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 8 Weeks to Hypertensive Subjects With Uncontrolled Blood Pressure

NCT04083222

4-December-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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure**
NCT Number:	**NCT04083222**
Document Date:	**Protocol Version 1.0: 15 July 2019**

IONIS PHARMACEUTICALS, INC.

ISIS 757456-CS3

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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure

Original Protocol – 15 July 2019

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

ISIS 757456-CS3

Original Protocol

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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

[redacted] MD, FACC
[redacted]

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 757456-CS3
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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure
Amendment:	Original Protocol
Date:	15 July 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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure," dated 15 July 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 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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure
Study Phase	Phase 2
Indication	Hypertension
Primary Objective	To evaluate the effect of ISIS 757456 on plasma angiotensinogen (AGT) in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications
Secondary Objectives	To evaluate the effect of ISIS 757456 on systolic (SBP) blood pressure in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications
[redacted]	
Safety Objective	To evaluate the safety and tolerability of ISIS 757456 vs. placebo
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 18–75 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 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. BMI ≤ 35.0 kg/m^2 5. Brachial circumference ≥ 22 and ≤ 37 cm (8.7 and 14.6 inches) 6. Subject must have been diagnosed with essential hypertension (HTN) for a minimum of 3 months prior to screening 7. At Screening, the subject must have a plasma AGT concentration ≥ 20 µg/mL. Up to 1 additional repeat test may be allowed in order to qualify with consultation of the Sponsor Medical Monitor 8. At Screening, the subject must have been on a stable regimen of 2 to 3 antihypertensive medications for at least 1 month prior to screening and will be required to maintain this regimen throughout the Study, using either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), as well as one or two additional antihypertensive medications in the following categories: a. beta blocker i. acebutolol ii. atenolol iii. betaxolol iv. bisoprolol v. carvedilol vi. labetalol vii. metoprolol viii. nadolol ix. nebivolol x. propranolol xi. pindolol b. calcium channel blocker or, c. non-potassium sparing diuretic 9. At Screening and pre-dose Study Day 1, the average office seated blood pressure (BP) must be within > 140 – ≤ 170 mmHg SBP and > 80 mmHg DBP. The average is to be derived from 3 assessments taken within 10 minutes. Up to 2 additional tests at each timepoint are allowed in order to qualify. 10. Agree to abstain from alcoholic beverages for at least 24 hours prior to clinic visits 11. Agree to maintain adequate hydration and adhere to a low sodium diet throughout the study (from the Screening Visit onward)

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. History of secondary HTN 3. 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 DBP of ≥ 7 mmHg 4. The use of the following at time of screening and during the course of the study: a. Other medications for the treatment of HTN (e.g., clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors) b. Medications that may cause hyperkalemia (e.g., cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins) c. Oral or subcutaneous (SC) anticoagulants (e.g., warfarin, rivaroxaban, apixaban, heparin, lovenox) d. Organic nitrate preparations (e.g., nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol) e. Phosphodiesterase 5 inhibitors (e.g., sildenafil, tadalafil, vardenafil, avanafil) f. Potassium sparing diuretics (e.g. eplerenone, spironolactone, amiloride, triamterene) 5. Treatment with another Study Drug, biological agent, or device within 1 month of screening, or 5 half-lives of study agent, whichever is longer 6. 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 7. Active infection with HIV, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor 8. 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 9. History of bleeding diathesis, coagulopathy, immune thrombocytopenic purpura, thrombotic cytopenic purpura, or any qualitative or quantitative platelet defect

PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Exclusion Criteria (Continued)** 10. Recent history of, or current drug or alcohol abuse 11. 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 electrocardiogram (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 12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 13. 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 subject is euthyroid 14. 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 > 4.9 mmol/L f. Estimated glomerular filtration rate (eGFR) of less than 45 mL/min/1.73 m^2 using the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula 15. Clinically-significant abnormalities upon physical examination which in the Investigator's opinion should exclude the subject from study participation 16. Subject works night time shifts (e.g., 11 PM to 7 AM) 17. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening

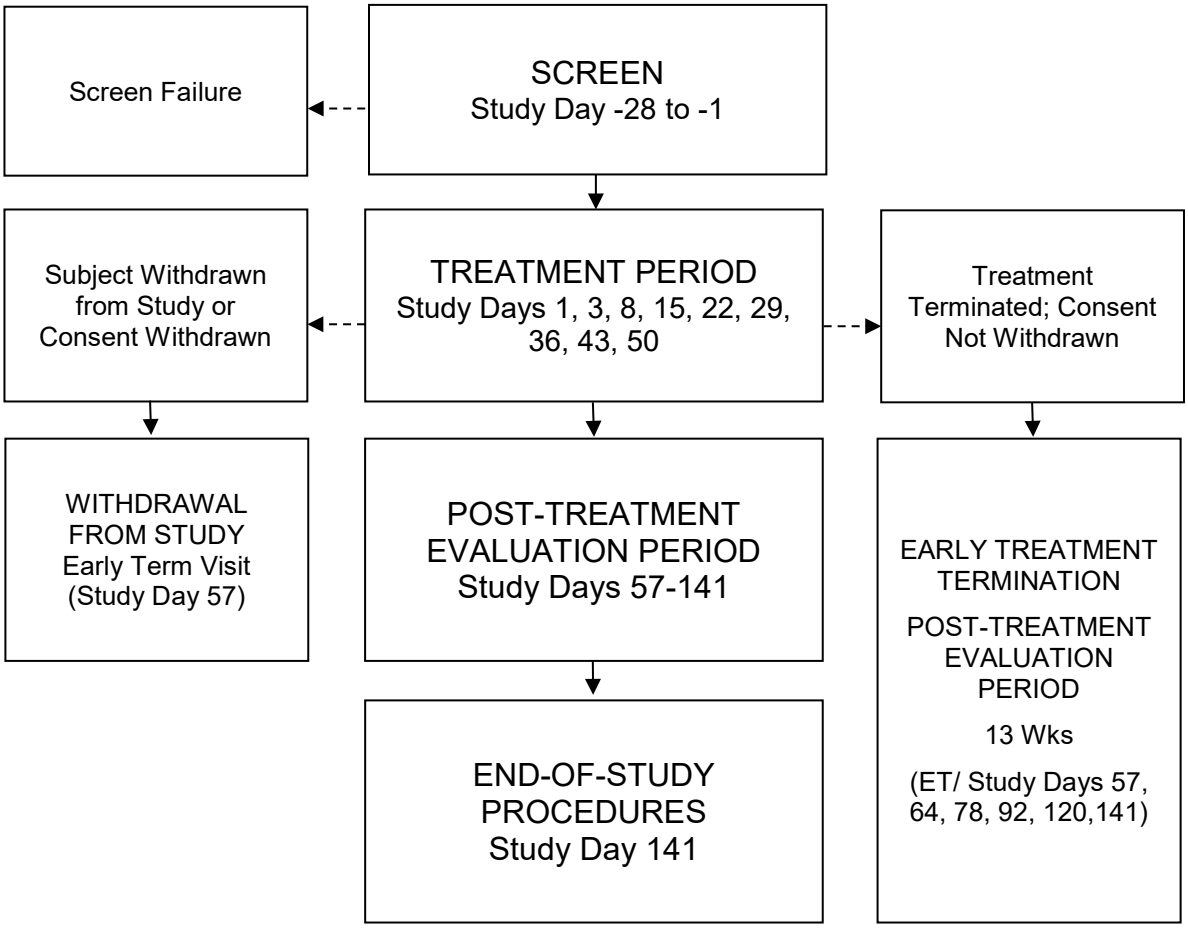
PROTOCOL SYNOPSIS (CONTINUED)

Study Population (Continued)	**Exclusion Criteria (Continued)** 18. 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 19. Unwilling to comply with study procedures, including the Post-Treatment Period, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
Treatment Groups	Approximately 30 subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose and randomized 2:1 (80 mg ISIS 757456: placebo). The **total** dose of the ACE or ARB taken per day is to be calculated based off their stable regimen of antihypertensive medications at Screening.
Study Drug Dosage and Administration	[redacted] All Study Drug injections will be administered SC in the clinic once weekly and as a loading dose on Study Day 3.
[redacted]	
Study Visit Schedule and Procedures	Blood and urine samples will be collected regularly throughout the study for safety, PK, and PD 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: Study Days -28 to -1** Laboratory and other study procedures will be performed to assess eligibility during the Screening Period. Subjects will be given a low sodium diet education at the Screening Visit. **Treatment: Study Days 1 to 50** Eligible subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose 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, 36, 43 and 50. Subjects will continue their previous antihypertensive medication regimen throughout the study.

PROTOCOL SYNOPSIS (CONTINUED)

Study Visit Schedule and Procedures (Continued)	**Treatment: Study Days 1 to 50 (Continued)** The study site will counsel and ask the subject at each visit if (s)he is maintaining a low sodium diet. The subject is expected to maintain a low sodium diet throughout the study. Subjects that discontinue treatment are encouraged to remain in the study for the Post-Treatment Evaluation Period and will conduct procedures outlined at Study Day 57 visit upon discontinuation of Study Drug. **Post-Treatment: Study Days 57 to 141** Subjects are to return to the Study Center for Post-Treatment visits on Study Days 57, 64, 78, 92, 120 and 141. The study site will continue to counsel and ask the subject at each visit if (s)he is maintaining a low sodium diet in the Post-Treatment Period. The final study visit will be Study Day 141 (Week 21).
Primary Endpoint	Percent change in plasma AGT from Baseline to Study Day 57 (Week 9) compared to placebo
Secondary Endpoints	• Change on SBP from Baseline to each scheduled, post-Baseline visit • Change and percent change in plasma AGT from Baseline to each scheduled, post-Baseline visit
[redacted]	
Safety Endpoint	Incidence and severity of treatment-emergent adverse events (TEAE) (including hypotension and orthostatic hypotension), use of concomitant medications, abnormal findings in laboratory assessments, ECG, and vital signs
Statistical Considerations	[redacted] Approximately 30 subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose 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 Day 57 (Study Week 9) in AGT between ISIS 757456 80-mg group and placebo group. 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
ARC	active renin mass concentration
ARF	acute renal failure
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CKD	chronic kidney disease
CMV	cytomegalovirus
CRF	case report form
CRNMB	clinically relevant non-major bleeding
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED_{50}	50% effective dose
eGFR	estimated glomerular filtration rate
FAS	full analysis set
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
hsCRP	CRP measured by high sensitivity assay
HTN	hypertension

Abbreviation	Definition
ICH	International Conference on Harmonization
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
KIM-1	kidney injury molecule 1
LLN	lower limit of normal
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NGAL	neutrophil gelatinase-associated lipocalin
NOAEL	no observed 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)
PK	pharmacokinetic(s)
PPS	per protocol set
PRA	plasma renin activity
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
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 subject
Study Drug	ISIS 757456 or placebo
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UACR	urine albumin-creatinine ratio
ULN	upper limit of normal
UPCR	urine protein-creatinine ratio
WBC	white blood cell
WOCBP	woman of child-bearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

To evaluate the effect of ISIS 757456 on plasma angiotensinogen (AGT) in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications

1.1.2. Secondary Objectives

To evaluate the effect of ISIS 757456 on systolic blood pressure (SBP) in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications

[redacted]

1.1.4. Safety Objective

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

1.2. Study Endpoints

1.2.1. Primary Endpoint

Percent change in plasma AGT from Baseline to Study Day 57 (Study Week 9) compared to placebo

1.2.2. Secondary Endpoints

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

[redacted]

[redacted]

1.2.4. Safety Endpoint

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

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 ≥ 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 antisense oligonucleotide (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.

2.3. ISIS 757456

[redacted]

[redacted]

[redacted]

2.3.4. Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 757456 can be found in the Investigator's Brochure. A summary is included below.

[redacted]

2.5. Benefit-Risk Assessment

Detailed information concerning the benefit-risk assessment of ISIS 757456 can be found in the Investigator's Brochure.

2.5.1. Benefit Assessment

This compound has been administered to healthy volunteers, and is currently being studied in hypertensive subjects washed out of their antihypertensive medications. 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 uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications (see Section 5.1 Inclusion Criteria). Subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose (see Section 10.1 and Appendix E). The subjects will be 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 8 weeks (See STUDY DESIGN AND TREATMENT SCHEMA).

All subjects will complete a 13-week Post-Treatment Period.

[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 an 8-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 and Post-Treatment Duration

The study will consist of Screen, Treatment, and Post-Treatment Periods. 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 4 weeks for screening, an 8-week Treatment Period, and 13 weeks of Post-Treatment Evaluation Period).

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

3.4.1. Screening

Subject eligibility for the study will be determined within 4 weeks prior to study entry, consisting of up to 4-week screening (Study Day -28 to -1).

3.4.2. Treatment

Subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose (see Section 10.1 and Appendix E). The subjects will be randomized in a 2:1 ratio to receive Study Drug (ISIS 757456 or placebo). Subjects will receive a total of 9 SC doses of Study Drug once weekly for 8 weeks (Study Days 1, 8, 15, 22, 29, 36, 43, 50) and an additional loading dose on Study Day 3.

3.4.3. Post-Treatment

Subjects are to return to the Study Center for Post-Treatment visits on Study Days 57, 64, 78, 92, 120, and 141. The final study visit will be Study Day 141 (Study Week 21).

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 at Study Day 1, after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Section 5.1 and Section 5.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

Subjects will be stratified based on low Screening ACE/ARB dose or high Screening ACE/ARB dose (see Section 10.1 and Appendix E) and then subjects will be randomized 2:1 to receive ISIS 757456 or placebo as outlined in Section 3.1.

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 suspected unexpected serious adverse reactions (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 18–75 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 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. BMI ≤ 35.0 kg/m^2
5. Brachial circumference ≥ 22 and ≤ 37 cm (8.7 and 14.6 inches)
6. Subject must have been diagnosed with essential HTN for a minimum of 3 months prior to screening
7. At Screening, the subject must have a plasma AGT concentration ≥ 20 µg/mL. Up to 1 additional repeat test may be allowed in order to qualify with consultation of the Sponsor Medical Monitor
8. At Screening, the subject must have been on a stable regimen of 2 to 3 antihypertensive medications for at least 1 month prior to screening and will be required to maintain this regimen throughout the Study, using either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), as well as 1 or 2 additional antihypertensive medications in the following categories:
    a. beta blocker
        i. acebutolol
        ii. atenolol
        iii. betaxolol
        iv. bisoprolol
        v. carvedilol
        vi. labetalol
        vii. metoprolol
        viii. nadolol
        ix. nebivolol
        x. propranolol
        xi. pindolol
    b. calcium channel blocker or,
    c. non-potassium sparing diuretic
9. At Screening and pre-dose Study Day 1, the average office seated BP must be within > 140 – ≤ 170 mmHg SBP and > 80 mmHg DBP. The average is to be derived from 3 assessments taken within 10 minutes. Up to 2 additional tests at each time point is allowed in order to qualify.
10. Agree to abstain from alcoholic beverages for at least 24 hours prior to clinic visits
11. Agree to maintain adequate hydration and adhere to a low sodium diet throughout the study (from the Screening visit onward)

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. History of secondary HTN
3. 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 DBP of ≥ 7 mmHg
4. The use of the following at time of screening and during the course of the study:
    a. Other medications for the treatment of HTN (e.g., clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors)
    b. Medications that may cause hyperkalemia (e.g., cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins)
    c. Oral or SC anticoagulants (e.g., warfarin, rivaroxaban, apixaban, heparin, lovenox)
    d. Organic nitrate preparations (e.g., nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol)
    e. Phosphodiesterase 5 inhibitors (e.g., sildenafil, tadalafil, vardenafil, avanafil)
    f. Potassium sparing diuretics (e.g., eplerenone, spironolactone, amiloride, triamterene)
5. Treatment with another Study Drug, biological agent, or device within 1 month of screening, or 5 half-lives of study agent, whichever is longer
6. 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
7. Active infection with human immunodeficiency virus (HIV), hepatitis C (HCV) or hepatitis B (HBV) diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor
8. 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
9. History of bleeding diathesis, coagulopathy, immune thrombocytopenic purpura, thrombotic cytopenic purpura, or any qualitative or quantitative platelet defect
10. Recent history of, or current drug or alcohol abuse
11. 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

12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
13. 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 subject is euthyroid
14. 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 > 4.9 mmol/L
    f. Estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 m^2 using the CKD Epidemiology Collaboration formula
15. Clinically significant abnormalities upon physical examination which in the Investigator's opinion should exclude the subject from study participation
16. Subject works night time shifts (e.g., 11 PM to 7 AM)
17. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
18. 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
19. Unwilling to comply with study procedures, including the Post-Treatment Period, 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 the study is approximately 6 months that includes a 4-week Screening Period, 8-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 BP Measuring Instructions at Each Visit) and Section 6.1.1.2 (Orthostatic BP Assessment).

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 4-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. AGT may be re-tested up to 1 additional time 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.

During the Screening Period the study site will also education subjects regarding a low sodium diet.

The study site will record basic personal details about you, including your 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 your medical history, and clinical data collected about your participation in the study.

6.1.1.1. Seated Blood Pressure Measuring Instructions at Each Visit

Subject Instructions

- Subject should have abstained from smoking, exercise and caffeine use at least 30 minutes prior to BP measurements
- Subject should be wearing a loose, short-sleeved top. If subject 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

- Confirm with that the subject has abstained from smoking, exercise and caffeine use at least 30 minutes prior to measurement
- Place the cuff on the subject's upper arm at the level of the heart and centered at the midpoint of the humerus
- Leave subject alone for 5 minutes in a quiet setting
- After 5 minutes, 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.

6.1.1.2. Orthostatic Blood Pressure Assessment

An orthostatic BP assessment will be done at Screening. BP and pulse rate will be assessed 2 times (Table 2). The subject will lie down (supine) for at least 5 minutes, then BP and pulse rate will be measured. The subject will then change to a standing position and the BP and pulse rate measurements will be repeated after standing greater than 1 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	BP and pulse rate after 5 minutes
Standing	> 1 to ≤ 3 minutes	BP and pulse rate assessed within > 1 to ≤ 3 minutes of standing

6.1.2. Treatment Period

Eligible subjects will be administered Study Drug (ISIS 757456 or placebo) on a weekly basis (8 weeks) as well as an additional dose on Study Day 3 for a total of 9 doses. Review of 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. All safety data including AEs, BP, and concomitant medications will be reviewed by the Sponsor's Medical Monitor or designee on an ongoing basis throughout the trial.

The subject is expected to maintain a low sodium diet throughout the study. The study site will counsel and ask the subject at each in-clinic visit if (s)he is maintaining a low sodium diet.

Subjects who discontinue the Treatment Period early will continue in the study following the post-treatment evaluations (Section 6.1.3).

6.1.3. Post-Treatment Period

After the last dose (Study Day 50) or last dose for early termination subjects, subjects will return to the clinic once weekly for the first 2 weeks (Study Days 57, 64) and then on Study Days 78, 92, 120, and 141 for safety assessments.

The study site will continue to counsel and ask the subject at each visit if (s)he is maintaining a low sodium diet in the Post-Treatment Period.

All safety data including AEs, 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 subject 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). Any uninterpretable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue. 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 1 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 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

†**Note:** Only true abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is 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

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

7. STUDY DRUG

[redacted]

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 ISIS 757456 or placebo SC

8.2. Other Protocol-Required Drugs

Per eligibility criteria, subjects must be on a stable regimen of 2 to 3 antihypertensives for at least 1 month prior to screening evaluations and will be required to continue the stable regimen throughout the duration of the study (Refer to Inclusion Criteria Section 5.1).

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 Investigator's Brochure.

For the purposes of the renal and platelet safety monitoring rules, Baseline is defined as:

- The last non-missing measurement prior to the first dose

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 of the protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009.

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 ideally within 48 to 72 hours. Liver chemistry tests (ALT, AST, ALP, INR, and total bilirubin) should be tested ideally within 48 to 72 hours as well. 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 2 to 3 times weekly. The frequency of retesting may decrease to once a week or less until ALT or AST levels become ≤ 1.2 x ULN or return to baseline levels or Study Drug has been discontinued and the subject is asymptomatic.

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 (CMV), immunoglobulin M (IgM), and Epstein-Barr Virus antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])
6. Additional tests may be conducted to rule out:
    - Nonalcoholic steatohepatitis
    - Hypoxic/ischemic hepatopathy
    - Biliary tract disease
    - Hepatitis types D and E

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 Platelet Count Results

Platelet count will be monitored at least every week during the Treatment Period and at the following visits in the Post-Treatment Period, Study Day 57/Study Week 9, Study Day 64/ Study Week 10, Study Day 78/Study Week 12, Study Day 92/Study Week 14, Study Day 120/Study Week 18, and Study Day 141/Study Week 21. The Investigator should review all platelet count results within 48 hours of receipt. 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 and additional laboratory investigations may be conducted Table 5.

Please refer also to Table 6.

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

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
To Be Performed at Local Lab
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.

8.5.3. Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding (MB) 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.

8.5.4. Safety Monitoring 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 subject 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.

8.5.5. Safety Monitoring for Blood Pressure

Should a subject experience a BP measurement of ≤ 90 mmHg (systolic) a second measurement must be done within a 30-minute period. If the subject is symptomatic (i.e., dizziness, light-headedness, clammy skin, fatigue, blurry vision), at any point in the study, the subject should contact the Study Center immediately. If the confirmed SBP is ≤ 90 mmHg and/or the subject remains symptomatic, dosing of a subject with Study Drug will be paused. Oral and/or IV hydration should be instituted. The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor after the SBP has normalized and/or subject is no longer symptomatic and will be based on the reversibility of initiating factors (e.g., decreased oral intake, cold/flu, other illness). If the subject remains symptomatic or if the SBP does not normalize Study Drug should be permanently discontinued (refer to Stopping Rules for BP Section 8.6.5).

8.6. Stopping Rules

For the purposes of the renal and platelet stopping rules, Baseline is 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 Section 8.6)
2. Confirmed 30% decline in eGFR from Baseline eGFR values
3. Confirmed proteinuria (UPCR ≥ 0.5 mg/mg)

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 Table 6 below.

Table 6: Actions in Subjects 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 MB or clinically relevant non-major bleeding* (CRNMB) *(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 subject for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor and will be based on factors such as the original rate of decline in the subject's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. The subject must have 3 successive values above 100,000/mm^3 before continued dosing is considered. • Perform additional labs in Table 5

Table 6: Actions in Subjects with Low Platelet Count (Continued)

Confirmed Platelet Count	Dosing	AESI?	Monitoring
< 50,000/mm^3 to 25,000/mm^3	Permanently Discontinue	Yes, if only accompanied by a MB 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 Sponsor 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 subject 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. (N**ote:** Subject 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 is defined as overt bleeding not meeting the criteria for MB but that resulted, for example, in medical examination, intervention, or had clinical consequences for a subject.

Definition of Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for MB or CRNMB (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 *with* new ECG changes consistent with hyperkalemia at any time during the study, dosing of a subject with Study Drug will be stopped permanently. The subject should stop any medications (e.g., ACE/ARB) 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 Rules for Blood Pressure

1. In the event of a confirmed BP measurement ≤ 90 mmHg (systolic) and/or the subject remains symptomatic (i.e., dizziness, light-headedness, clammy skin, fatigue, blurry vision) after instituting oral or IV hydration, Study Drug should be permanently discontinued, and the subject should be referred to urgent care or the emergency room.

   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 BP inclusion criteria (see Section 5.1) will not be necessary.

2. Should a subject experience a BP measurement > 180 mmHg (systolic) or > 110 mmHg (diastolic) a second measurement must be done within a 30-minute period. If the subject then experiences a second BP measurement > 180 mmHg (systolic) or > 110 mmHg (diastolic), they will then be withdrawn from further blinded, randomized treatment. Study Drug is to be permanently discontinued unless the hypertensive event is transient and dependent on reversable initiating factors (e.g., stressful event). The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor after the subject's BP has normalized. Additional antihypertensive medication(s) may be added per Investigator and Sponsor Medical Monitor judgement if the subject has discontinued Study Drug. If the subject has not discontinued Study Drug, changes to the stable regimen of antihypertensives may result in withdrawal of the subject from the Treatment Period. The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to BP inclusion criteria (see Section 5.1) will not be necessary.

Table 7: Blood Pressure Monitoring and Stopping Rules Reference Table

Confirmed Blood Pressure	Dosing	Additional Actions
SBP ≤ 90 mmHg* and/or subject is symptomatic (e.g., decreased oral intake, cold/flu, other illness).	Pause	Institute oral and/or IV hydration. If hypotension or symptoms of hypotension persist proceed to stopping rules below The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor after the SBP has normalized and/or subject is no longer symptomatic and will be based on the reversibility of initiating factors (e.g., decreased oral intake, cold/flu, other illness)
SBP ≤ 90 mmHg* and/or the subject remains symptomatic after instituting oral and/or IV hydration and there is no other reason contributing to hypotensive event	Permanently Discontinue	The subject should be referred to urgent care or the emergency room 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 BP inclusion criteria (see Section 5.1) will not be necessary
SBP > 180 mmHg* or DBP > 110 mmHg*	Pause if BP elevation is thought to be transient, reversible and related to external initiating factors (e.g., stressful event) Permanently discontinue if no other reason contributing to hypertensive event	The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor after the subject's BP has normalized Additional antihypertensive medication(s) may be added per Investigator and Sponsor Medical Monitor judgement if the subject has discontinued Study Drug. If the subject has not discontinued Study Drug, changes to the stable regimen of antihypertensives may result in withdrawal of the subject from the Treatment Period The subject will continue to be followed per protocol in the study. Follow-up for subjects that screen fail due to BP inclusion criteria (see Section 5.1) will not be necessary

* BP measurements must be confirmed by a second measurement within 30 minutes

8.7. Adjustment of Dose and/or Treatment 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 8.6.5
- The subject experiences an AE that necessitates unblinding of the Investigator

The reason for discontinuation of Study Drug 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 of 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).

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

8.10. Concomitant Therapy and Procedures

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

8.10.1. Concomitant Therapy

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

Allowed Concomitant Therapy

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

Disallowed Concomitant Therapy

The following are disallowed concomitant therapies:

- Other medications for the treatment of HTN (e.g., clonidine, guanfacine, guanabenz, alpha-methyldopa, hydralazine, minoxidil, diazoxide, renin inhibitors)
- Medications that may cause hyperkalemia (e.g., cyclosporine or tacrolimus, pentamidine, trimethoprim-sulfamethoxazole, all heparins)
- Oral or SC anticoagulants (e.g., warfarin, rivaroxaban, apixaban, lovenox, heparin)
- Organic nitrate preparations (e.g., nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, or pentaerythritol)
- Sildenafil, tadalafil, vardenafil
- Potassium sparing diuretics (e.g., eplerenone, spironolactone, amiloride, triamterene)

Changes to the stable regimen of antihypertensives allowed at Screening may result in withdrawal of the subject from the Treatment Period.

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 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 SAEs including SUSARs per the International Conference on Harmonization (ICH) guidelines E2A and ICH Good Clinical Practice (GCP). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

IRBs will be notified of any SAE according to applicable regulations.

The Sponsor 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 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

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

9.3.2. Adverse Drug Reaction and Suspected Unexpected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

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

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

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

Suspected Unexpected Adverse Drug Reaction

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

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

9.3.3. Serious Adverse Event

A 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 AE 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 AEs [NCI CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

9.3.4. AE of Special Interest (AESI)

For the purpose of this study, severe reductions in platelet count < 50,000/mm^3 accompanied by a MB event or CRNMB event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event 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 AEs

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 AEs

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 Post-Treatment Period which is defined as Study Day 141/ Study Week 21. 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 a paper SAE submission form. An Initial Serious AE Form should be completed, and a copy should be faxed or emailed to the Sponsor or designee. The SAE reporting instruction, including the fax number and email address can be found in the Study Reference Manual for the study.

Detailed information should be actively sought and included on Follow-Up Serious AE 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 AEs

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 Post-Treatment Period, which is defined as Study Day 141/ Study Week 21. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the AE Case Report Form.

9.4.3. Evaluation of AEs (Serious and Non-Serious)

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

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 757456 or placebo) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, 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 (ISIS 757456 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 757456 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the 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 tests and AEs at the injection site will be graded based on criteria from the Common Terminology Criteria for AEs (CTCAE) Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the 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 (ISIS 757456 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 757456 or placebo) administration and dose
- **Not Applicable:** SAE/AE was reported during the Screening Period prior to Study Drug administration or during the Post-Treatment Period
- **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 AE

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the AE 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 AE

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

- **AE Persists:** Subject terminates from the trial and the AE continues
- **Recovered:** Subject 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):** Subject 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:** Subject 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:** Subject 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., subject 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 subject is lost to follow-up, or the subject 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 AE eCRF and in the subject'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 has 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 as AEs rather than as abnormal laboratory values. 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 by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should be deemed CS 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 (ISIS 757456 or placebo) 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 (ISIS 757456 or placebo) 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 AE 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, Subsets, and Covariates

Subjects will be stratified based on either low Screening ACE/ARB dose or high Screening ACE/ARB dose. The **total** dose of the ACE or ARB taken per day is to be calculated based off their stable regimen of antihypertensive medications at Screening. Please refer to Appendix E for stratification criteria.

[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: All FAS subjects who received at least 7 of the 9 doses of Study Drug, did not alter Screening antihypertensive medications during the Treatment Period and prior to Study Day 57, 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 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 case report form (CRF) data, lab data transfers, and any outcomes derived from the data may 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.

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 Population.

Treatment duration and amount of Study Drug (ISIS 757456 or placebo) received will be summarized by treatment group. Subject incidence rates of all AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA™) system organ class, and by MedDRA™ term. Narratives of treatment emergent deaths, serious and AEs of special interest, 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, and all treatment emergent serious AEs potentially related to Study Drug (ISIS 757456 or placebo) will be summarized.

Laboratory tests to ensure subject safety including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 757456 or placebo) 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 Day 57 (Study Week 9) 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 (low ACE/ARB dose regimen vs. high ACE/ARB dose regimen) 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 Per Protocol Set (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

Plasma ISIS 757456 concentrations at trough during the Treatment Period and concentrations observed during the Post-Treatment Evaluation Period will be listed by dose, study day, time point, and summarized using descriptive statistics.

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.

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 clinical endpoints with 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.

[redacted]

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 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 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 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 or designee.

12.3. Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated 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 case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, imaging, and correspondence. In this study, eCRF 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 case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the 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 case report forms 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., case report forms and other pertinent data) provided that subject confidentiality is respected.

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

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. 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 case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content.

12.5. Language

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

All written information and other material to be used by 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

Altmann K-H, Dean NM, Fabbro D, et al. Second generation of antisense oligonucleotides: From nuclease resistance to biological efficacy in animals. CHIMIA Int J Chem 1996; 50: 168-176.

Crooke ST, and Bennett CF. Progress in antisense oligonucleotide therapeutics. Annu Rev Pharmacol Toxicol 1996; 36: 107-129.

Geary RS, Yu RZ, Watanabe T, et al. Pharmacokinetics of a tumor necrosis factor-alpha phosphorothioate 2'-O-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos 2003; 31: 1419-1428.

Henry SP, Kim T-W, Kramer-Strickland K, et al. Toxicologic Properties of 2'-O-Methoxyethyl Chimeric Antisense Inhibitors in Animals and Man. In In Antisense Drug Technology, Principles, Strategies and Applications, 2008. 327-364. Boca Ratan, FL: Taylor & Francis Group. 2

Inoue H, Hayase Y, Iwai S, et al. Sequence-dependent hydrolysis of RNA using modified oligonucleotide splints and RNase H. FEBS Lett 1987; 215: 327-330.

Judd E, and Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens 2014; 28: 463-468.

McKay RA, Miraglia LJ, Cummins LL, et al. Characterization of a potent and specific class of antisense oligonucleotide inhibitor of human protein kinase C-α expression. J Biol Chem 1999; 274: 1715-1722.

Monia BP, Lesnik EA, Gonzalez C, et al. Evaluation of 2'-modified oligonucleotides containing 2'-deoxy gaps as antisense inhibitors of gene expression. J Biol Chem 1993; 268: 14514-14522.

Prakash TP, Graham MJ, Yu J, et al. Targeted delivery of antisense oligonucleotides to hepatocytes using triantennary *N*-acetyl galactosamine improves potency 10-fold in mice. Nucleic Acids Res 2014; 42: 8796-8807.

Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115: 168-186.

Schulman S, and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-694.

Stockert RJ. The asialoglycoprotein receptor: relationships between structure, function, and expression. Physiol Rev 1995; 75: 591-609.

Te Riet L, van Esch JH, Roks AJ, et al. Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res 2015; 116: 960-975.

Zhang H, Lowenberg EC, Crosby JR, et al. Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. Blood 2010; 116: 4684-4692.

14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

	Screen	**Treatment Period (8 Weeks)**									**Post-Treatment Period (13 Weeks)**					
Study Week		**Wk1**		**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**	**Wk7**	**Wk8**	**Wk9**	**Wk10**	**Wk12**	**Wk14**	**Wk18**	**Wk21**
Study Day	**D-28 to D-1**	**D1**	**D3**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**Treatment Early Term[9]/ D57**	**D64**	**D78**	**D92**	**D120**	**PT Early Term[9]/ D141**
Visit Window (Days)	**NA**	**NA**	**+2**	**± 2**	**± 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**
Informed Consent	X															
Inclusion/Exclusion	X	X[a]														
Medical History	X															
Low Sodium Diet Education	X	◄ Continuous Counseling & Monitoring ►														
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					
Vital Signs (clinic)[2]	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
HIV, Hep B & C	X															
FSH[3]	X															
Pregnancy Test[4]	X															
Chemistry Panel (Fasting)[7, 10]	X	X[a]		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Renal Urine Biomarkers and Archived Urine Sample[6]	X	X[a]		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[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[a]	X	X	X	X	X	X
Plasma AGT	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
Exploratory	X	X[a]				X[a]					X		X	X	X	X
hsCRP		X[a]									X					X
PT, INR, aPTT	X															
Study Drug Administration		X	X	X	X	X	X	X	X	X						

Appendix A Schedule of Procedures (Continued)

	Screen	Treatment Period (8 Weeks)									Post-Treatment Period (13 Weeks)					
Study Week		**Wk1**		**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**	**Wk7**	**Wk8**	**Wk9**	**Wk10**	**Wk12**	**Wk14**	**Wk18**	**Wk21**
Study Day	**D-28 to D-1**	**D1**	**D3**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**Treatment Early Term[9]/ D57**	**D64**	**D78**	**D92**	**D120**	**PT Early Term[9]/ D141**
Visit Window (Days)	**NA**	**NA**	**+2**	**± 2**	**± 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**
AEs	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
PK Blood Sampling[5]		X[a]	X[a]	X[a]	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

Note: D = Day
W = Week

1 Full physical exam to be given at Screening and abbreviated physical exam to be given during Treatment and Post-Treatment Period as indicated to assess changes from Screening

2 Vital Signs (clinic): Blood Pressure (SBP/DPB; sitting), Orthostatic assessment (supine and standing, required at Screening), HR, RR, T. Vital sign assessments will be reviewed by the study doctor at each visit prior to dosing.

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

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; should be re-drawn as soon as possible (ideally within 7 days) and not meet a stopping rule 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 D57 or Study D141 assessments should be conducted, respectively

10 Fasting is not required at Screening visit. Fasted samples should be taken after fasting for at least 8 hours. During this time the subject 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 (ISIS 757456 or placebo) administration)

a Pre-dose

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 beta-subunit of human chorionic gonadotropin (βhCG) (women only, if applicable)

Coagulation

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

Efficacy

- Plasma AGT

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 (PRA)
- Renin (ARC)
- 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

D1	**D3**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D78**	**D92**	**D120**	**D141**
Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime	Anytime	Anytime
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

SC = subcutaneous
D = Day

APPENDIX D. GRADING SCALE FOR AES RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for AEs Relating to Laboratory Abnormalities

The following grading recommendations for AEs relating to lab test abnormalities and AEs at the injection site are based upon the 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

Appendix D Grading Scale for AEs Relating to Laboratory Abnormalities (Continued)

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

Appendix D Grading Scale for AEs Relating to Laboratory Abnormalities (Continued)

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

APPENDIX E. STRATIFICATION CRITERIA

The **total** dose of the ACE or ARB taken per day is to be calculated based off the subject's stable regimen of antihypertensives at Screening. The stratification criteria are as follows:

ACE/ARB	**Low Dose Stratum (total mg per day)**	**High Dose Stratum (total mg per day)**
ACE		
benazepril	≤ 20	> 20
captopril	≤ 75	> 75
enalapril	≤ 10	> 10
fosinopril	≤ 20	> 20
lisinopril	≤ 20	> 20
perindopril	< 8	≥ 8
quinapril	< 40	≥ 40
ramipril	≤ 10	> 10
trandolapril	≤ 4	> 4
ARB		
azilsartan	≤ 40	> 40
candesartan	< 16	≥ 16
eprosartan	≤ 400	> 400
irbesartan	≤ 150	> 150
losartan	≤ 50	> 50
olmesartan	≤ 20	> 20
telmisartan	≤ 40	> 40
valsartan	≤ 160	> 160

Should a subject be on a stable regimen of an ACE/ARB at Screening that is not listed in the above table the Sponsor Medical Monitor or designee must be consulted prior to stratification.

Official Title:	**A Double-Blind, Placebo-controlled, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of IONIS-AGT-L_{RX}, an Antisense lnhibitor Administered Subcutaneously for 8 Weeks to Hypertensive Uncontrolled Blood Pressure**
NCT Number:	**NCT04083222**
Document Date:	**SAP Version 1.0: 04 December 2019**

Statistical Analysis Plan

ISIS 757456-CS3

CONFIDENTIAL

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 8 Weeks to Hypertensive Subjects with Uncontrolled Blood Pressure

Date: DEC 04, 2019

Version: 1.0

. Statistical Analysis Plan Signature Page

Ionis Pharmaceuticals, Inc

2855 Gazelle Court Carlsbad, CA 92010

Compound Name: 757456

Protocol: CS3

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 8 Weeks to Hypertensive Subjects with uncontrolled Blood Pressure

Issue Date: 15 July 2019 (Original Protocol)

Signature: [redacted] Date: [redacted]

[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]

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Signature: [redacted] Date: [redacted]

[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 uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications. Subjects will be stratified based on a screening ACE/ARB dose (low vs high) 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 8 weeks.

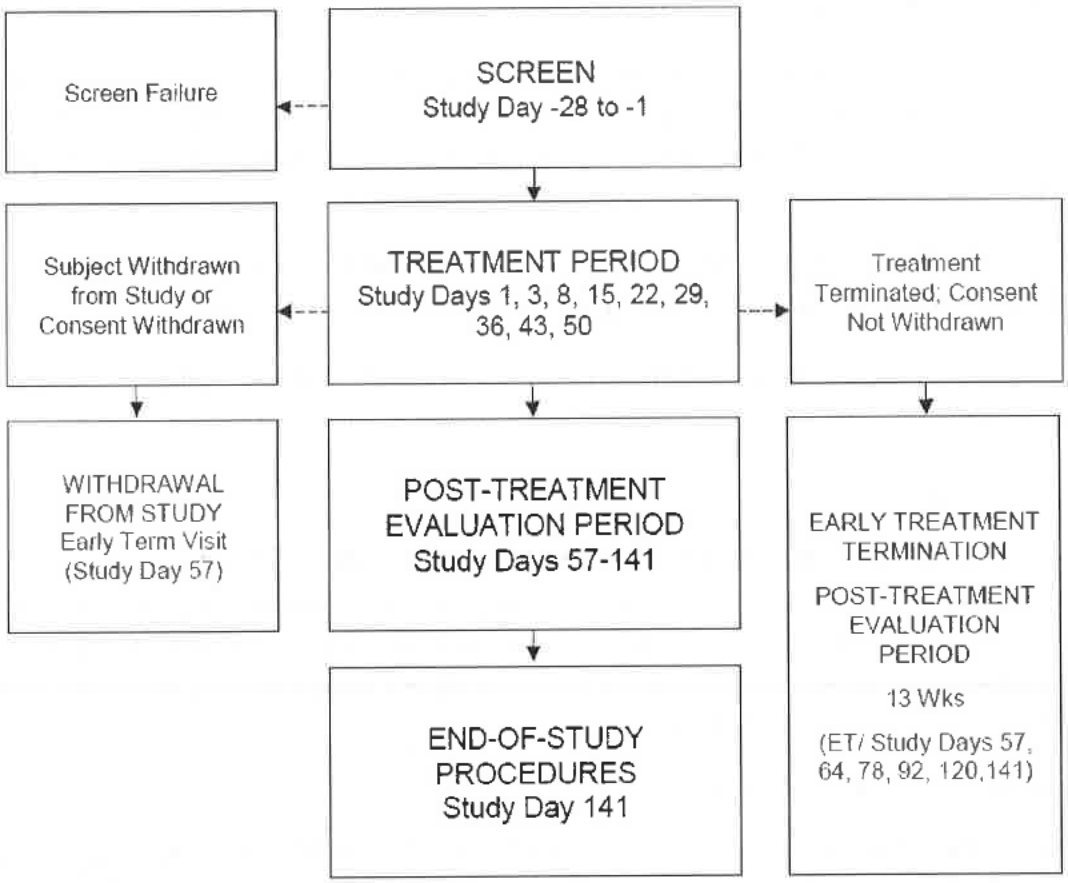
All subjects will complete a 13-week Post-Treatment Period.

[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 Screening, Treatment, and Post-treatment. The overall length of a subject's participation will be approximately 25 weeks (up to 4 weeks for Screening, an 8-week Treatment Period, and a 13 weeks Post-Treatment Evaluation Period).

The study design and treatment schema are depicted as follows:



1.2 Objective

1.2.1 Primary Objective(s)

- To evaluate the effect of ISIS 757456 subcutaneous (SC) injection on plasma angiotensinogen (AGT) in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications

1.2.2 Secondary Objective(s)

- To evaluate the effect of ISIS 757456 on systolic blood pressure (SBP) in uncontrolled hypertensive subjects on 2 to 3 antihypertensive medications

1.2.3 Safety Objectives

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

[redacted]

1.3 Endpoints

1.3.1 Primary Endpoint

- Percent change in plasma angiotensinogen from baseline to Study Day 57 (Week 9) compared to placebo

1.3.2 Secondary Endpoints

- Change on SBP from baseline to each scheduled, post-Baseline visit
- Change and percent change in plasma AGT 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, abnormal findings in laboratory assessments, electrocardiogram (ECG), and vital signs

[redacted]

2 PROCEDURE

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 Endocrine Lab, Ludwig-Maximulians-University (LMU) Munich via Medpace Reference Laboratories (MRL), and from Pharmaceutical Product Development (PPD) Inc. (plasma concentration data) to Ionis Pharmaceuticals, Inc.

2.2 Randomization & Treatment Allocation

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in protocol Sections 5.1 and 5.2. 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 ACE/ARB dose (low or high) 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 and have been on a stable regimen of 2 to 3 antihypertensive medications for at least 1 month prior to screening in order 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.

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 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, source data verified, 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 and the transfer schedule. Ionis Pharmaceuticals, Inc. is responsible for the review of the clinical laboratory data. This data is not stored in the EDC system. Investigator sites have access to the data via lab reports sent directly from the laboratory and online using the MRL ClinTrak® database.

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 Statistical Design Summary

Approximated 30 subjects will be randomized into two treatment cohort (ISIS 757456 80 mg or placebo). Eligible subjects will be stratified based on a screening ACE/ARB dose (low or high) and then subjects will be randomized 2:1 to receive ISIS 757456 or placebo.

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

3.2 General Overview of Analyses

3.2.1 Statistical Methods

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 provided to summarize most data. Additional subject listings included case report form (CRF) data and derived outcomes from the data may be presented.

All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. P-values will also be provided as an indicator to summarize how incompatibility between ISIS757456 and placebo cohort based on the statistical model. Unless specified, the stratification factor (screening ACE/ARB dose status) and treatment received are included in the model as independent variables.

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 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.

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.

3.2.2 Subject Population 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 7 of the 9 doses of Study Drug, did not alter antihypertensive medications during the Treatment Period and prior to Study Day 57, 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.
- Pharmacokinetics (PK) Set: All subjects who are randomized and receive at least 1 dose of ISIS 757456 and have at least 1 evaluable PK sample.

In addition to the above analysis sets, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis will be executed in these populations.

3.2.3 Handling of Missing Data

Missing values will not be imputed. Patients with missing data for a scheduled assessment time point were excluded from the summary for that time point.

3.2.4 Demographic and Baseline Characteristics

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

BMI will be computed using the formula: BMI = (weight in kilograms) / [screening 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.

3.3 Primary Analysis

3.3.1 Primary Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to Study Day 57 (Study Week 9) 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 ACE/ARB dose status) 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 (van Elteren, 1960) will be employed instead. Additional analysis summary based on the FAS will also be provided.

3.3.2 Planned Interim Analysis

An interim analysis may be conducted after at least 50% of the subjects have been enrolled. All study primary and secondary efficacy endpoints will be summarized descriptively.

[redacted]

3.4 Secondary Efficacy Analyses

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

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

[redacted]

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). PK analysis summary will be based on 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, 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, 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 f SC administration. 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. Since only trough and post-treatment follow up PK samples are to be collected, only the following PK parameters will be calculated:

- C_{trough}
- $t1/2\lambda z$

Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

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

3.6.3 Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response correlations maybe explored graphically between plasma exposure (e.g. $C_{trough,}$), 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 (C_{trough}) 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 adverse events (AEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 (or higher) preferred term and system organ class for:

- Any treatment emergent adverse events (TEAEs).
- Related TEAEs. Related is defined as "Related", "Possible", or missing relationship to study drug.
- Any TEAEs by severity. At each severity level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be categorized as "Missing" for this summary.
- Serious TEAEs (Treatment-emergent SAEs).
- TEAEs leading to permanent study drug discontinuation.

Serious and non-serious AEs that lead to study discontinuation or investigational drug discontinuation will be listed separately. Non-treatment emergent adverse event will be included and be noted in the subject AE listing.

To determine the AE as treatment-emergent or not, 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.

In addition, 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) and seriousness (Yes/No) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AE.

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

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

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

If the AE severity or seriousness of the second record is worse than that of the first record, then two TEAEs are recorded. Otherwise only the first AE record is deemed as a TEAE.

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

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

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; 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.

Local cutaneous reactions at the injection site will be listed by preferred term.

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.

AE of special interest (AESI): Platelet reduction

Per protocol, severe reductions in platelet count < 50,000/mm3 accompanied by a major bleeding (MB) event or clinically-relevant non-major bleeding (CRNMB) event, or platelet count of < 25,000/mm3 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. A listing of AESI will also be provided.

3.7.3 Laboratory Measurements

Chemistry including thyroid panel and inflammatory, 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 tabulated.

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 orthostatic assessment (supine and standing), heart rate, respiratory rate, body temperature, BMI and systolic and diastolic blood pressure. Except for systolic and diastolic blood pressure, which are pharmacodynamic endpoints for this study and will be summarized separately, other 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.

3.7.5 12-Lead Electrocardiograms (ECG)

Safety 12 lead ECG will be performed at the visits indicated in the protocol Schedule of Procedures.

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 results at study screening and study Wk 9 visit, as well as the change and percent change from Baseline, will be presented in summary tables; for the categorical responses to overall interpretation, the worst results and the associated findings at scheduled visit will be summarized by counts and percentages. All the ECG data collected will be listed.

3.7.6 Concomitant Medications

Concomitant medications will be coded using WHO Drug dictionary (Global B3 March 2019) and summarized by ATC class, generic name and treatment group.

4 REFERENCES

van Elteren, P. H. (1960). "On the combination of independent two-sample tests of Wilcoxon," *Bulletin of the International Statistical Institute*, 37, 351-361.