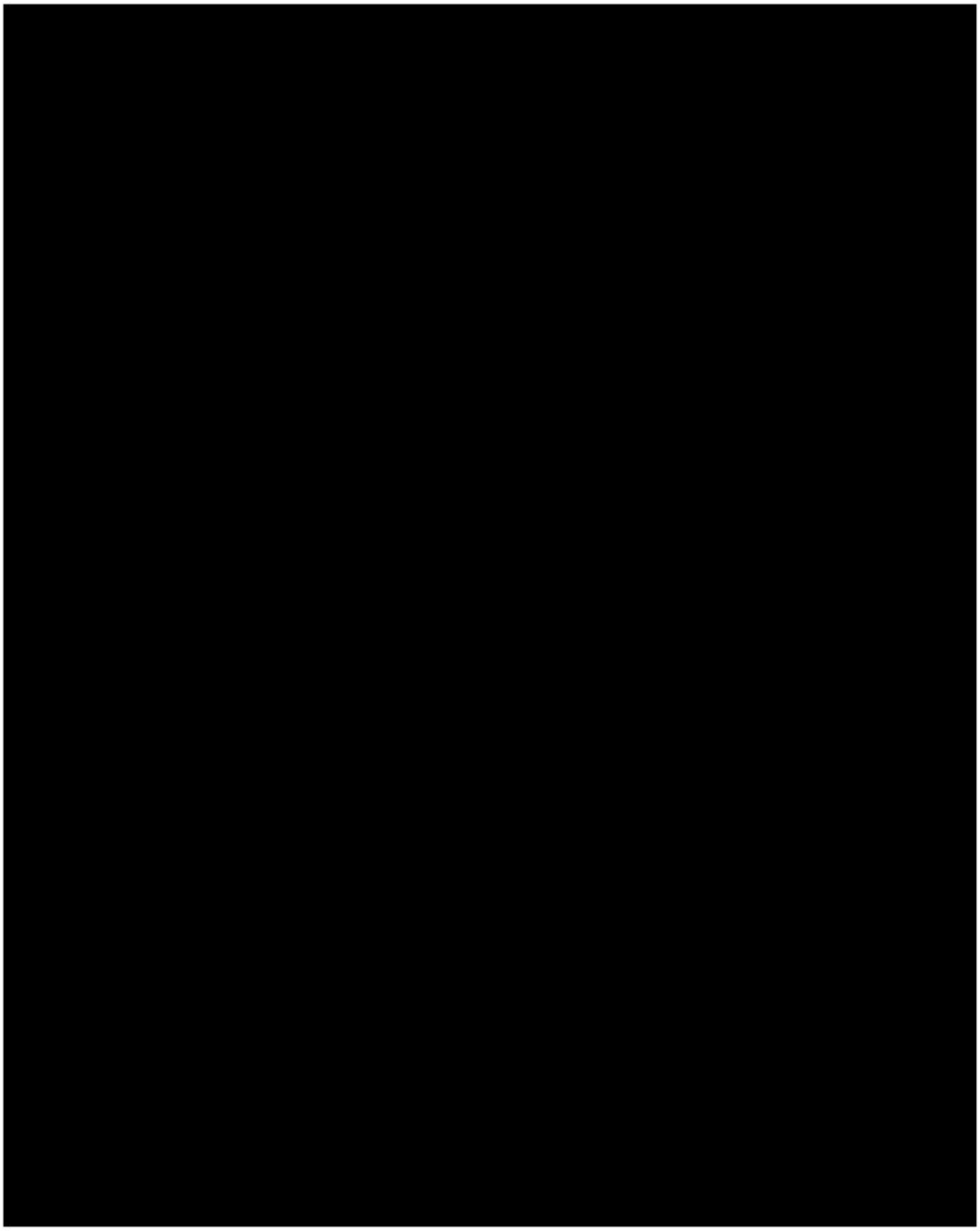
these pathways. The *N*-acetyl galactosamine (GalNAc) ASOs have more prominent effect in the liver. As such, the renal sparing effects of this ASO may result in an improved therapeutic index compared with RAAS inhibitors, especially important in subjects with CKD and/or those at submaximal RAAS blockage.

[redacted]

2.3. ISIS 757456

[redacted]

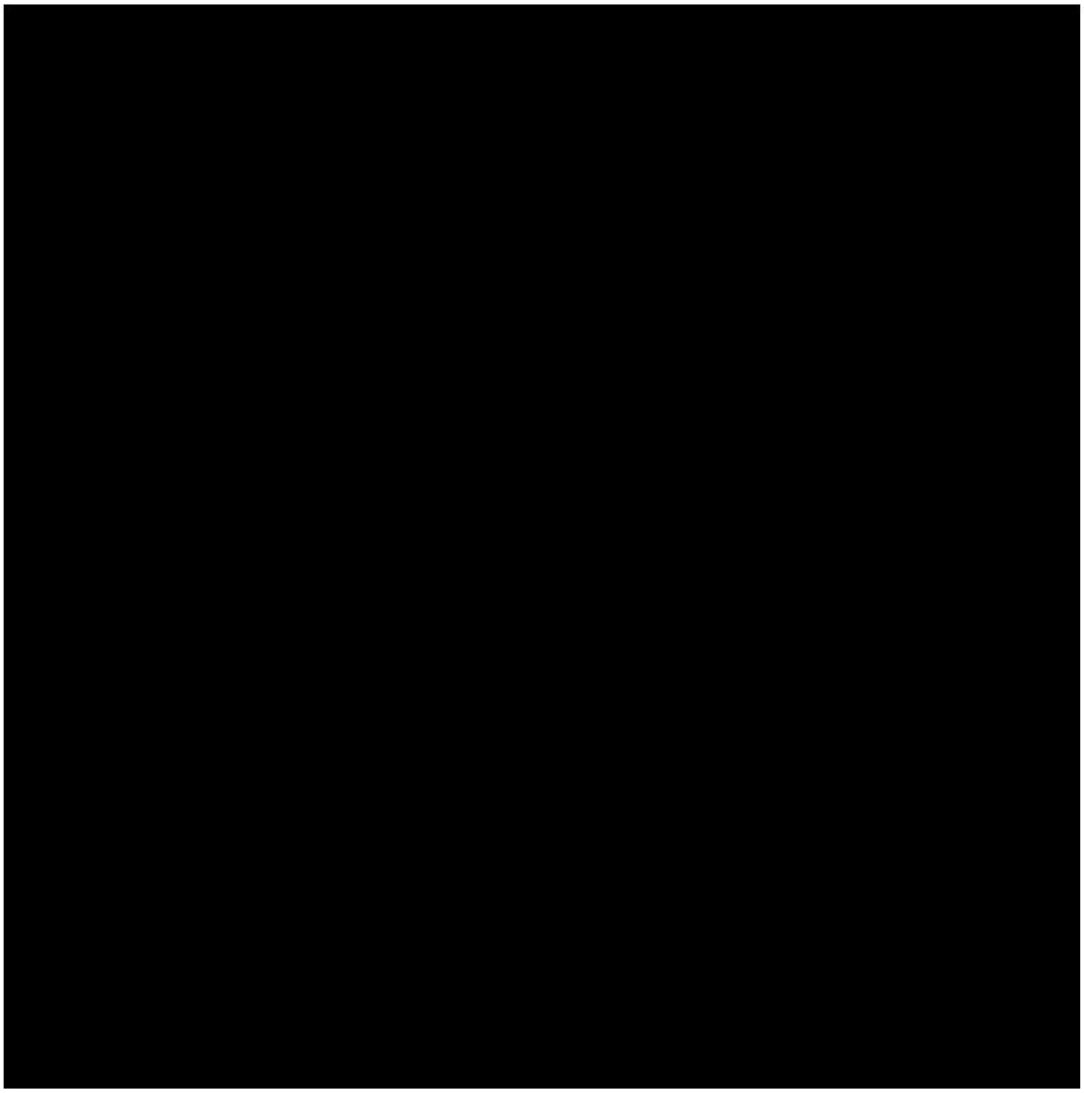




2.5. Benefit-Risk Assessment

2.5.1. Benefit Assessment

While this compound has been administered to healthy volunteers, it has not been administered to subjects with HTN. Based on its MOA of blocking the RAAS pathway it is expected to lower the BP in subjects with HTN. While there are other compounds (ACEi, ARB, aldosterone blockers, renin inhibitors) that block different components of this pathway, this compound blocks AGT, the most upstream factor in the pathway.



3. EXPERIMENTAL PLAN

3.1. Study Design

This will be a Phase 2, double-blind, randomized, placebo-controlled study of ISIS 757456 conducted in mild hypertensive subjects on an ACEi/ARB and an additional hypertensive medication (see Section 5.1 Inclusion Criteria). Subjects will be stratified based on a screening plasma AGT concentration (≤ 30 µg/mL vs. > 30 µg/mL) and randomized in a 2:1 ratio to receive a once-weekly SC treatment and an additional loading dose on Study Day 3 with either ISIS 757456 80 mg or placebo for 6 weeks (See Study Design and Treatment Schema).

All subjects will complete a 13-week Post-Treatment Period. In the Post-Treatment Period, should a subject's sitting BP on home monitoring exceed 140 mmHg systolic or 100 mmHg diastolic on 2 consecutive days (confirmed by triplicate measurement at the Study Center), the subject's initial HTN medication(s) may be added back per Investigator and Sponsor Medical Monitor judgment and the subject will continue to be followed per protocol in the study.

[redacted]

Refer to Section 8.1 for additional details.

3.2. Number of Study Centers

This study will be conducted at multiple centers in the United States.

3.3. Number of Subjects

Approximately 30 subjects are planned to be enrolled in this study.

The 80 mg once-weekly dose is designed to assess the safety, tolerability, and efficacy of Study Drug (ISIS 757456 or placebo) given over a 6-week period. An additional loading dose will be given on Study Day 3. The sample size was selected to ensure that the safety and tolerability of ISIS 757456 will be adequately assessed while minimizing unnecessary subject exposure.

3.4. Overall Study Duration and Follow-up

The study will consist of screen, run-in, WO, treatment, and post-treatment. Please refer to the Schedule of Procedures in Appendix A.

The overall length of a subject's participation will be approximately 25 weeks (up to 3 weeks for screening, 1-week run-in, 2 weeks for WO, a 6-week Treatment Period, and 13 weeks of Post-Treatment Evaluation Period.

Subjects may be required to attend additional visits for monitoring of adverse events (AE) or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

3.4.1. Screening and Run-In

Subject eligibility for the study will be determined within 4 weeks prior to study entry, consisting of up to 3-week screening (Week -6 to Week -4) and a 1-week Run-In Period (Week -3).

During the 1-week Run-In Period the subjects will have home-based blood pressure monitoring (BPM) and an in-clinic visit for vital signs, including BPM. Compliance with antihypertensive medications will be assessed.

3.4.2. Washout

After this 1-week run-in, the subject will withdraw from all of their antihypertensive medications. Antihypertensive medications should be washed out for a period of 2 weeks prior to dosing on Study Day 1.

3.4.3. Treatment

Eligible subjects will be stratified based on a screening plasma AGT concentration ($\leq$ 30 µg/mL vs. > 30 µg/mL) and randomized 2 active:1 placebo. Subjects will receive a total of 7 SC doses of Study Drug once-weekly for 6 weeks (Study Days 1, 8, 15, 22, 29, and 36) and an additional loading dose on Study Day 3.

3.4.4. Post-Treatment

Subjects are to return to the Study Center for follow-up visits on Study Days 43, 50, 64, 78, 106 and 127. The final study visit will be Study Day 127 (Week 19).

3.5. End-of-Study

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

4. SUBJECT ENROLLMENT

4.1. Screening

Before subjects may be enrolled into the study, the Sponsor requires a copy of the Study Center's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

Subjects must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of randomization, subjects will be assigned a unique subject identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to that subject. The screening number and subject identification number must remain constant throughout the entire trial. Screening numbers and subject identification numbers, once assigned, will not be re-used.

4.2. Randomization

Subjects will be randomized after all screening, run-in, and WO assessments through Study Day -7 have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2 and after review by Sponsor Medical Monitor or designee. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

Eligible subjects will be stratified based on a screening plasma AGT concentration screening plasma AGT concentration (≤ 30 µg/mL vs. > 30 µg/mL) and then subjects will be randomized 2:1 to receive ISIS 757456 or placebo as outlined in Section 3.1. Eligible subjects must have a plasma AGT concentration ≥ 20 µg/mL to participate in the study (see Section 5.1 Inclusion Criteria). The Sponsor or designee will prepare the randomization list and utilize an automated IRT (Interactive Response Technology) system.

4.3. Replacement of Subjects

Subjects who withdraw from the study or whose randomization code has been broken will not be replaced.

4.4. Unblinding of Treatment Assignment

The Sponsor and all subjects, monitors, and Study Center personnel will be blinded throughout the study. However, if a subject has suffered a Serious Adverse Event (SAE) (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the automated IRT system. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's designated vendor. In addition, all SUSARs will be unblinded by the Sponsor or designee for the purpose of regulatory reporting (see Section 9.2).

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

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 28 days of Study Day 1 or at the time point specified in the individual eligibility criterion listed.

5.1. Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females aged 18-72 inclusive and weighing ≥ 50 kg at the time of informed consent

3. Satisfy the following:
   a. Females: must be non-pregnant and non-lactating, and either:
      i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or,
      ii. 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 postmenopausal range for the laboratory involved)
   b. Males: Surgically sterile (i.e., bilateral orchidectomy) or abstinent*, if engaged in sexual relations with a woman of child-bearing potential (WOCBP), the subject or subject's non-pregnant female partner must be using a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 757456 or placebo)

   * True abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable. 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
4. Willing to refrain from strenuous exercise/activity (e.g., heavy lifting, weight training, intense aerobics classes, etc.) for at least 24 hrs prior to study visits
5. BMI ≤ 35.0 kg/m^2
6. Brachial circumference is ≥ 22 and ≤ 37 cm (8.7 and 14.6 inches)
7. Subject must have been diagnosed with essential hypertension for a minimum of 3 months prior to screening
8. At Screening, the subject must have a plasma AGT concentration ≥ 20 µg/mL
9. At Screening, the subject must have been on a stable regimen of antihypertensive medications (a total of 2) for at least 1 month prior to screening, using either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), as well as a single other antihypertensive medication in the following categories:
   a. beta blocker
      i. acebutolol (≤ 400 mg q.d.)
      ii. atenolol (≤ 50 mg q.d.)
      iii. betaxolol (≤ 10 mg q.d.)
      iv. bisoprolol (≤ 5 mg q.d.)
      v. carvedilol (≤ 25 mg b.i.d.)
      vi. labetalol (≤ 200 mg b.i.d.)
      vii. metoprolol (≤ 100 mg q.d.)
      viii. nadolol (≤ 40 mg q.d.)

ix. nebivolol (≤ 10 mg q.d.)

x. propranolol (≤ 120 mg q.d.)

xi. pindolol (≤ 5 mg b.i.d.)

b. calcium channel blocker or

c. diuretic

10. At Screening, the average office seated BP must be within ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic. The average is to be derived from 3 assessments taken within 10 minutes. Up to 2 additional tests allowed in order to qualify
11. On Study Day -7, the average office seated systolic blood pressure (SBP) must be within the following ranges with > 140 - ≤ 165 mmHg. The average is to be derived from 3 assessments taken within 10 minutes. Up to 2 additional tests allowed for eligibility purposes
12. In the opinion of the Investigator, the subject could be safely withdrawn from antihypertensive therapy for at least 12 weeks
13. Agree to conduct at home BP and HR monitoring (in triplicate using study provided device) thrice weekly and document the average of the triplicate measurements assessed on a day in the patient diary
14. Agree to abstain from alcoholic beverages for at least 24 hours prior to clinic visits
15. Agree to maintain adequate hydration and current diet regimen
16. Agree to abstain from smoking, exercise, and caffeine use 30 minutes prior to blood pressure measurements.

5.2. Exclusion Criteria

1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening, type I diabetes mellitus) or physical examination
2. Unwilling to discontinue antihypertensive mediations during WO and Treatment Period of study
3. Subject has a history of secondary hypertension
4. Subject with borderline orthostatic hypotension (assessed at Screening), when they assume a standing position (within 3 minutes of standing up), defined as:
   a. A decrease in SBP of ≥ 17 mmHg or
   b. A decrease in diastolic blood pressure (DBP) of ≥ 7 mmHg
5. The use of the following at time of screening and during the course of the study:
   a. Other medications for the treatment of hypertension (e.g., clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors)

b. Medications that also may cause hyperkalemia (e.g., cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins)

c. Oral or subcutaneous anticoagulants (e.g., warfarin, rivaroxaban, apixaban, heparin, lovenox)

d. Organic nitrate preparations (e.g., nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol)

e. Sildenafil, tadalafil, vardenafil

6. Treatment with another Study Drug, biological agent, or device within 1 month of screening, or 5 half-lives of study agent, whichever is longer

7. Previous treatment with an oligonucleotide or other RNA therapeutic (including siRNA) within 4 months of screening if single-dose received, or within 12 months of screening if multiple doses received

8. Known history of or positive test for human immunodeficiency virus, hepatitis C, or chronic hepatitis B

9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if reviewed by the Sponsor Medical Monitor

10. History of bleeding diathesis, coagulopathy, immune thrombocytopenic purpura (ITP), thrombotic cytopenic purpura (TTP), or any qualitative or quantitative platelet defect

11. Recent history of or current drug or alcohol abuse that could impact study compliance

12. Unstable/underlying cardiovascular disease defined as:

a. Any history of congestive heart failure (NYHA class II-IV)

b. Any history of previous stroke, transient ischemic attack, unstable or stable angina pectoris, or myocardial infarction prior to screening

c. 12-lead ECG demonstrating a QT interval (corrected using Fridericia's formula [QTcF]) > 450 msec in males and > 470 msec in females at Screening, or a history or evidence of long QT syndrome

d. Any clinically-significant active atrial or ventricular arrhythmias

e. Any history of coronary bypass or percutaneous coronary intervention

13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1

14. Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening. Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that patient is euthyroid

15. Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion
    a. Urine protein/creatinine (P/C) ratio ≥ 0.3 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24 hr
    b. Positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
    c. Alanine aminotransferase (ALT), aspartate aminotransferase, bilirubin, alkaline phosphatase (ALP), serum creatinine, blood urea nitrogen (BUN) > 1.5 x upper limit of normal (ULN)
    d. Platelet count < Lower Limit of Normal (LLN)
    e. Serum potassium > 4.85 mmol/L
    f. Estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration formula
16. Clinically significant abnormalities upon physical examination which in the Investigator's opinion should exclude the subject from study participation
17. Subject works night time shifts (e.g., 11 PM to 7 AM)
18. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
19. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study
20. Unwilling to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator

6. STUDY PROCEDURES

6.1. Study Schedule

All required study procedures are outlined in Appendix A, Appendix B and Appendix C.

The length of each subject's participation in this portion of the study is approximately 5 months that includes a 3-week Screening Period, a 1-week Run-In Period, a 2-week WO Period, a 6-week Treatment Period, and a 13-week Post-Treatment Evaluation Period.

All BP assessments will be conducted according to Section 6.1.1.1 (Seated Blood Pressure Measuring Instructions at Each Visit), Section 6.1.1.2 (Orthostatic Blood Pressure Assessment) and Section 6.1.1.3 (At Home Blood Pressure and Heart Rate Monitoring).

The safety of ISIS 757456 will be continually monitored throughout the trial by the Investigator and the Sponsor Medical Monitor.

6.1.1. Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. A 3-week period is provided for completing screening assessments and determining subject eligibility for the study. Safety labs may be re-tested up to 2 additional times for determination of subject eligibility after consultation with the Sponsor Medical Monitor.

During the Screening Period, subjects will undergo a medical history (including cardiovascular disease risk factors) and physical examination including vital signs, orthostatic hypotension assessment, 12-lead ECG, and have blood and urine samples taken for clinical laboratory testing. Subjects will be screened for HIV, HepB, and HCV.

The study site will record basic personal details about the subject, including the subject's name, contact details, gender, height, weight, date of birth, age, ethnicity, and racial origin (to be used only for clinical purposes), as well as information on the subject's medical history, and clinical data collected about the subject's participation in the study.

6.1.1.1. Seated Blood Pressure Measuring Instructions at Each Visit

Subject Instructions:

- Subject should be wearing a loose, short-sleeved top. If patient is wearing a long-sleeved or tight garment around the arm, provide a gown or remove the arm from the sleeve
- Subject should be comfortably seated (e.g., with his/her back against the chair, feet flat on the floor)
- Subject's arm should be bent at the elbow and supported by a table

Observer Instructions:

- Place the cuff on the subject's upper arm at the level of the heart and centered at the midpoint of the humerus
- Leave patient alone for 5 minutes in a quiet setting
- After 5 mins, return and take 3 readings, with 60 seconds between readings
- Document the average of the 3 readings

BP Results:

- At the screening visit, measure the BP per instructions above with both the right and left arm. The arm with the highest BP (that meets inclusion/exclusion criteria) will be used at each subsequent visit and during the 3 times a week at-home BPM

6.1.1.2. Orthostatic Blood Pressure Assessment

An orthostatic BP assessment will be done at Screening. Blood pressure and pulse rate will be assessed 2 times (Table 2). The patient will lie down (supine) for at least 5 minutes, then BP and pulse rate will be measured. The patient will then change to a standing position and the BP and

pulse rate measurements will be repeated after standing greater than one minute, but less than or equal to 3 minutes.

Borderline orthostatic hypotension will be defined as a confirmed (sequence must be repeated to confirm) decrease in SBP ≥ 17 mmHg and/or a decrease in DBP of ≥ 7 mmHg from BP at supine position. During the study, orthostatic hypotension will be defined as a confirmed (sequence must be repeated to confirm) decrease in SBP of ≥ 20 mmHg and/or a decrease in DBP of ≥ 10 mmHg after standing greater than 1 minute, but less than or equal to 3 minutes. The diagnosis will be made specific to each visit with no comparison to Baseline (Study Day 1 pre-dose) values.

Table 2: Orthostatic Hypotension Assessment

Position	Time in Position	Vital Signs Assessed
Supine	5 minutes	Blood Pressure and Pulse Rate after 5 minutes
Standing	> 1 to ≤ 3 minutes	Blood Pressure and Pulse Rate assessed within > 1 to ≤ 3 minutes of standing

6.1.1.3. At Home Blood Pressure and Heart Rate Monitoring

Subjects will be provided with a study BPM kit. Subjects will be required to measure their BP and HR at approximately the same time in the morning 3 times a week throughout the study (up to 1 missed BP and HR every 7 days is allowed). Three (3) at home BP and HR measurements should be taken every 7 calendar days on non-sequential days no more than 2 calendar days apart (e.g., Monday, Thursday, Saturday). During the assessments, subjects will first rest in a quiet setting for 5 minutes and then evaluate BP and HR in triplicate each time, with 60 seconds between each measurement and then record the average value. All subjects will be trained by the clinic staff and provided written instructions on how to use the BPM kit. Subjects will contact the Investigator if BP results meet the criteria as outlined in the Safety Monitoring Rules for Blood Pressure and Stopping Rules for Blood Pressure outlined in Section 8.

6.1.2. Run-In Period

The Run-In Period will be 1 week, and subjects will conduct thrice weekly at home evaluations for vital signs (e.g., BP, HR) and will be assessed for compliance with their antihypertensive medications. Subjects who do not complete the Run-In Period or do not continue to meet the eligibility criteria will be considered a screen failure.

6.1.3. Washout Period

The WO Period will be 2 weeks and subjects will stop all of their antihypertensive medications at the beginning and conduct thrice weekly evaluations for vital signs (e.g., BP, HR) at home. Vital signs will be performed on Study Day -14 at the clinic.

On Weeks -2 and -1 subjects will return to the clinic for study assessments outlined in Appendix A. Subject vital signs and safety assessments will be conducted to confirm eligibility

on Week -1 (Study Day -7). Subjects who do not complete the WO Period or do not continue to meet the eligibility criteria will be considered a screen failure.

6.1.4. Treatment Period

Eligible subjects will be administered Study Drug (ISIS 757456 or placebo) on a weekly basis (6 weeks) as well as an additional dose on Study Day 3 for a total of 7 doses. Review of the at-home blood pressures and the in-clinic BP should be performed prior to administering the Study Drug,

Safety and clinical laboratory evaluations as well as blood sampling for PK analysis will be performed periodically throughout the Treatment Period (Appendix A, Appendix B, and Appendix C). Any AEs and concomitant medications will be recorded. If antihypertensive medications are re-instated this will be captured in the concomitant medications eCRF. All safety data including AEs, at home and in-clinic BP, and concomitant medications will be reviewed by the Sponsor's Medical Monitor or designee on an ongoing basis throughout the trial.

Subjects will continue at home BP and HR monitoring during the Treatment Period as outlined in Section 6.1.1.3 and Appendix A. Subjects who discontinue the Treatment Period early will continue in the study following the post-treatment evaluations (Section 6.1.5)

6.1.5. Post-Treatment Evaluation Period

After the last dose (Study Day 36) or last dose for early termination subjects, subjects will return to the clinic once-weekly for the first 2 weeks (Study Days 43, 50) and then on Study Days 64, 78, 106, and 127 for safety assessments.

Subjects will continue at home BP and HR monitoring during the Post-Treatment Period as outlined in Section 6.1.1.3 and Appendix A.

All safety data including AEs, at home and in-clinic BP, and concomitant medications will be reviewed by the Sponsor's Medical Monitor or designee on an ongoing basis throughout the trial.

6.2. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. Blood chemistry should be taken be taken after fasting for at least 8 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

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). Due to time constraints, a local lab draw is recommended if a repeat blood specimen is necessary to continue dosing at any time after Study Day 1 to Study Day 8. If there is suspicion of EDTA mediated platelet clumping, a repeat platelet count should be collected in a sodium citrate tube as soon as possible.

6.3. Restriction on the Lifestyle of Subjects

6.3.1. Contraception Requirements

All male subjects must refrain from sperm donation and either be abstinent† or use highly effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

For male subjects engaged in sexual relations with a WOCBP either the subject or their female partner must use highly effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

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

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

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

For male subjects:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the non-pregnant female partner of WOCBP uses a highly effective contraceptive method (defined below)
- Male subjects with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug

For female subjects and female partners of male subjects, highly effective female contraception methods comprise:

- Surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS)

†Note: True abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

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

6.3.2. Other Requirements

Subjects must refrain from strenuous exercise/activity (e.g., heavy lifting, weight training, intense aerobics classes etc.) for at least 24 hrs prior to study visits.

All subjects will be required to fast for at least 8 hours before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1. Study Drug Description

Study Drug (ISIS 757456 or Placebo) characteristics are listed in Table 3.

The Study Drug (ISIS 757456 or placebo) is contained in 2-mL stoppered glass vials. The Study Drug (ISIS 757456 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 757456 or placebo) must be stored securely at 2–8 °Celsius and be protected from light.

Table 3: Study Drug Characteristics

Study Drug	ISIS 757456	Placebo
Strength	100 mg/ mL	Not Applicable
Volume/Formulation	0.80 mL solution per vial	0.80 mL solution per vial
Route of Administration	SC	SC

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 757456 or placebo) labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drug (ISIS 757456 or Placebo) supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF SUBJECTS

8.1. Study Drug Administration

Blinded vials of Study Drug will be provided by the Sponsor. Vials are for single use only. Study staff blinded to the identity of the drug will administer the Study Drug. Doses of 80 mg will be administered as a single SC injection at the Study Center. Volume to be administered is shown in Table 4. Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug (ISIS 757456 or placebo) preparation and administration.

Table 4: Study Drug Dosing Information

Volume to Administer	Total Dose
0.80 mL	80 mg or placebo

8.2. Other Protocol-Required Drugs

There are no other protocol-required drugs concurrent with the Study Drug.

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4. Treatment Precautions

There are no treatment precautions required.

8.5. Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the ISIS 757456 Investigator's Brochure.

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 757456 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects 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 subject is appropriate. If any of the stopping criteria described below (refer to Section 8.6.1 to Section 8.6.5) are met, the subject will be permanently discontinued from further treatment with Study Drug (ISIS 757456 or placebo), 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.

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.

In the event of an ALT or AST measurement that is > 3 x 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 x ULN.

Frequency of Repeat Measurements: Subjects with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN.

Further Investigation into Liver Chemistry Elevations: For subjects with confirmed ALT or AST levels > 3 x ULN, the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, Cytomegalovirus, IgM, and Epstein-Barr Virus antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (CT) or magnetic resonance imaging (MRI) 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 subject's ALT and/or AST levels reach 5 x ULN.

8.5.2. Safety Monitoring Rules for Potassium

In the event of a potassium measurement ≥ 5.5 mmol/L at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed. If the initial potassium measurement is confirmed to be ≥ 5.5 mmol/L study drug is to be held. An ECG evaluation should be performed if the value is confirmed and signs of hyperkalemia should be assessed (delayed conduction, heart block, arrhythmias). If new signs consistent with hyperkalemia are present, proceed to stopping rules. The patient will start oral hydration with 1-liter fluids not containing potassium to induce diuresis. Measure potassium frequently until documented to be < 5.5 mmol/L. Dosing with study drug may continue after a confirmed potassium measurement < 5.5 mmol/L with Investigator and Sponsor Medical Monitor or designee consultation.

8.5.3. Safety Monitoring Rules for Blood Pressure

1. In the event of a SBP ≤ 100 mmHg a second measurement must be done within a 30-minute period. If the subject's SBP is ≤ 100 mmHg within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home. If the subject then experiences an additional SBP measurement ≤ 100 mmHg (confirmed by triplicate measurement at the Study Center), or if the subject is symptomatic (i.e., dizziness, light-headedness, clammy skin, fatigue, blurry vision), the dose will be withheld. Vital signs should be confirmed, and orthostatic hypotension assessment should be performed (See Section 6.1.1.2). In addition, the subject will have home BPM 2 times per day for 1 week. Subject should orally hydrate with 1-liter fluids, including fluids with electrolyte solution (sports drink, etc.). If the subject is symptomatic the Investigator should consider admitting for observation and consider instituting intravenous (IV) hydration with 1-liter normal saline solution and reassess symptoms and orthostatic hypotension assessment. When SBP is > 100 mmHg and is asymptomatic then patient should continue dosing. If the patient has orthostatic vital signs and is asymptomatic, the dose should be withheld until orthostatic hypotension is resolved. The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.
2. Prior to Study Day 64 in the Post-Treatment Period or in the Washout Period, should a subject's BPM exceed 170 mmHg (systolic) or 110 mmHg (diastolic) a second measurement must be done within a 30-minute period. If the subject's BP is > 170 mmHg (systolic) or > 110 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home. If the subject then experiences an additional BP measurement > 170 mmHg (systolic) or > 110 mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), they will then be withdrawn from further blinded, randomized treatment. The subject's pre-study antihypertensive medication(s) may be added back per Investigator and Sponsor Medical Monitor judgement. The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.
3. On or after Study Day 64 in the Post-Treatment Period, should a subject's BPM exceed 140 mmHg (systolic) or 90 mmHg (diastolic) a second measurement must be done within a 30-minute period. If the subject's BP is > 140 mmHg (systolic) or > 90 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home. If the subject then experiences an additional BP measurement > 140 mmHg (systolic) or > 90 mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), the subject's pre-study antihypertensive medication(s) may be added back per Investigator and Sponsor Medical Monitor judgement. The subject will continue to be followed per protocol in the study.

8.5.4. Safety Monitoring Rules for Platelet Count Results

Platelet count will be monitored at least every week during the Treatment Period and for the first 4 weeks after discontinuation of treatment. The Investigator should review all platelet count results within 48 hours of receipt. 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 8.6.3) should be followed.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations should be conducted (Table 5).

Table 5: Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets Coagulation panel (PT/INR, aPTT) CBC with reticulocytes and mean platelet volume (MPV)
Serum B12 and folate
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

Note: The above labs may change as additional data is assessed, and sites will be updated regarding any changes.

8.5.5. Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event

occurs, additional testing of coagulation parameters (aPTT, PT, INR) and platelet count should be performed.

8.6. Stopping Rules

For the purposes of the stopping rules, Baseline is defined as:

- Temporary stopping rules for renal function tests – Baseline is defined as the last non-missing measurement prior to the first dose
- Stopping rules for platelets – Baseline is defined as the defined as the last non-missing measurement prior to the first dose

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 subject with Study Drug (ISIS 757456 or placebo) will be stopped permanently; values that are not confirmed due failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN, which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x 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 Renal Function Test Results

In the event of laboratory results for either of the following criteria, dosing of a subject with Study Drug (ISIS 757456 or placebo) will be stopped permanently:

1. Confirmed serum creatinine increase that is both ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above Baseline creatinine values (refer to Definition of Baseline in Section 8.6)
2. Confirmed 30% decline in eGFR from Baseline eGFR values
3. Confirmed proteinuria (UPCR ≥ 500 mg/g)

The follow-up schedule for any events meeting either of these stopping criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee. At the discretion of the Investigator, a decision to hold or permanently stop study drug may be made based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities.

8.6.3. Stopping Rule for Platelet Count Results

In the event of any platelet count less than 75,000/mm^3, monitoring frequency and dosing should be adjusted as recommended in the table below.

Table 6: Actions in Patients with Low Platelet Count

Confirmed Platelet Count	Dosing	AESI?	Monitoring
≥ 75,000/mm^3	Yes	No	• Monitor weekly
< 75,000/mm^3 to 50,000/mm^3, *in the absence of major bleeding or clinically-relevant non-major bleeding (defined below)*	Pause	No	• Monitor at least twice per week until 3 successive values above 75,000/mm^3. Then monitor weekly until values normalize. • The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study 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. The patient must have 3 successive values above 100,000/mm^3 before continued dosing is considered. • Perform additional labs in Table 5
< 50,000/mm^3 to 25,000/mm^3	Permanently Discontinue	Yes, if only accompanied by a major bleeding event or CRNMB event, subject to 15-day expedited reporting	• Monitor at least twice per week until 3 successive values above 75,000/mm^3. Then monitor weekly until values normalize. • A hematologist consultation may be considered at the discretion of the Investigator and Study Medical Monitor • Perform additional labs in Table 5
< 25,000/mm^3	Permanently Discontinue	Yes, subject to 15-day expedited reporting	• Monitor daily until 2 successive values above 25,000/mm^3. Then monitor twice per week until 3 successive values above 75,000/mm^3. Then monitor weekly until values normalize. • Administration of steroids* and a hematologist consultation is recommended • Perform additional labs in Table 5
< 10,000/mm^3	Permanently Discontinue	Yes, subject to 15-day expedited reporting	• Monitor daily until 2 successive values above 25,000/mm^3. Then monitor twice per week until 3 successive values above 75,000/mm^3. Then monitor weekly until values normalize. • Hospitalize patient and expedite a hematologist consultation. • Administer platelet transfusions and steroids*, if deemed necessary. • Perform additional labs in Table 5

* Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days. (**Note:** Patient may require continuation with oral steroids after methylprednisolone).

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
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 mg/dL (1.24 mmol/L) or more within 24 hours

Definition of Clinically-Relevant Non-Major Bleeding Events

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

Definition of Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, gingival bleeding on brushing teeth.

8.6.4. Stopping Rule for Potassium

In the event of confirmed potassium of ≥ 6.0 mmol/L or ≥ 5.5 mmol/L at any time during the study *with* new ECG changes consistent with hyperkalemia, dosing of a subject with Study Drug will be stopped permanently. The subject should stop any medications (e.g., ACE/ARB, K+ sparing diuretics, eplerenone) or high K+ diet/supplements affecting potassium levels. Measure potassium frequently until documented to be < 5.5 mmol/L. If there are ECG changes consistent with hyperkalemia or muscle weakness the subject should be admitted to the hospital. The Investigator may consider obtaining a nephrology consultation with consideration for dialysis to treat hyperkalemia. Additional consultation of the Investigator with the Sponsor Medical Monitor may be considered to individualize treatment plan.

8.6.5. Stopping Rule for Blood Pressure

1. In the event of a SBP ≤ 90 mmHg with symptoms of hypotension (i.e., dizziness, light-headedness, clammy skin, fatigue, blurry vision), as measured by home BPM, at any point in the study, the patient should contact the Study Center immediately and have the SBP confirmed by the Study Center. If confirmed and the patient remains symptomatic, dosing of a subject with Study Drug will be interrupted. If patient is still symptomatic after instituting IV hydration (see Section 8.5.3 Safety Monitoring Rules for Blood Pressure), the patient should be admitted to the hospital. Timing for re-institution should be assessed depending on the reversibility of initiating factors (decreased oral intake, cold/flu, other illness). If the subject remains symptomatic Study Drug should be stopped permanently. If this occurs in the follow-up period, any other antihypertensives or other medications that could affect BP should be stopped, if feasible. The use of IV angiotensin II or vasopressors should be considered in subjects that remain symptomatic and are hemodynamically unstable. The subject will continue to be followed per protocol

in the study. Follow-up for subjects that screen fail due to blood pressure inclusion criteria (see Section 5.1) will not be necessary.

2. During the Treatment Period, should a subject experience a BP measurement > 170 mmHg (systolic) or > 110 mmHg (diastolic) a second measurement must be done within a 30-minute period. If the subject's BP is >170 mmHg (systolic) or > 110 mmHg (diastolic) within the 30-minute period, an additional BP measurement should be taken within 48 hours at the Study Center, regardless of whether the initial BP measurements were taken in clinic or at home. If the subject then experiences a BP measurement > 170 mmHg (systolic) or > 110 mmHg (diastolic) (confirmed by triplicate measurement at the Study Center), they will then be withdrawn from further blinded, randomized treatment. The subject's pre-study antihypertensive medication(s) may be added back per Investigator and Sponsor Medical Monitor judgement. The subject will continue to be followed per protocol in the study.

8.7. Adjustment of Study Drug Dose or Schedule

If the safety profile warrants, and subjects have not met a stopping rule, Study Drug may be adjusted downward in consultation with the Sponsor Medical Monitor or designee.

8.8. Discontinuation of Study Drug

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

- The subject withdraws consent
- The subject experiences an AE that necessitates permanent discontinuation of Study Drug
- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6.1 to Section 8.6.3
- The subject experiences an AE that necessitates unblinding of the Investigator to the subject's treatment assignment

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

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A) and ideally within 2 weeks from the last dose of Study Drug.

8.9. Withdrawal of Subjects from the Study Procedures

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

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

Other reasons for withdrawal of subjects from study procedures might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- 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 subject who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These subjects should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (Appendix A) and ideally within 2 weeks from the last dose of Study Drug.

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination 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 subject's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

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

8.10.1.1. Allowed Concomitant Therapy

Any other medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

If the criteria in Section 8.5.3 (blood pressure monitoring rules) are met and the patient is in the Post-Treatment Period, antihypertensive agents may be added for BP control in consultation with the Investigator and Sponsor Monitor or designee.

8.10.1.2. Disallowed Concomitant Therapy

The following are disallowed concomitant therapies:

- Medications for the treatment of HTN (e.g., clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors) (unless required for safety reasons to control BP in the Post-Treatment Period)
- Medications that may also cause hyperkalemia (e.g., cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins)

- Oral or subcutaneous anticoagulants (e.g., warfarin, rivaroxaban, apixaban, lovenox, heparin). Organic nitrate preparations (e.g., nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol)
- Sildenafil, tadalafil, vardenafil

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between screening and the end of the Post-Treatment Evaluation 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 SOPs throughout the conduct of the clinical trial.

9.2. Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH GCP. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRBs) will be notified of any SAE according to applicable regulations.

The Sponsor or designee will evaluate the available information for all reported SAEs and decide if there is a reasonable possibility that the Study Drug (ISIS 757456 or placebo) caused the AE and, therefore, meets the definition of a SUSAR.

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

For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population. For Study Drug (ISIS 757456 or placebo) "expected" AEs, refer to the Investigator's Brochure.

9.3. Definitions

9.3.1. Adverse Event

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

An 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 Study Drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2. Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

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

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

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the 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 (SAE)

A 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 subject 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 subject (whether the subject 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 subject 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 [NCI CTCAE]; OR Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; the event itself may be of relatively minor medical significance [such as severe headache without any further findings]).

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

9.3.4. Adverse Event of Special Interest

For the purpose of this study, severe reductions in platelet count < 50,000/mm^3 accompanied by a major bleeding (MB) event or clinically-relevant non-major bleeding (CRNMB) event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event are considered as AEs of special interest 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 subject 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 subject safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period which is defined as Study Day 127. When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. SAEs should be reported using an electronic SAE submission form whenever possible. In situations where the electronic SAE submission is unavailable, an Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee. The SAE reporting instruction, including the fax number and email address, for reporting SAEs can be found in the Study Reference Manual for the study.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject'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 subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as Study Day 127 / Week 19. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test

- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug 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 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 subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory test and adverse events at the injection site may be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017 (refer to Appendix D) and the Investigator should classify events and laboratory findings as mild, moderate, or severe based on the clinical significance of the event and laboratory finding in the study subject. Any AE not listed in Appendix D will be graded as follows:

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

Action taken with Study Drug due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug administration and dose
- **Not Applicable:** SAE/AE was reported during Screening Period prior to Study Drug administration
- **Permanently Discontinued:** Study Drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing and/or dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose
- **Reduced Dose:** Dosing was reduced, temporarily interrupted or delayed due to the AE and restarted at the next lower dose or reduced dosing frequency

9.4.3.4. Treatment Given for Adverse Event

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

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

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

If the event is an SAE, then the event's outcome is characterized by 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 subject 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 Study Drug or related to study procedures until a final outcome can be reported.

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

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

Sponsor Follow-Up

For SAEs, AESI and pregnancy cases in subjects who have completed or terminated study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of 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 subject 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 subject'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 subject'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 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 subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject takes a dose of Study Drug that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

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

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

9.5.4. Contraception and Pregnancy

Male subjects must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a male subject 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 subject's responsibility.

Male subjects: The progress of the pregnancy of a male subject'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

10.1. Stratification

Subjects will be stratified based on screening plasma AGT concentration (≤ 30 µg/mL vs. > 30 µg/mL).

[redacted]

10.3. Populations

Full Analysis Set (FAS): All randomized subjects who have received at least 1 injection of Study Drug (ISIS 757456 or Placebo) and who have at least 1 post-Baseline efficacy or exploratory measurements.

Per Protocol Set (PPS): All FAS subjects who received at least 5 of the 7 doses of Study Drug, did not receive antihypertensive medications during the Treatment Period and prior to Study Day 43, and have no significant protocol deviations that would be expected to affect efficacy or exploratory assessments.

Safety Set: All subjects who are randomized and receive at least 1 dose of Study Drug.

PK Set: All subjects who are randomized and receive at least 1 dose of Study Drug and have at least 1 evaluable PK sample.

10.4. Definition of Baseline

The baseline for plasma AGT will be define as the average of all values on or after Study Day -7 and prior to the first dose of Study Drug. The baseline for all other assessments will be defined as the last non-missing measurement prior to the first dose.

10.5. Interim Analysis

An interim analysis may be conducted after at least 50% of the subjects have been enrolled.

10.6. Planned Methods of Analysis

All CRF data, lab data transfers, and any outcomes derived from the data will be provided in the subject data listings. Subject data listings will be presented for all subjects randomized in the study. Descriptive summary statistics including n, 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. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

10.6.1. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. Subject randomization will be summarized by treatment group. The subject disposition will be summarized. All subjects enrolled will be included in a summary of subject disposition.

10.6.2. Safety Analysis

The safety analysis will be conducted on the Safety Set.

Treatment duration and amount of Study Drug received will be summarized by treatment group. Subject incidence rates of all treatment-emergent AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) coding system by system organ class, preferred term, relationship to Study Drug, and severity. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, all treatment-emergent serious AEs potentially related to Study Drug, and treatment-emergent Adverse Event of Special Interest (AESI) will be summarized.

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

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

10.6.3. Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to Study Week 7 (Study Day 43) in plasma AGT between ISIS 757456 80 mg group and placebo group in the Per Protocol Set. The data will be analyzed using analysis of variance (ANOVA) with treatment and randomization stratification factor (screening AGT concentration) as independent variables. In the case data departs substantially from normality, the nonparametric van Elteren test will be employed instead.

The secondary efficacy analyses will be performed in a similar way to the primary analysis, which include:

- Comparison of change and percent change from Baseline to each schedule post-Baseline visit in AGT between ISIS 757456 80 mg group and placebo group in PPS and FAS
- Comparison of change from Baseline to each schedule post-Baseline visit in in-clinic SBP and DBP between ISIS 757456 80 mg group and placebo group in PPS and FAS

10.6.4. Pharmacokinetic Analysis

The plasma PK of ISIS 757456 (total Full Length ASO, including fully conjugated, partially conjugated, and unconjugated ISIS 757456) will be assessed following SC administration. Non-compartmental PK analysis of ISIS 757456 (total Full Length ASO) will be carried out on each individual subject data set.

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 Statistical Analysis Plan (SAP).

Analysis of potential exposure-response relationship between plasma AGT and ISIS 757456 exposure (such as C_{trough}) will be conducted. Relationships between other relevant biomarkers and PK measures may also be explored, if deemed appropriate.

Population PK and PK/PD analysis may be performed using PK data from this Study, and/or combined with other ISIS 757456 clinical PK/PD data later in the development timeline.

10.6.5. Exploratory Analyses

The change of the weekly average of at-home BP from Baseline to each schedule post-Baseline visit, and the change and percent change from Baseline to each schedule post-Baseline visit in angiotensin II, renin (Plasma renin activity [PRA]; active renin mass concentration [ARC]), and plasma aldosterone will be compared between ISIS 757456 80 mg group and placebo group in PPS and FAS. The data will be analyzed in a similar way to the primary analysis.

The percentage of subjects reaching the following goals for the in-clinic BP over time will be summarized, comparison of which will be made between ISIS 757456 80-mg group and placebo group using Fisher's exact test.

- Percentage of subjects reaching SBP goal of $\leq$ 140 mmHg
- Percentage of subjects reaching DBP goal of $\leq$ 90 mmHg
- Percentage of subjects reaching both goals of SBP $\leq$ 140 mmHg and DBP $\leq$ 90 mmHg

In addition, the percentage of subjects requiring antihypertensive therapy during the study, as well as the time in days from first dose of Study Drug to the first administration of antihypertensive therapy during the study will be compared between ISIS 757456 80-mg group and placebo group in PPS and FAS. The analyses will be detailed in the SAP.

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.

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 757456 or placebo) are administered. The subject must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the subject's agreement or refusal to notify his/her primary care physician should be documented in the subject's medical records and the informed

consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form 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 subject.

11.2. Ethical Conduct of the Study

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

11.3. Institutional Review Board

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

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

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

11.4. Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, subjects should be identified by initials (if permitted by local law) and a subject identification number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) 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 IRB direct access to review the subject'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 subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

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

12.2. Study Termination

The Sponsor 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 site contract. The Investigator should notify the IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3. Study Documentation and Storage

An electronic case report form (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 trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

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

The Investigator 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 and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed CRFs, 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 IRB and the Sponsor
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

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

No study document should be destroyed without prior written agreement between the Sponsor 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.

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 trial (e.g., CRFs and other pertinent data) provided that subject confidentiality is respected.

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

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 CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial 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 subject data received by the Sponsor. During this review, subject 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.

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

12.5. Language

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

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

12.6. Compensation for Injury

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

13. REFERENCES

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

Study Week	Screen	Run-In	WO		Treatment (6 Weeks)							Post-Treatment Evaluation Period (13 Weeks)					
		Wk -3	Wk -2	Wk -1	Wk1		Wk 2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk10	Wk12	Wk16	Wk19
Study Day	D-42 to D-22	D-21	D-14	D-7	D1	D3	D8	D15	D22	D29	D36	Treatment Early Term[9]/ D43	D50	D64	D78	D106	PT Early Term[9]/ D127
Visit Window	N/A		± 1	± 1		+2	+2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5	± 5
Scheduled Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed Consent	X																
Inclusion/Exclusion	X			X													
Medical History	X																
CVD Risk Factors	X																
Body Weight and Height[8]	X				X							X					X
Physical Exam[1]	X				X							X					X
ECG (12-Lead)	X				X[c]						X[c]	X					
Vital Signs (clinic)[2]	X	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Home BP/HR[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HepB & C	X																
FSH[3]	X																
Pregnancy Test[4]	X																
Chemistry Panel (Fasting)[7, 11]	X				X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Renal Urine Biomarkers	X				X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
TSH, FT3, FT4	X																
Hematology[7]	X				X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Urinalysis[10]	X				X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Angiotensinogen	X			X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

	Screen	Run-In	WO		Treatment (6 Weeks)							Post-Treatment Evaluation Period (13 Weeks)					
Study Week		Wk -3	Wk -2	Wk -1	Wk1		Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk10	Wk12	Wk16	Wk19
Study Day	D-42 to D-22	D-21	D-14	D-7	D1	D3	D8	D15	D22	D29	D36	Treatment Early Term[9]/ D43	D50	D64	D78	D106	PT Early Term[9]/ D127
Visit Window	N/A		± 1	± 1		+2	+2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5	± 5
Scheduled Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Exploratory	X			X	X[a]				X[a]			X		X	X	X	X
hsCRP					X[a]						X[a]	X					X
PT, INR, aPTT	X				X[b]	X[a]	X[a]			X[a]	X[a]	X					
Study Drug Administration					X	X	X	X	X	X	X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Blood Sampling[5]					X[d]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Immunogenicity Testing					X[a]							X					X
Archived Serum Sample[6]					X	X	X			X	X	X			X		X

Run-in = Subjects will measure their SBP/DBP/HR while on their current antihypertensive medications for 1 week prior to withdrawal of HTN medications
WO = Washout from antihypertensive medications (ACE/ARB and any other antihypertensive medications)
If not specifically labeled, "X" means anytime
A 10-minute time window applies to all procedures to allow for flexibility where multiple procedures are scheduled at the same time

1 Full physical exam to be given at Screening and abbreviated physical exam to be given thereafter
2 Vital Signs (clinic): Blood Pressure (SBP/DPB; sitting), Orthostatic assessment (supine and standing, required at Screening), Heart Rate (HR), Respiratory rate (RR), Temperature (T); Vital Signs (home) = Blood Pressure (SBP/DPB), Heart Rate (HR). Please adhere to the blood pressure guidance document as closely as possible. Home vital sign assessments will be reviewed by the study doctor at each visit prior to dosing. Based on Study Doctor judgment, and in consultation with the Sponsor Medical Monitor, during the Post-Treatment Period and no sooner than 4 weeks after the last dose, the frequency of the home assessments may be decreased.
3 Women who are not surgically sterile, as confirmation of menopause
4 Women who are not surgically sterile. Serum test to be done
5 Refer to Appendix C for PK sampling schedule

Appendix A Schedule of Procedures *Continued*

Legend Continued

6 Stored at -80 C 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.) in this or subsequent clinical studies of ISIS 757456

7 If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen for should be re-drawn as soon as possible (ideally within 7 days) prior to next dose. Due to time constraints, a local lab draw is recommended if a repeat blood specimen is necessary to continue dosing at any time after Study Day 1 to Study Day 8.

8 Height at Screening only

9 Subjects who terminate treatment or post-treatment early from the study should be encouraged to participate in an early termination visit, at which time the Study D43 or Study D127 assessments should be conducted, respectively

10 Archived sampled to be collected as well. Samples will be stored at -80 C for follow-up exploration of laboratory findings and/or AEs in this or subsequent clinical studies of ISIS 757456

11 Fasting is not required at Screening visit. Fasted samples should be taken after fasting for at least 8 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

Time (time is in reference to Study Drug administration):

a Pre-dose

b Pre-dose, 3hr

c Pre-dose, 2 hr

d Pre-dose, 1, 2, 4, 6 hrs post-SC injection

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 757456 or other similar oligonucleotides.

Clinical Chemistry Panel
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Creatinine Clearance
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatinine kinase
- GGT

Thyroid Panel
- TSH
- Free T4
- Free T3

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only, if applicable)
- Serum βhCG (women only, if applicable)

Coagulation
- aPTT (sec)
- PT (sec)
- INR

Efficacy
- Plasma Angiotensinogen

Pharmacokinetics[1]
- ISIS 757456 levels in plasma

Immunogenicity
- Anti-ISIS 757456 antibodies[3]

Renal Urine Biomarkers
- NGAL[3]
- NAG[3]
- KIM-1

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

Exploratory
- Angiotensin II
- Renin (plasma renin activity)
- Renin (active renin mass concentration)
- Plasma Aldosterone
- Angiotensin I[3]
- Angiotensin (1-7)[3]
- Angiotensin III[3]
- Angiotensin IV[3]
- B-type natriuretic peptide[3]
- Atrial natriuretic peptide[3]
- Plasma Neprilysin[3]
- Endothelin I[3]

Inflammatory
- Hs-CRP

Urinalysis
- Color
- Appearance
- Specific gravity
- pH
- P/C Ratio (UPCR)
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]
- Angiotensinogen[3]
- Albumin[3]
- Creatinine[3]
- Protein[3]
- Sodium[3]
- Cortisol[3]
- Aldosterone[3]
- A/C Ratio (UACR)[3]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation) or to assess other actions of ISIS 757456 with plasma constituents
2 Will be performed on abnormal findings unless otherwise specified
3 May be analyzed

APPENDIX C. PK SAMPLING SCHEDULE

Appendix C PK Sampling Schedule

PK Sampling Schedule

Time Points for PK Blood Draws												
D1	**D3**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D64**	**D78**	**D106**	**D127**
Pre-dose, 1, 2, 4, 6 hrs post-D1 SC injection	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime	Anytime	Anytime
Number of PK Blood Draws												
5	1	1	1	1	1	1	1	1	1	1	1	1

Note: Time is shown as hours relative to dose of Study Drug
SC = subcutaneous
D = Day

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 upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017.

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	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	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

Signature Page for VV-CLIN-011295 v2.0

Approval	[redacted] 29-Mar-2019 02:00:49 GMT+0000

Signature Page for VV-CLIN-011295 v2.0

[redacted]

[redacted]

Date

Ionis Pharmaceuticals, Inc.

Official Title:	**A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-LRX, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure**
NCT Number:	**NCT03714776**
Document Date:	SAP Version 1.1 : 14 November 2019

Statistical Analysis Plan

ISIS 757456 –CS2

A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure

Date: November 14, 2019

Version: 1.1

CONFIDENTIAL

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court Carlsbad, CA 92010

Compound Name: 757456

Protocol: CS2

Study Title: A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense Inhibitor Administered Subcutaneously for 6 Weeks to Hypertensive Subjects with Controlled Blood Pressure

Issue Date: 29 March 2019 (Protocol Amendment 1)

Signature: [redacted] Date: [redacted]

[redacted]

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Signature: [redacted] Date: [redacted]

[redacted]

[redacted]

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Signature: [redacted] Date: [redacted]

[redacted]

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Table of Contents

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.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

Within this document, the terms 'patient' and 'subject' are both used to describe the individual who enrolls in this study.

1.1 Study Overview

This will be a Phase 2, double-blind, randomized, placebo-controlled study of ISIS 757456 conducted in mild hypertensive subjects on an ACEi/ARB and an additional hypertensive medication. Subjects will be stratified based on a screening plasma AGT concentration (≤ 30 µg/mL vs. > 30 µg/mL) and randomized in a 2:1 ratio to receive a once-weekly subcutaneous (SC) treatment and an additional loading dose on Study Day 3 with either ISIS 757456 80 mg or placebo for 6 weeks.

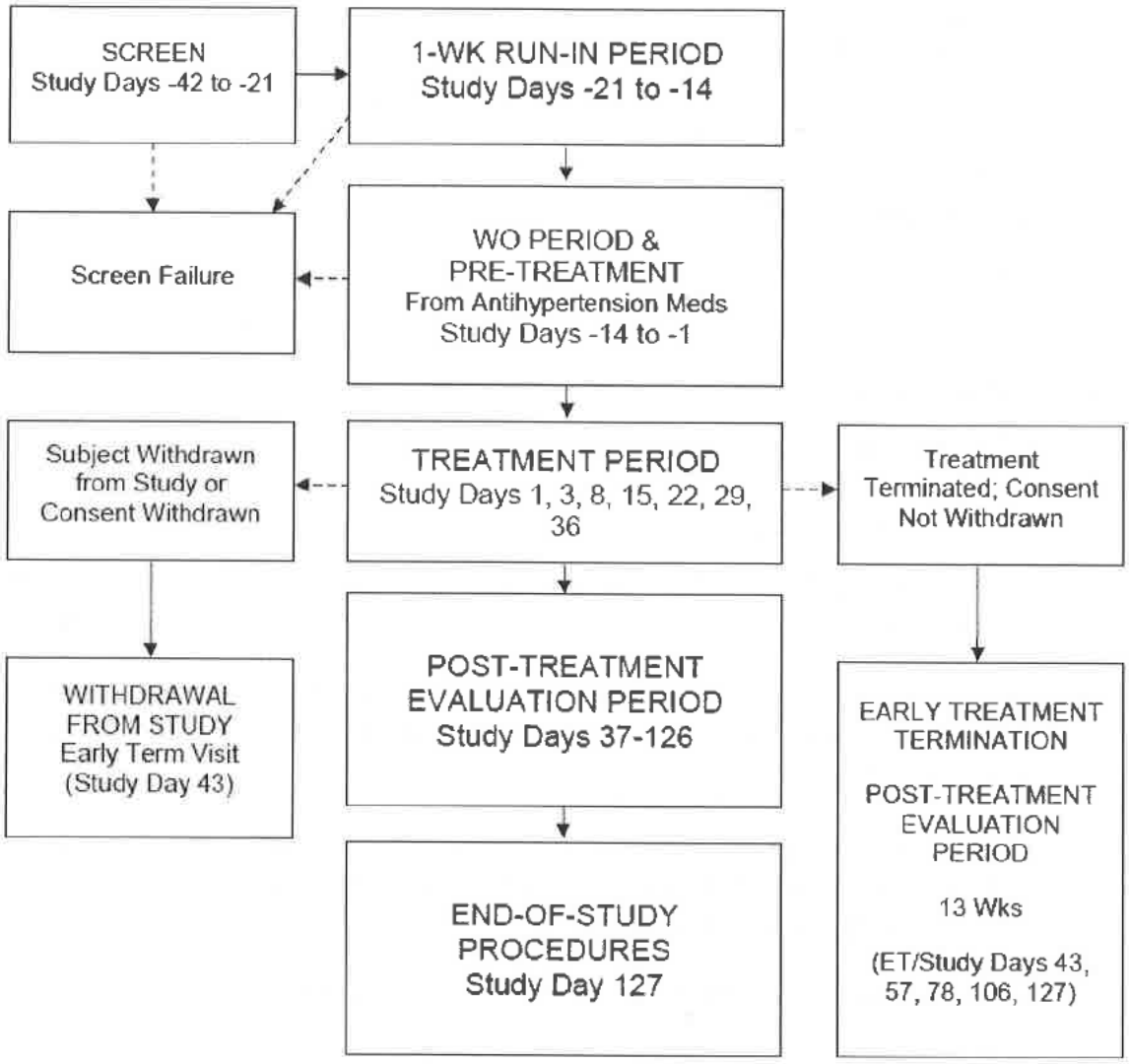
All subjects will complete a 13-week Post-Treatment Period. In the Post-Treatment Period, should a subject's sitting BP on home monitoring exceed 140 mmHg systolic or 100 mmHg diastolic on 2 consecutive days (confirmed by triplicate measurement at the Study Center), the subject's initial hypertension (HTN) medication(s) may be added back per Investigator and Sponsor Medical Monitor judgment and the subject will continue to be followed per protocol in the study.

[redacted] All Study Drug injections will be SC administered in the clinic.

This study will be conducted at multiple centers in the United States. Approximately 30 subjects are planned to be enrolled in this study.

The study will consist of screen, run-in, washout (WO), treatment, and post-treatment. The overall length of a subject's participation will be approximately 25 weeks (up to 3 weeks for screening, 1-week run-in, 2 weeks for WO, a 6-week Treatment Period, and 13 weeks of Post-Treatment Evaluation Period.

The study design and treatment schema are depicted as follows:


SCREEN
Study Days -42 to -21
1-WK RUN-IN PERIOD
Study Days -21 to -14
Screen Failure
WO PERIOD &
PRE-TREATMENT
From Antihypertension Meds
Study Days -14 to -1
Subject Withdrawn from Study or Consent Withdrawn
TREATMENT PERIOD
Study Days 1, 3, 8, 15, 22, 29, 36
Treatment Terminated; Consent Not Withdrawn
WITHDRAWAL FROM STUDY
Early Term Visit
(Study Day 43)
POST-TREATMENT EVALUATION PERIOD
Study Days 37-126
EARLY TREATMENT TERMINATION
POST-TREATMENT EVALUATION PERIOD
13 Wks
(ET/Study Days 43, 57, 78, 106, 127)
END-OF-STUDY PROCEDURES
Study Day 127

1.2 Objective

1.2.1 Primary Objective(s)

- To evaluate the effect of ISIS 757456 subcutaneous (SC) injection on plasma angiotensinogen concentration

1.2.2 Secondary Objective(s)

- To evaluate the effect of ISIS 757456 on in-clinic systolic blood pressure over time in Treatment and Post-Treatment Periods

1.2.3 Safety Objectives

- To evaluate the safety and tolerability of ISIS 757456 vs. placebo

1.2.4 Exploratory Objectives

- To evaluate the effect of ISIS 757456 on at-home blood pressure over time in the Treatment and Post-Treatment Periods
- To evaluate the exploratory effects of ISIS 757456 administered subcutaneously {e.g., angiotensin II, renin [Plasma renin activity (PRA); active renin mass concentration (ARC)], plasma aldosterone}
- To evaluate the pharmacokinetics (PK) of ISIS 757456 (as total Full Length ASO, including fully conjugated, partially conjugated, and unconjugated ISIS 757456) administered subcutaneously in subjects with hypertension
- To evaluate potential PK/PD correlation with relevant biomarkers

1.3 Endpoints

1.3.1 Primary Endpoint

- Percent change in plasma angiotensinogen from Baseline to Study Day 43 (Week 7) compared to placebo

1.3.2 Secondary Endpoints

- Change on in-clinic SBP from Baseline to each scheduled, post-Baseline visit
- Change and percent change in plasma angiotensinogen from Baseline to each scheduled, post-baseline visit

1.3.3 Safety Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAE) (including hypotension and orthostatic hypotension), use of concomitant medications, laboratory assessments, ECG, and vital signs

1.3.4 Exploratory Endpoints

- Change of the weekly average of at-home BP from Baseline to each scheduled, post-baseline visit
- Change and percent change of angiotensin II, renin (Plasma renin activity [PRA]; active renin mass concentration [ARC]), and plasma aldosterone from Baseline to each scheduled, post-baseline visit
- Percentage of subjects reaching the goals of in-clinic SBP ≤ 140 mmHg, DBP ≤ 90 mmHg, and both over time
- Percentage of subjects and time to requiring antihypertensive therapy during the study
- Assessments of urinary analytes (e.g., cortisol, aldosterone, angiotensin II, albumin, creatinine, protein and sodium) from Baseline to each scheduled, post-baseline visit may be performed
- PK parameters including but not limited to Cmax (maximum observed ISIS 757456 plasma concentration), Tmax (time to maximal plasma concentration) and AUC (area under the plasma concentration time profile for ISIS 757456)
- Potential exposure-response analysis using relevant exposure parameters and biomarkers including, but not limited to Ctrough and plasma AGT may be performed

2 PROCEDURES

2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. (or designee) will review all study data including source documents, case report forms, and laboratory reports. The study site will enter subject source data into the case report form. Some laboratory data will be transferred electronically from PPD Development (plasma PK) to Ionis Pharmaceuticals, Inc.

2.2 Randomization

Subjects will be randomized after all screening, run-in, and WO assessments through Study Day -7 have been completed and after the Investigator has verified that they are eligible per criteria in protocol Sections 5.1 and 5.2 and after approval reviewed by Sponsor Medical Monitor or designee. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

Eligible subjects will be stratified based on a screening plasma AGT concentration screening plasma AGT concentration (≤ 30 µg/mL vs. > 30 µg/mL) and then subjects will be randomized 2:1 to receive ISIS 757456 or placebo as outlined in protocol Section 3.1. Eligible subjects must have a plasma AGT concentration ≥ 20 µg/mL to participate in the study (see protocol Section 5.1 Inclusion Criteria). The Sponsor or designee will prepare the randomization list and utilize an automated IRT (Interactive Response Technology) system.

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. Please refer to protocol section 8.5 for details.

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 (CRF) 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. 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 are 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. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets or Excel files.

2.5.3 Pharmacokinetics (PK) Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma drug concentration data. Final data, which has been approved by Quality Assurance, will be stored in version-controlled repository

3 ANALYSIS PLAN

3.1 General Overview of Analyses

Descriptive summary statistics including number of subjects, mean, median, standard deviation, standard error of mean, 25th percentile, 75th percentile, minimum, and maximum for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

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

Baseline definition:

The baseline for plasma AGT will be define as the average of all values on or after Study Day -7 and prior to the first dose of Study Drug. The baseline for all other assessments will be defined as the last non-missing measurement prior to the first dose, unless otherwise specified.

Analytical visits:

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 the analysis of confirmed ALT/AST category (see section 3.7.3) but will be presented in data listings.

[redacted]

3.3 Statistical Methods

3.3.1 Subject Populations Analyzed

The following analysis populations are defined for this study:

- Full Analysis Set (FAS): All randomized subjects who have received at least 1 injection of Study Drug (ISIS 757456 or Placebo) and who have at least 1 post-Baseline efficacy or exploratory measurements.

- Per Protocol Set (PPS): All FAS subjects who received at least 5 of the 7 doses of Study Drug, did not receive antihypertensive medications during the Treatment Period and prior to Study Day 43, and have no significant protocol deviations that would be expected to affect efficacy or exploratory assessments.

- Safety Set: All subjects who are randomized and receive at least 1 dose of Study Drug.

- PK Set: All subjects who are randomized and receive at least 1 dose of ISIS 757456 and have at least 1 evaluable PK sample.

3.3.2 Handling of Missing Data

Missing values will not be imputed.

3.3.3 Planned Interim Analysis

An interim analysis may be conducted after at least 50% of the subjects have been enrolled.

3.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics (e.g., age, gender, ethnicity, race, weight, height, BMI, and CVD risk) will be summarized using descriptive statistics by treatment group.

BMI will be computed using the formula: BMI = (weight in kilograms) / [height in cm / 100]^2

Subject randomization and disposition will be summarized by treatment group. All subjects enrolled will be included in the summary.

Protocol deviations will be listed.

3.5 Efficacy Analysis

3.5.1 Primary Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to Study Week 7 (Study Day 43) in plasma AGT between ISIS 757456 80 mg group and placebo group in PPS. The data will be analyzed using analysis of variance (ANOVA) with treatment and randomization stratification factor (screening AGT concentration) as independent variables. The normality assumption for the ANOVA model will be assessed by the Shapiro-Wilks test on the residuals. In the case data departs substantially from normality, the nonparametric van Elteren test will be employed instead.

3.5.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed in a similar way to the primary analysis, which include:

- Comparison of change and percent change from Baseline to each schedule post-Baseline visit in AGT between ISIS 757456 80 mg group and placebo group in PPS and FAS
- Comparison of change from Baseline to each schedule post-Baseline visit in in-clinic SBP and DBP between ISIS 757456 80 mg group and placebo group in PPS and FAS. Subsequent SBP and DBP measurements will be completely removed from this analysis once the subjects received first administration of antihypertensive therapy during the study.

3.5.3 Exploratory Analyses

The exploratory analyses will be conducted using the PPS and FAS.

The change of the weekly average of at-home BP from Baseline to each schedule post-Baseline visit, and the change and percent change from Baseline to each schedule post-Baseline visit in angiotensin II, renin (Plasma renin activity [PRA]; active renin mass concentration [ARC]), and plasma aldosterone will be compared between ISIS 757456 80 mg group and placebo group. The data will be analyzed in a similar way to the primary analysis. For the at-home BP analysis, subsequent SBP and DBP measurements will be completely removed from this exploratory analysis once the subjects received first administration of antihypertensive therapy during the study.

The percentage of subjects reaching the following goals for the in-clinic BP over time will be summarized, comparison of which will be made between ISIS 757456 80-mg group and placebo group using Fisher's exact test. Subsequent SBP and DBP measurements will be completely removed from this exploratory analysis once the subjects received first administration of antihypertensive therapy during the study.

- Percentage of subjects reaching SBP goal of ≤ 140 mmHg
- Percentage of subjects reaching DBP goal of ≤ 90 mmHg
- Percentage of subjects reaching both goals of SBP ≤ 140 mmHg and DBP ≤ 90 mmHg

The antihypertensive therapy will be identified through medical review when database is locked. The percentage of subjects requiring antihypertensive therapy during the study will be compared between ISIS 757456 80 mg group and placebo group in PPS and FAS using Chi-Square test or Fisher's exact test as appropriate. The time in days from first dose of Study Drug to the first administration of antihypertensive therapy during the study will be summarized using the following descriptive statistics: mean, standard deviation, median, P25, P75, and minimum and maximum. The Kaplan-Meier curves [1] for time to the first administration of antihypertensive therapy will be provided for ISIS 757456 80 mg group and placebo group, comparison of which may be made statistically using the log rank test. The time to the first administration of antihypertensive therapy will be calculated as:

- [Date of the first administration of antihypertensive therapy – Date of first dose of study drug +1]

Patients who did not receive any antihypertensive therapy during the study will be censored at the date of end of study.

3.6 Pharmacokinetic Analysis

The plasma pharmacokinetics of ISIS 757456 (as total full-length oligonucleotides or ISIS 757456-equivalent, ISIS 757456-eq.) will be assessed following SC administration(s). The analyses will be conducted on the PK Set.

Metabolite identification and profiling may be determined in some of the collected plasma samples and will be reported separately.

3.6.1 Plasma Concentration Data of Total Full-Length Oligonucleotides

Plasma concentrations of ISIS 757456 (ISIS 757456eq.), along with the scheduled (nominal) and actual samples times (i.e., time from SC dosing) will be listed (when applicable) for each patient, by treatment group, dose cohort, nominal dose, and day. In addition, percent differences between scheduled and actual sampling times will also be listed for all patients. Percent differences between actual administered dose and nominal dose will also be listed.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as "BLQ", and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 757456 plasma concentrations will be tabulated by treatment group, dose cohort, nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 757456eq. plasma concentration versus time (actual) profiles for each patient that received ISIS 757456 active treatment, as well as the mean (± SD or SE) plasma concentrations versus time (scheduled) profiles, will be presented graphically on linear and semilogarithmic scales. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times.

3.6.2 Plasma Pharmacokinetic Parameters

The plasma PK of ISIS 757456 (as total full-length oligonucleotides) will be assessed following the first SC dose. Non-compartmental PK analysis of ISIS 757456 (total full-length oligonucleotides) will be carried out on each individual subject data set using Phoenix WinNonlin version 8.0 or higher (Pharsight Corporation, Mountain View, CA). For calculation of PK parameters, all BLQ values will be set to zero. The plasma PK parameters for ISIS 757456eq. will be calculated based on actual sampling times. The plasma PK parameters to be calculated or determined (when applicable) are listed in Table 1. Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Table 1 Plasma Pharmacokinetic Parameters to be Calculated or Determined

Parameter	Definition/Method	Multiple-dose D1
C_{max}	Maximum observed concentration	X
T_{max}	Observed time at which C_{max} occurs	X
T_{last}	Time of last measurable (positive) concentration	X
AUC_{0-t}	Partial AUC: Area under the concentration-time curve from time zero to time t (e.g., t may be 24, 48, 72, or 168 hrs, as applicable), calculated using linear-up log-down method	X
CL_{0-t}/F	Partial clearance divided by F (fraction of the dose absorbed) determined by Dose/AUC_{0-t}	X

Note: X designates parameters to be calculated or determined assuming sufficient data

Plasma pharmacokinetic parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment group, dose cohort, nominal dose, and day.

3.6.3 Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response correlations maybe explored graphically between plasma exposure (AUC, Cmax, Cmin, as appropriate), and selected PD measures (e.g. serum AGT level), other relevant biomarkers (such as plasma renin activity, angiotensin II, etc) and relevant clinical endpoints (such as in-clinic systolic blood pressure). In addition, the relationship between serum AGT level with plasma concentrations (Cmax, Cmin, as appropriate) of ISIS 757456 eq. may be further evaluated with an inhibitory effect E_{max} model.

Population PK and PKPD analysis may be performed using the PK and PD data from this Study, and/or combined with other ISIS 757456 clinical PK/PD data from any previous and future studies in the development timeline.

3.6.4 Immunogenicity (IM) Analysis

The samples for immunogenicity are not planned to be analyzed.

3.7 Safety Analyses

The safety analysis will be conducted on the Safety Set.

3.7.1 Exposure

Treatment duration and amount of Study Drug (ISIS 757456 or placebo) received will be summarized by treatment group. The treatment duration for each subject is defined as last dose date - first dose date +1.

3.7.2 Adverse Events

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 preferred term and system organ class for:

- 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 subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. Adverse events with missing severity will categorized as "Missing" for this summary
- Serious treatment emergent adverse events

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

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug or placebo and subsequently worsened, or is not present prior to receiving the first dose of study drug or placebo but subsequently appeared.

If there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, then we compare them pairwise, and consider two cases, where we compare the AE severity (mild/moderate/severe) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AEs.

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

If the AE severity on the second record is worse than the severity on the first record, then only count the second AE as treatment-emergent. But, if the severity improves (second record severity is less severe than the first record severity), then neither record is counted as treatment-emergent.

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.

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.

3.7.2.1 Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe Injection Site Erythema, Swelling, Pruritus, Pain or Tenderness that started on the day of injection, persisted for at least two days, i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after the injection, will be included. Events with onset date on the day of injection and missing resolution date will also be included; or (B) any AE at the injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the injection site is the principal reason for discontinuation.

Percentage of injections leading to local cutaneous reaction at the injection site will be calculated as follows for each subject: (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.

3.7.2.2 Flu-like Reactions

Flu-like reactions will also be summarized by preferred term.

Flu-like reactions are defined as either (A) flu-like illness or (B) Pyrexia or feeling hot or body temperature increased, plus at least two of the following: Chills, Myalgia, and Arthralgia, starting on day of injection or the next day.

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

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

Flu-like reactions will be listed by preferred term.

3.7.2.3 AE of special interest (AESI): Platelet reduction

Per protocol, severe reductions in platelet count < 50,000/mm^3 accompanied by a major bleeding (MB) event or clinically-relevant non-major bleeding (CRNMB) event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event are considered as AESI. The AEs meeting the AESI criteria will be captured in the AE CRF page with a check box to indicate. AESI will be summarized by preferred term.

3.7.3 Laboratory Measurements

Chemistry, hematology, coagulation, complement and urinalysis (result, change and percent change from baseline) will be summarized by treatment group and each post-baseline visit. All ALT, AST, and Platelet data from both the central and local laboratories will be summarized. For the rest of the parameters, only the central laboratory values will be summarized. For urinalysis, only P/C ratio, Protein, and Urine Creatinine will be summarized.

For ALT and AST, the number and percent of subjects falling in each of the following categories will be tabulated by treatment group:

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

A confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If that value is in the same or worse category then 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.

3.7.4 Vital Signs

Vital signs will include heart rate, respiratory rate, body temperature, BMI and systolic and diastolic blood pressure. Vital signs will be summarized by treatment group for vital sign values as well as the change and percent change from baseline at each post-baseline visit.

The study provided at-home blood pressure monitor (Omron Device) is used to assess each at-home triplicate measurement. The device automatically conducts three successive blood pressure assessments with 60 seconds in between each measurement. The device records one time for the triplicate assessments - the time provided is the start time of the triplicate sequence, therefore, the data reported in the subject diary and in EDC has one collection time for all three blood pressure assessments. The triplicate average will be based on the first 3 blood pressure assessments.

3.7.5 12-Lead Electrocardiograms (ECG)

Safety 12 lead ECG will be performed in triplicate at the visits indicated in the protocol Schedule of Procedures. The baseline is defined as the average of the triplicate prior the first dose of study drug.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, and corrected QT intervals, and overall interpretation.

For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum) of the average of triplicate results at each study visit, as well as the change and percent change from Baseline to each study visit, will be presented in summary tables; for the categorical responses to overall

interpretation, the worst of triplicate results and the associated findings at each visit will be summarized by counts and percentages. All the ECG data collected in triplicate will be listed.

3.7.6 Concomitant Medications

Concomitant medications will be coded using WHO Drug dictionary (version September 2018) and summarized by ATC class, generic name and treatment group.

4 REFERENCES

1) Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 53:457–81, 1958.

5 APPENDICES

5.1 Visit window for prior-treatment visit

For the at-home blood pressure results summary, the weekly average approach is applied, which is similar to the post-baseline summary approach. If there are multiple results on the same day for a subject, the average daily values were calculated first. Daily subject values within consecutive seven-day periods are averaged to determine the subject weekly result value. The visit window is as following: subject values from Days -21 to-15, -14 to -8, and -7 to -1 inclusively represent Week -3 (Run-In), Week -2 (washout first week) and Week -1 (washout second week), respectively.