A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients With Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at a High Risk for CVD

NCT03385239

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Official Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

NCT Number: NCT03385239

Document Date: Protocol Amendment 3: 12 June 2019

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AKCEA THERAPEUTICS

ISIS 678354-CS2

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Amendment 3 – 12 June 2019

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Amendment 3 – 12 June 2019

Protocol History

Original Protocol:	20 October 2017
Protocol Amendment 1:	31 January 2018
Protocol Amendment 2:	05 December 2018

Approved by:

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ISIS 678354-CS2

Ionis Protocol Number ISIS 678354-CS2

Amendment 3

Clinical Phase: 2

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

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Date: 12 June 2019

Confidentiality Statement

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

Protocol Signature Page

Protocol Number:	ISIS 678354-CS2
Protocol Title:	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD
Amendment:	Amendment 3
Date:	12 June 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD," dated 12 June 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 (E6).

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. and Akcea Therapeutics, Inc.

_____

Investigator's Signature

_____ _____

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL SUMMARY OF CHANGES

Protocol Number: ISIS 678354-CS2

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

Amendment Number: 3

Amendment Date: 12 June 2019

The following modifications to the Protocol ISIS 678354-CS2 Amendment 2 have been made.

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

The following table provides a summary list of major changes to the original protocol:

Protocol Section	Description of Change	Rationale
Section 5.2 Exclusion Criteria	Removed from exclusion criteria 24-hr urine sample to confirm eligibility	[redacted]
Section 8.5.2 Safety Monitoring for Renal Function	Changed the order of monitoring rules: interruption of the study drug followed by confirmation of the abnormal result. Additional tests moved to Section 8.6.2	To align with the reworded Section 8.6.2
Section 8.6.2 Stopping Rules for Renal Function Test Results	Changed stopping rules to confirmed monitoring rules in cases without an alternative etiologies.	[redacted]

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-controlled, Dose-ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD
Study Phase	2
Indication	Patients with hypertriglyceridemia and established CVD or at high risk for CVD.
Investigational Drug	ISIS 678354 is a second generation 2'-MOE modified, $GalNAc_3$–conjugated antisense oligonucleotide inhibitor of apolipoprotein C-III (apoC-III).
Primary Objective	To evaluate the safety, including tolerability, of ISIS 678354 and to assess the efficacy of different doses and dosing regimens of ISIS 678354 for reduction of serum triglyceride (TG) levels in patients with hypertriglyceridemia and established CVD or at high risk for CVD.
Secondary Objective(s)	To evaluate the efficacy of ISIS 678354 on serum levels of apolipoprotein C-III (apoC-III), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein B100 (apoB), and apolipoprotein A-1 (apoA-I). To evaluate pharmacokinetics (PK) of ISIS 678354 across different doses and dose regimens in patients with hypertriglyceridemia and established CVD or at high risk for CVD.
Exploratory Objective(s)	To evaluate the efficacy of ISIS 678354 on serum levels of lipoprotein (a) Lp(a) and angiopoietin-like 3 (ANGPTL3).
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. After an up to 4-week screening period, including an up to 2-week qualification period following an at least a 2-week diet stabilization period, approximately 100 eligible patients will be randomized in a 4:1 ratio to receive ISIS 678354 or placebo. Patients on stable diet known to the investigator and followed at the site may go from Screening to qualification period without a 2-week diet stabilization phase. Study Drug (ISIS 678354 or placebo) will be administered by subcutaneous (SC) injection every week, every 2 weeks, or every 4 weeks, depending on cohort assignment, for up to 52 weekly doses, up to 26 every 2-week doses, or up to 13 every 4-week doses. Minimum treatment duration is 6 months. Maximum treatment duration is 12 months. The treatment portion of the study will be complete when the last patient reaches 6 months of exposure. All patients still on treatment will then enter a 13-week post-treatment follow-up period. Refer to Section 3.4.2 for additional detail regarding End of Treatment period and scheduling of End of Treatment Visits. The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-B) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts C and D, respectively). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy and safety analyses will be repeated at the completion of Study Drug treatment. An independent Data and Safety Monitoring Board (DSMB) will be established to review safety, tolerability and efficacy data collected on ISIS 678354 during this study, both individual events and aggregate data.

PROTOCOL SYNOPSIS *Continued*

Number of Subjects	Approximately 100
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 and ≤ 80 years old at the time of informed consent 3. a. Clinical diagnosis of CVD (defined as documented coronary artery disease, stroke, or peripheral artery disease; refer to Section 3.1), or b. High risk for CVD defined as: ○ Type 2 Diabetes Mellitus requiring treatment, and ○ Age ≥ 50 years, and ○ at least one additional CV risk factor: ▪ men ≥ 55 years of age and women ≥ 65 years of age, or ▪ current cigarette smoker, or stopped smoking within 3 months prior screening, or ▪ hypertension requiring antihypertensive treatment 4. Fasting serum TG ≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥ 5.7 mmol/L) at Screening. If the fasting TG value at Screening is < 200 mg/dL (< 2.3 mmol/L) but ≥ 150 mg/dL (≥ 1.7 mmol/L) one additional test may be performed in order to qualify 5. Fasting TG ≥ 200 mg/dL and ≤ 500 mg/dL at Qualification visit. If fasting TG is < 200 mg/dL but ≥ 150 mg/dL one additional test may be performed in order to qualify 6. Must be on standard-of-care preventative therapy for their known CVD risk factors (e.g., hyperlipidemia, hypertension, diabetes) 7. Patients on the following medications must be on a stable regimen for at least 4 weeks prior to Screening and expected to remain on a stable regimen through the end of the post-treatment follow-up period: a. Lipid lowering drugs (statins, ezetimibe, PCSK9 inhibitors, niacin, fibrates, fish oil or other products containing omega-3 fatty acids including OTC preparations) b. Antiplatelet drugs c. Testosterone, estrogens, progesterone, growth hormone or progestins 8. Females: must be non-pregnant and non-lactating and either: a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); b. 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 FSH levels in the postmenopausal range for the laboratory involved); c. Abstinent* or, d. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 678354 or placebo) * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	9. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 678354
	Exclusion Criteria 1. Within 3 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke/transient ischemic attack 2. Within 3 months of Screening: coronary, carotid, or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis 3. Heart failure NYHA class III and IV 4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg) 5. History of acute kidney injury within 12 months of Screening 6. Uncontrolled hyper or hypothyroidism 7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 8. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 10. Patients at high-risk of bleeding diathesis 11. Recent history of, or current drug or alcohol abuse 12. Hypersensitivity to the active substance or to any of the excipients 13. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following: a. 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 b. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. c. Estimated GFR < 60 mL/min/1.73 m^2 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN e. Bilirubin > 1.2 x ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL f. Alkaline phosphatase (ALP) > 1.5 x ULN g. Platelet count < LLN h. LDL-C > 130 mg/dL (> 3.4 mmol/L) 14. Type 1 diabetes mellitus 15. Type 2 diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of Screening

<table>
<tr><td>Study Population
Continued</td><td>
b. HbA1c ≥ 9.0% at Screening
c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Screening [with the exception of ± 10 units of insulin])
d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units for insulin)
e. Current use of GLP-1 agonists, if patient has history of pancreatitis
16. Use of warfarin or other vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors
17. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
18. Treatment with any non-Akcea/non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Patients that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months has elapsed since dosing
19. BMI > 40 kg/m^2
20. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
21. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
22. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study
</td></tr>
<tr><td>Treatment Groups</td><td>
Patients will be randomized to 4 parallel cohorts (Cohorts A, B, C and D).
Cohort A (n = 25): Patients will be randomized 4:1 to receive 10 mg ISIS 678354 or placebo SC once every 4 weeks for up to 13 doses.
Cohort B (n = 25): Patients will be randomized 4:1 to receive 50 mg ISIS 678354 or placebo SC once every 4 weeks for up to 13 doses.
Cohort C (n = 25): Patients will be randomized 4:1 to receive 15 mg ISIS 678354 or placebo SC every 2 weeks for up to 26 doses.
Cohort D (n = 25): Patients will be randomized 4:1 to receive 10 mg ISIS 678354 or placebo SC every week for up to 52 doses.
<table>
<tr><th>Cohort</th><th>Treatment</th><th># Doses</th><th>Total ISIS 678354</th></tr>
<tr><td>A</td><td>10 mg ISIS 678354 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 130 mg</td></tr>
<tr><td>B</td><td>50 mg ISIS 678354 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 650 mg</td></tr>
<tr><td>C</td><td>15 mg ISIS 678354 or placebo (Every 2 weeks)</td><td>≤ 26</td><td>≤ 390 mg</td></tr>
<tr><td>D</td><td>10 mg ISIS 678354 or placebo (Every week)</td><td>≤ 52</td><td>≤ 520 mg</td></tr>
</table>
</td></tr>
</table>

PROTOCOL SYNOPSIS *Continued*

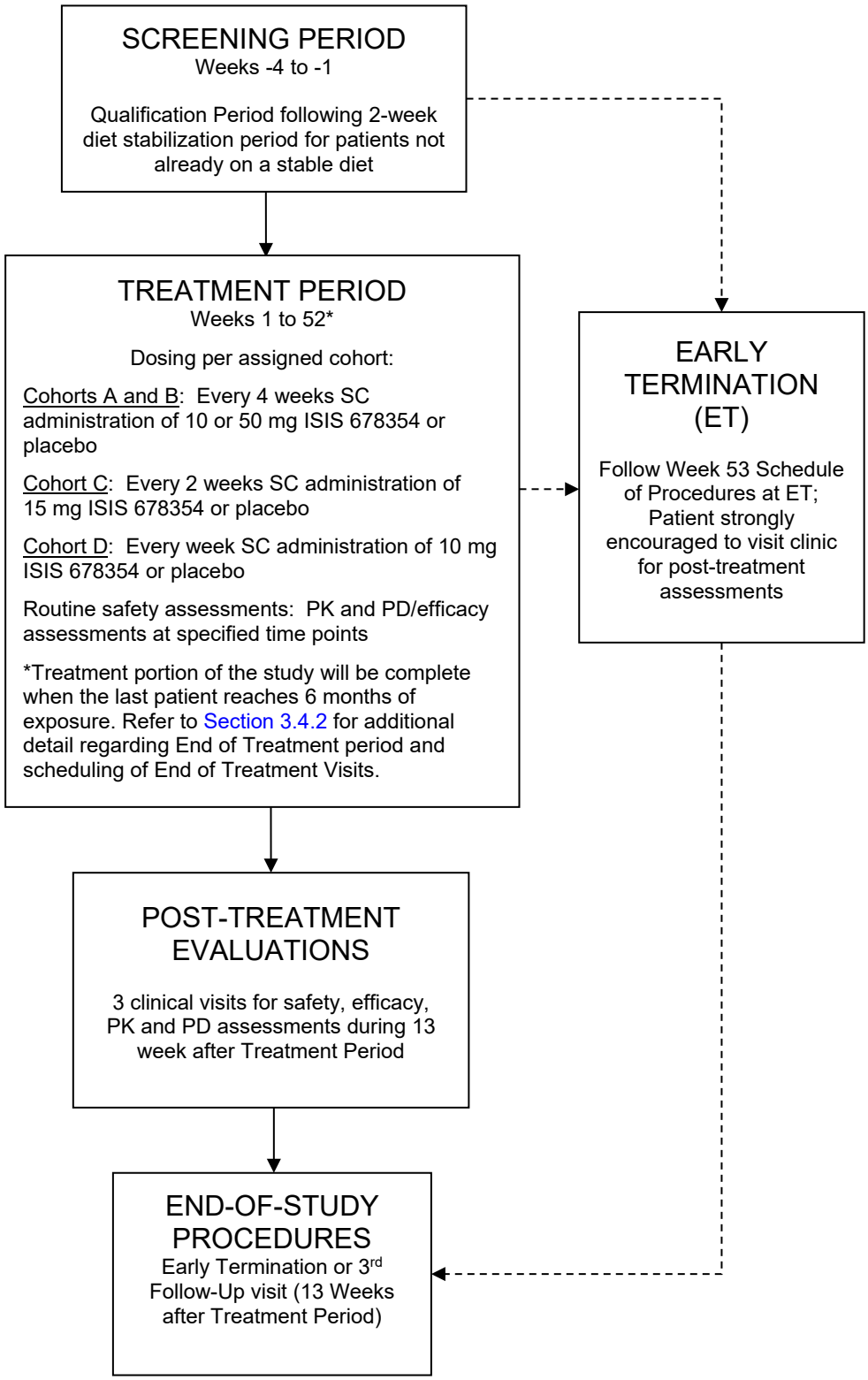
Study Drug Dosage and Administration	The Sponsor will provide ISIS 678354 in a concentration of 100 mg/mL and matching volume placebo: Cohort A: 10 mg every 4 weeks ISIS 678354 or placebo (0.10 mL) Cohort B: 50 mg every 4 weeks ISIS 678354 or placebo (0.50 mL) Cohort C: 15 mg every 2 weeks ISIS 678354 or placebo (0.15 mL) Cohort D: 10 mg every week ISIS 678354 or placebo (0.10 mL) All doses will be given by SC injection. Self-administration will be allowed after appropriate training of patient and/or caregiver.
Rationale for Dose and Schedule Selection	The Phase 1 program evaluated ISIS 678354 doses of 15 mg and 30 mg given weekly and 60 mg given every 4 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in TG. Four dosing regimens are planned for the present study, which are proposed to provide total monthly drug exposures equivalent to 10, 30, 40, and 50 mg administered as 10 mg every 4 weeks, 15 mg every 2 weeks, 10 mg every week, and 50 mg every 4 weeks, respectively. These doses are predicted to provide reductions from Baseline in serum TG ranging from approximately 30% to 64% at the end of the dosing interval at steady-state based on a preliminary PK/PD model developed using the available Phase 1 data. The present study will evaluate the safety and efficacy of ISIS 678354 in a 5-fold range of drug exposure utilizing 3 different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hypertriglyceridemia will require chronic treatment and thus every 2 weeks or every 4 weeks dosing regimens, if safe and well-tolerated, may provide advantages over weekly dosing in terms of convenience and compliance for patients. The proposed range of doses are expected to provide sufficient data to characterize the dose- and exposure-response relationship.
Adjustment of Dose and/or Treatment Schedule	Dose adjustments, including dose interruptions, and/or decreasing the dose frequency may be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in Section 6. All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 4 treatment cohorts. On completion of the 6 months, patients will continue treatment within the same randomized cohort until the last patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. Refer to Section 3.4.2 for additional detail regarding End of Treatment period and scheduling of End of Treatment Visits. The study for an individual patient will generally consist of the following periods: • An up to 4-week screening period, including a up to 2-week qualification period following an at least 2-week diet stabilization period where appropriate • An up to 52-week treatment period during which Study Drug will be administered per assigned cohort by SC injection • A 13-week post-treatment follow-up period Patients in Cohorts A and B will receive up to 13 SC doses of ISIS 678354 or placebo every 4 weeks. Patients in Cohort C will receive up to 26 SC doses of ISIS 678354 or placebo every 2 weeks and patients in Cohort D will receive up to 52 SC doses of ISIS 678354 or placebo weekly. Patients will return regularly for outpatient visits throughout the treatment and post-treatment follow-up periods according to the Schedule of Procedures (Appendix A).

Study Visit Schedule and Procedures *Continued*	Blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B shows a list of analytes required for the study and Appendix C details the PK sample schedules.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: adverse events, vital signs and weight, physical examinations, clinical laboratory tests, ECGs (including serial ECGs in a subgroup of patients undergoing serial PK sampling) and use of concomitant medications. Safety and tolerability results in patients receiving ISIS 678354 will be compared with those receiving placebo.
Efficacy Evaluations	The primary analysis time point is at 6 months (Week 25 for patients who received every 4-week dosing (Cohorts A and B) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts C and D)). The primary endpoint is the percent change in serum TG from Baseline at the primary analysis time point for ISIS 678354 treatment groups compared to placebo. The secondary endpoints comprise the effect of ISIS 678354 as compared to placebo at the primary analysis time point on the following: • Percent change from Baseline in apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I • Proportion of patients who achieve serum TG ≤ 150 mg/dL (≤ 1.7 mmol/L) Proportion of patients achieving TG ≤ 100 mg/dL (≤ 1.13 mmol/L)
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 678354 plasma trough levels throughout treatment and during the post-treatment follow-up period. In addition, in a subset of patients (approximately 10 patients per cohort), more frequent plasma samples will be taken following the first and Day 169 (for every week and every 2-week dosing cohorts) or Day 141 (for every 4-week dosing cohort) dose to determine PK parameters. Plasma sample collection time points are detailed in Appendices A and C. The plasma ISIS 678354 levels over time will be descriptively summarized by treatment with and without stratification by subject immunogenicity status. Apparent terminal elimination half-life will be calculated in patients who received ISIS 678354 treatment using a non-compartmental method, if data permitted. In addition, C_{max}, T_{max}, and AUC values will be calculated for the PK subgroup. PK parameters will be descriptively summarized by treatment with and without stratification by subject immunogenicity status
Statistical Considerations	The primary efficacy analysis for the primary endpoint will be the pairwise comparison of percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354 treated groups and placebo group in the Full Analysis Set. The data will be analyzed using an ANCOVA model with the baseline TG level as a covariate. Dose selection for the further development will be based on the following efficacy and safety considerations; more than 1 dose may meet these criteria. An effective dose, or dose regimen, will be one that achieves a clinically-meaningful reduction in serum TG levels. Safety will be evaluated on the basis of incidence of expected and unexpected treatment-related SAEs, and other specific safety considerations including the incidence of platelet reductions.

PROTOCOL SYNOPSIS *Continued*

Statistical Considerations *Continued*	[redacted]
Sponsor/ Collaborator	Akcea Therapeutics/ Ionis Pharmaceuticals

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ANA	antinuclear antibody
ANGPTL3	angiopoietin-like 3
ApoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
AUC_t	area under the plasma concentration-time curve from time zero to time t
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BP	blood pressure
BUN	blood urea nitrogen
C	centigrade
C5a	complement factor C5a (activated complement split product)
CAD	coronary artery disease
C_{max}	maximum concentration
CBC	complete blood count
CKD-EPI	Chronic Kidney Disease –Epidemiological Collaboration
CMV	cytomegalovirus
CRF	case report form
CRP	C-reactive protein

STUDY GLOSSARY *Continued*

Abbreviation	Definition
CVD	cardiovascular disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cys-C	cystatin 3
dL	deciliter
DNA	phosphorothioate-modified oligodeoxynucleotides
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
$GalNAc_3$	triantennary *N*-acetyl galactosamine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HAV	hepatitis A virus
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
hr, hrs	hour(s)
hsCRP	C-reactive protein measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M

STUDY GLOSSARY *Continued*

Abbreviation	Definition
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 678354	antisense inhibitor of apolipoprotein C-III
IV	intravenous(ly)
IXRS	interactive voice/internet response system
KIM-1	kidney injury molecule 1
kg	kilogram
L	liter
LDL-C	low density lipoprotein cholesterol
LICA	ligand conjugated antisense
Lp(a)	lipoprotein (a)
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mRNA	messenger ribonucleic acid
NAG	*N*-acetyl-β D-glucosaminidase
NCS	not clinically-significant
NGAL	neutrophil gelatinase-associated lipocalin
Non-HDL-C	non- high-density lipoprotein cholesterol
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCSK9	proprotein convertase subtilisin/kexin type 9
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)

STUDY GLOSSARY *Continued*

Abbreviation	Definition
PPS	per protocol set
PT	prothrombin time
RBC	red blood cells
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	Statistical Analysis Plan
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Drug	ISIS 678354 or placebo
SUSAR	suspected unexpected serious adverse reaction
TC	total cholesterol
TG	triglyceride
T_{max}	time to maximal concentration
TSH	thyroid stimulating hormone
UACR	urine albumin -creatinine ratio
ULN	upper limit of normal
UPCR	urine protein- creatinine ratio
VLDL-C	very low density lipoprotein cholesterol
WBC	white blood cell
WMA	World Medical Association

1. STUDY OBJECTIVES

1.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 678354 and to assess the efficacy of different doses and dosing regimens of ISIS 678354 for reduction of serum triglyceride (TG) levels in patients with hypertriglyceridemia and established cardiovascular disease (CVD) or at a high risk for CVD.

1.2 Secondary Objectives

To evaluate the efficacy of ISIS 678354 on serum levels of apolipoprotein C-III (apoC-III), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein B100 (apoB), and apolipoprotein A-1 (apoA-I).

To evaluate pharmacokinetics (PK) of ISIS 678354 across different doses and dose regimens in in patients with hypertriglyceridemia and established CVD or at a high risk for CVD.

1.3 Exploratory Objective

To evaluate the efficacy of ISIS 678354 on serum levels of lipoprotein (a) (Lp(a)) and angiopoietin-like 3 (ANGPTL3).

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Despite advances in diagnosis and treatment, CVD remains the most common underlying cause of death, being responsible for ~30% of all deaths in the United States, according to the Heart Disease and Stroke Statistics-2017 (Benjamin et al. 2017).

Elevated low density lipoprotein cholesterol (LDL-C) has long been recognized and established as an independent risk factor for CVD, and therapies aimed to reduce LDL-C levels, such as statins which have been available for over 25 years, and PCSK9-inhibitors more recently, while showing a benefit in reduction of CV events (Cannon et al. 2006, Sabatine et al. 2017), have not changed the position of CVD as the leading cause of mortality in the western world. Despite lowering LDL-C levels with these therapies, the residual CV risk remains high and the rate of major adverse cardiac events (MACE) ranges from 32% in a 6 year follow-up in the IMPROVE-IT study with simvastatin/ezetimibe (Cannon et al. 2015) to 12% in a 3 year follow-up in the FOURIER study with PCSK9-inhibitor evolocomab (Sabatine et al. 2017). These results indicate that to achieve further reduction in CV events other risk factors also need be addressed.

An association between elevated TG levels (especially postprandial) and CV events has been suggested by several earlier observational studies (Hokanson et al.1996, Austin et al. 2000, Nordestgaard et al. 2007). Subgroup analysis from PROVE-IT TIMI 22 study with atorvastatin showed that patients who continued to have TG level >150 mg/dL had an increased risk for future CV events despite achieving low LDL-C levels, while patients with normal TG levels achieved CV benefit from treatment with statins (Miller et al. 2008). This finding has been recently confirmed by the large outcome trial and registry with bezafibrate (BIP) (> 15,000

patients with coronary heart disease followed for 22 years), demonstrating that elevated fasting TG levels were independently associated with increased mortality even after adjusting for other known risk factors (Klempfner et al 2016).

Several non-statin drug therapies are currently available for the management of hypertriglyceridemia, including fibrates, niacin and omega-3 fatty acids. Unfortunately, clinical trials that evaluated the use of these agents in addition to optimal statin therapy for CV event reduction failed to clearly show additional benefit (Ginsberg et al 2010, Guyton et al 2013, Roncaglioni et al 2013, Sampson et al 2012). As a result of these negative trials and the potential harm of these agents the 2013 ACC AHA cholesterol guidelines currently do not recommend routinely adding TG lowering medications to statin therapy in patients with elevated TGs (Stone et al 2014).

Taking into account the amount of data that links even mildly elevated TG levels to an increased risk for CV events, these negative results of current TG lowering drugs clearly indicate the unmet need for an effective TG-lowering agent in patients with, or at risk for, CVD.

ApoC-III plays a pivotal role in regulating plasma TG levels (Sacks 2015), and elevated apoC-III levels have been shown to be an independent risk factor for CVD, especially when apoC-III is present on apolipoprotein B-containing lipoproteins (Sacks et al. 2000, Mendivil et al. 2011). Reduction of apoC-III levels by targeting apoC-III mRNA by ISIS 304801 antisense oligonucleotide (ASO) resulted in substantial lowering of TG levels in patients with hypertriglyceridemia (Gaudet et al. 2015).

Therefore, the present study was designed to evaluate a new approach to lowering TG and apoC-III levels, specifically in high-risk patients, those with established CVD whose LDL-c levels are controlled by standard therapeutic strategies but whose elevated TG and apoC-III levels place them at continued risk of recurrent CV events, or in patients at high risk for CVD. The study will evaluate treatment efficacy using a range of doses and dose interval treatment cohorts, while further assessing the safety and tolerability of a ligand conjugated antisense (LICA)-based ASO in this indication.

2.2 Therapeutic Rationale

Elevated triglyceride levels are thought to play an important role in development of atherosclerosis and subsequently CVD due to accumulation of TRL and their remnant cholesterol in the arterial wall. ApoC-III is an integral part of this process.

ApoC-III, a key regulator of plasma TG levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008, Figure 1). Multiple apoC-III protein molecules reside on the surface of apoB-containing lipoproteins and high-density lipoprotein (HDL) and exchanges rapidly between these particles. The majority of apoC-III is associated with triglyceride-rich lipoprotein (TRL) in hypertriglyceridemic patients. In subjects with normolipidemia, the majority of the protein is associated with HDL (Chan et al. 2008).

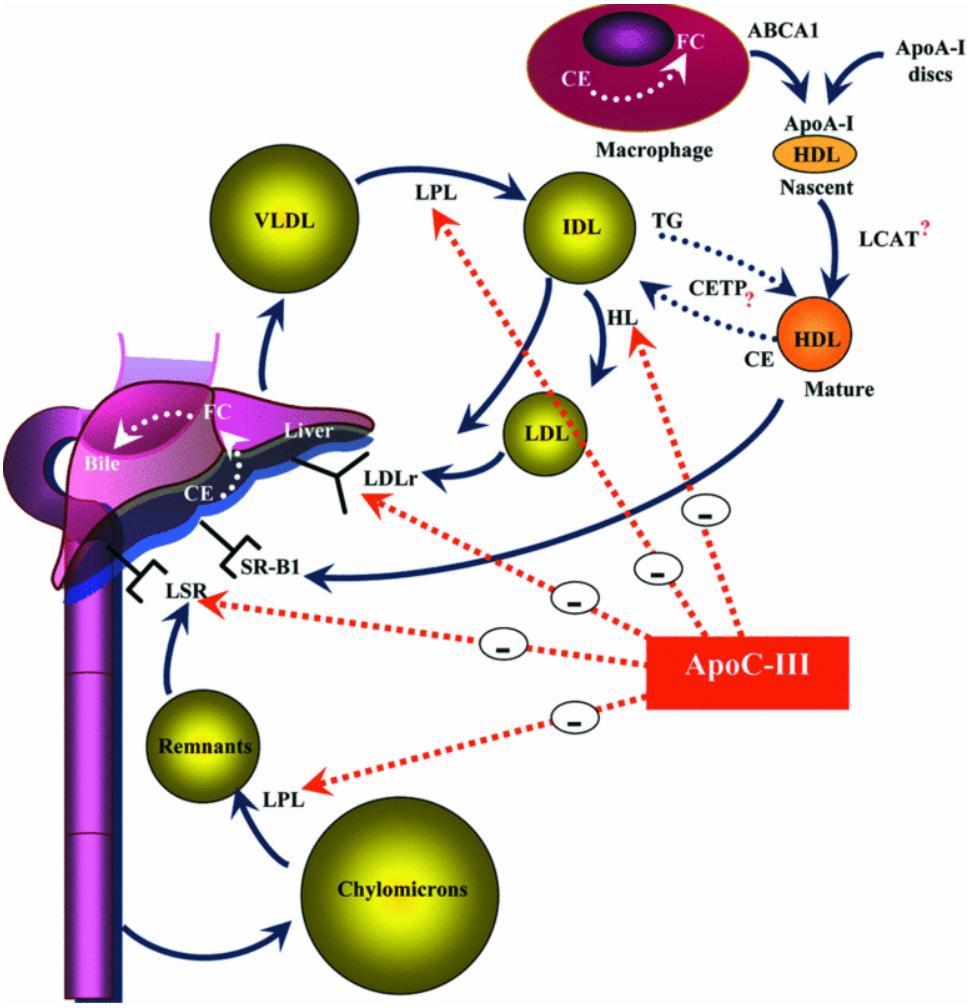


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

The apoC-III gene is located in a cluster between the apolipoprotein A (apoA) apoA-I and apoA-IV genes on chromosome 11q23 (Bruns et al. 1984). ApoC-III expression is down-regulated, in part, by insulin via the insulin response element in the promoter of the apoC-III gene (Li et al. 1995). More recent findings indicate that TRL carrying apoC-III impair insulin signaling in vascular endothelial cells and suggest that apoC-III could link dyslipidemia with endothelial dysfunction (Kawakami et al. 2006). Regulation of transcription of the apoC-III gene is also mediated by peroxisome proliferator activated receptors (PPAR). Activation of PPAR-α reduces apoC-III expression, accounting in part for the hypotriglyceridemic action of these compounds (Staels et al. 1995).

ApoC-III is a potent inhibitor of LPL-catalyzed lipolysis of TRL, which antagonizes lipoprotein lipase (LPL) activation via apoC-III (Lemieux et al. 2003). ApoC-III also inhibits hepatic lipase,

which plays an important role in the conversion of dense very low-density lipoprotein (VLDL) to intermediate-density lipoproteins (IDL) to low-density lipoprotein (LDL) (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). ApoC-III has other recognized properties as a direct player in inflammation and atherogenesis, which may further contribute to its positive correlation with risk of coronary events. ApoC-III stimulates the recruitment of blood monocytes to vascular endothelial cells by activating adhesion molecules on both cell types, and also promotes endothelial dysfunction (Kawakami et al. 2006). Taken together, these results support the concept that apoC-III is a multifunctional protein that not only regulates the metabolism of TRL, but it is also influences endothelial function and cardiovascular risk (Figure 2).

A growing body of human genetic data have demonstrated associations with functional mutations affecting apoC-III gene expression and CVD risk (Atzmon et al. 2006, Pollin et al. 2008, Petersen et al. 2010, Crosby et al. 2014, Jørgensen et al. 2014). The Cholesterol and Recurrent Events (CARE) trial demonstrated that apoB particles containing apoC-III more strongly predicted coronary events than plasma TG levels (Sacks et al. 2000). In a substudy of the CARE trial, the plasma concentration of LDL particles containing apoC-III was an independent risk factor for coronary events in patients with diabetes, supporting the role of apoC-III in promoting atherosclerosis (Lee et al. 2003). Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations. Recently, a novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and a cardioprotective profile characterized by lower LDL-C, increased high-density lipoprotein cholesterol (HDL-C) and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (*APOC3*641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC--III protein, a favorable lipoprotein profile, a lower incidence of hypertension, and greater insulin sensitivity, cardiovascular health, and longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have been recently described as well (Petersen et al. 2010). In a cohort of otherwise healthy, lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear post-prandial plasma TG from the circulation. Furthermore, they were also noted to have an increased risk of nonalcoholic fatty liver disease (NAFLD) and insulin resistance compared to patients with homozygous wild-type alleles.

In a recent study of 75,725 Danish participants, loss-of-function mutations in the apoCIII gene were associated with low levels of non-fasting triglycerides and a reduced risk of ischemic cardiovascular disease (Jørgensen et al. 2014). An unrelated exome sequencing study found that rare loss-of-function mutations in apoC-III associated with triglycerides carry reduced risk of coronary heart disease in a population of European, African, and Hispanic ancestry in a database of 110,970 participants (Crosby et al. 2014).

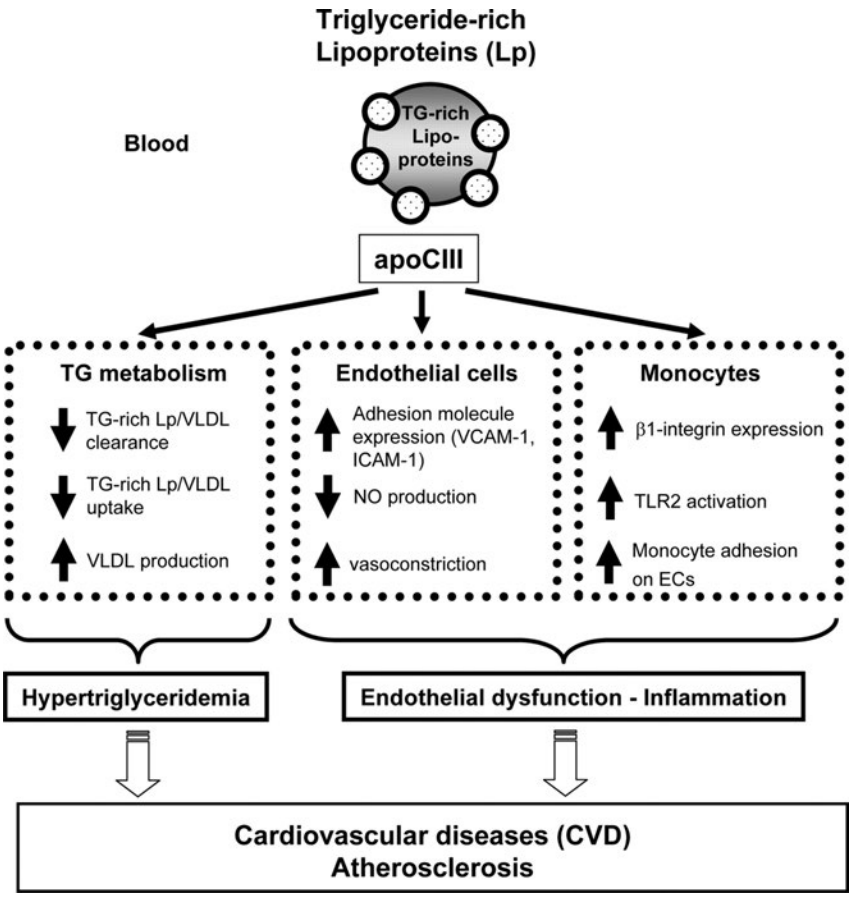


Figure 2 ApoC-III is a Multifunctional Protein

ApoC-III modulates TG metabolism, enhances vasoconstriction, and enhances monocyte adhesion to endothelial cells. These apoC-III-mediated effects may independently contribute to the risk of CVD. From Caron and Staels 2008; EC = endothelial cell, ICAM-1 = intracellular adhesion molecule-1, NO = nitric oxide, TG = triglyceride, TLR2 = toll-like receptor-2, VCAM-1 = vascular cell adhesion molecule-1, VLDL = very low-density lipoprotein.

Potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in patients with hypertriglyceridemia include: (1) by enhancing the activity of LPL, (2) through potentially enhanced activity of other lipases also involved in the metabolism and breakdown of triglycerides, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) it is known that apoC-III interacts with apoE, an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. ISIS 678354-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

In summary, inhibition of apoC-III by ISIS 678354 is expected to lower TRLs, and reverse the pro-inflammatory and proatherogenic effects of apoC-III. Through this novel mechanism of action ISIS 678354 is expected to effectively lower TG levels and has potential to reduce CV risk in patients with hypertriglyceridemia.

2.3.3 Preclinical Experience

General toxicology and pharmacokinetic studies for ISIS 678354 included sub-chronic (13-week repeat dose studies with a 13-week recovery) and chronic (26-week in mice and 39-week in monkey) toxicity studies. ISIS 838707 (mouse-specific apoC-III inhibitor) was also included in the chronic toxicity study in mice to evaluate any potential toxicity associated with apoC-III inhibition. The following findings in the ISIS 678354 mouse and monkey studies are considered non-specific class effects related to the uptake and accumulation of 2′-MOE ASOs, and the targeted delivery of ASO to the hepatocytes by the GalNAc3 conjugate which results in higher hepatocellular concentrations compared to unconjugated 2'-MOE ASOs. This is most apparent in mice at doses of 20 and 24 mg/kg/wk and in monkey at doses of 12 and 30 mg/kg/wk.

- dose-dependent microscopic findings related to ASO tissue accumulation included the presence of basophilic granules in various tissues in mice and monkeys (liver, kidney, lymph node, bone marrow and skin/injection sites) resulting in adaptive responses such as hypertrophy and/or vacuolation at 30 mg/kg/wk.
- in mice, dose-dependent increases in mitotic figures, cytoplasmic alteration and karyomegaly of hepatocytes and/or infiltration by vacuolated/granular macrophages predominantly at ≥ 6 mg/kg/wk (~50 to ~100 mg/wk human equivalent dose (HED) assuming 70 kg human body weight and 5- to 8-fold scaling factor for mouse plasma PK established for 2′-MOE ASO; Yu et al. 2015), and mild to occasionally marked increases in ALT (~6.5-fold over control) and/or AST (~2.6-fold over control) predominantly at 20 mg/kg/wk (~ 165 to 350 mg/wk HED). Individual hepatocellular necrosis was observed in one male at 20 mg/kg/wk after 26 weeks of treatment which correlated with an increase in ALT and AST.

- in monkeys, compared to baseline values, increases in glutamate dehydrogenase (GLDH) and ALT (up to ~5- and 4-fold over control, respectively) were observed at ≥ 6 mg/kg/wk (420 mg/wk human equivalent dose (HED) assuming 70 kg human body weight and direct scaling to humans on the basis of body weight) after 39 weeks of treatment with no microscopic correlates.
- pro-inflammatory changes in mice and monkeys after up to 26 and 39 weeks of treatment, respectively, included slight increases in liver weights (up to ~1.6- and up to ~2.1-fold over control) mainly at ≥ 6 and ≥ 12 mg/kg/wk in mice and monkeys, respectively. Increased spleen weights (up to ~1.9- and up to ~2.5-fold over control) were also observed mainly at ≥ 6 and ≥ 12 mg/kg/wk in mice and monkeys, respectively. In mice, increased MCP-1 (up to 7.7-fold over control) was accompanied by splenomegaly and multi-organ vacuolated/granular macrophage infiltrates in the 20 mg/kg/wk dose group.
- in monkeys, sporadic incidences of minimal to marked mononuclear cell infiltration at injection site skin were seen in all dose groups.

The most noteworthy finding in the monkey study was a marked PLT reduction, which occurred in one male monkey at the mid-high dose level, 12 mg/kg/wk (840 mg/wk HED). At Day 65, this animal presented with petechia and oral mucosal bleeding with a PLT count of 8x103/µL. This animal was treated with methylprednisolone on Days 65 and 72, and the PLT count quickly recovered to 145x103/µL on Day 70. This animal continued treatment with ISIS 678354, without a dosing holiday, until scheduled necropsy on Day 93 (interim) with the last clinical pathology evaluation on Day 93 again showing a marked reduction in PLT count (6x103/µL). Marked PLT reductions were not observed in the 30 mg/kg/wk dose group (2100 mg/wk HED) for up to 13 weeks or in any of the remaining dose groups for up to 39 weeks.

In vivo safety pharmacology and *in vitro* genetic toxicity studies indicate that ISIS 678354:

- had no effects on cardiovascular (blood pressure [BP], heart rate [HR], electrocardiogram [ECG]), respiratory (respiration rate, arterial blood gases), or central nervous system (CNS) parameters in the monkey consistent with previous experience with 2′-MOE ASOs (Kim et al. 2014).
- was not genotoxic and did not increase the rate of mutations in the *in vitro* bacterial reverse mutation assay nor induce chromosomal abnormalities in mammalian cells

Taken together, these data support the evaluation of ISIS 678354 as a potential new therapeutic approach to reduce hepatic apoC-III expression in patients with elevated TGs to reduce triglycerides, potentially improve their insulin sensitivity and reduce CVD risk.

Lower doses afforded by the $GalNAc_3$ technology will reduce overall drug exposure in plasma, non-hepatocyte cells in the liver, and kidney. Therefore, ISIS 678354 has the possibility of delivering similar efficacy results with lower dose levels and thereby fewer class-related adverse effects.

2.3.4 Clinical Experience

Detailed information concerning the clinical study conducted with ISIS 678354 can be found in the Investigator's Brochure. A summary of the study that has been conducted with ISIS 678354 is included below.

ISIS 678354-CS1 was a Phase 1, double-blind, placebo-controlled, dose escalation study designed to assess the safety, tolerability and pharmacokinetics of single and multiple doses of ISIS 678354 administered by subcutaneous (SC) injection to healthy subjects (age 18 to 65). In the single ascending dose (SAD) part of the study, five dose levels (10, 30, 60, 90, and 120 mg) were evaluated sequentially. In the multiple ascending dose (MAD) part, two dose levels (15 and 30 mg) were evaluated at weekly dosing for 6 weeks and one dose level (60 mg) was evaluated at every 4-week dosing for 3 months. The SAD and weekly MAD dose levels were studied in a cohort of 8 subjects, where 6 were randomized to active treatment with ISIS 678354 and 2 were randomized to placebo. In the every 4-week MAD cohort 10 subjects were studied (6 active and 4 placebo). In the 90 and 120 mg SAD and all of the MAD cohorts, the pharmacodynamic effects of ISIS 678354 vs. placebo were examined in healthy subjects with elevated triglycerides (TG > 200 mg/dL).

Results from the SAD portion of the Phase 1 study showed significant dose-dependent sustained reductions in fasting total apoC-III and TG levels. ApoC-III reductions of -4%, -32%, -65%, -78%, and -91%, and TG reductions of -12%, -11%, -43%, -68%, and -77% were observed with single doses of 10, 30, 60, 90 and 120 mg of ISIS 678354 respectively 14 days after dosing. In the MAD cohorts, mean apoC-III reductions of -65%, -84%, and -83% and mean TG reductions of -61%, -71%, and -65% were observed in the 15 and 30 mg weekly and 60 mg every 4-week dosing cohorts, respectively, 1 week after the last dose. Significant dose-dependent reductions of up to ~-30% in apoB and increases of up to ~100% in HDL-C were also observed. There were no notable increases in LDL-C in any dose group. Effects were sustained for at least 4 weeks after the last dose, consistent with the drug's long terminal elimination half-life.

Overall, ISIS 678354 was well tolerated and there were no safety concerns. There were no deaths, no serious adverse events related to ISIS 678354, no adverse events leading to treatment discontinuation, and no clinically-significant trends in laboratory assessments observed in any of the ISIS 678354 Phase 1 dose groups. Elevations in ALT > 3x ULN were reported as treatment-related in 2 ISIS-678354-treated subjects in MAD every-4-week cohort (60 mg). Both subjects had prior history of ALT elevation. There were no other treatment related laboratory abnormalities in the liver, kidney function or platelet counts and no clinically significant changes in vital signs or ECGs in any cohort studied.

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 678354 doses of 15 mg and 30 mg given weekly and 60 mg given every 4 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in TG. Four dosing regimens are planned for the present study, which are proposed to provide total monthly drug exposures equivalent to 10, 30, 40, and 50 mg administered as 10 mg every 4 weeks, 15 mg every 2 weeks, 10 mg every week, and 50 mg every 4 weeks, respectively. These doses are predicted to provide reductions from Baseline in serum TG ranging from approximately 30% to 64% at the end of the dosing interval at steady-state based on a preliminary PK/PD model developed using the available Phase 1 data.

The present study will evaluate the safety and efficacy of ISIS 678354 in a 5-fold range of drug exposure utilizing 3 different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hypertriglyceridemia will require chronic treatment and thus every 2 weeks or every 4 weeks dosing regimens, if safe and well-tolerated, may provide advantages over weekly dosing in terms of convenience and compliance for patients. The proposed range of doses are expected to provide sufficient data to characterize the dose- and exposure-response relationship.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. After an up to 4-week screening period, including an up to 2-week qualification period following an at least a 2-week diet stabilization period, where appropriate, approximately 100 eligible patients will be randomized in a 4:1 ratio to receive ISIS 678354 or placebo. Patients on a stable diet known to the investigator and followed at the site may go from Screening to qualification period without a 2-week diet stabilization phase. Study Drug (ISIS 678354 or placebo) will be administered by subcutaneous (SC) injection every week, every 2 weeks, or every 4 weeks, depending on cohort assignment, for up to 52 weekly doses, up to 26 every 2-week doses, or up to 13 every 4-week doses. Minimum treatment duration is 6 months. Maximum treatment duration is 12 months

The treatment portion of the study will be complete when the last patient reaches 6 months of exposure. All patients still on treatment will then enter a 13-week post-treatment follow-up period. Refer to Section 3.4.2 for additional detail regarding End of Treatment period and scheduling of End of Treatment Visits.

The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A and B) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts C and D, respectively). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy and safety analyses will be repeated at the completion of Study Drug treatment.

Patients ≥ 18 and ≤ 80 years old with elevated plasma TG levels (≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥ 5.7 mmol/L)) and a clinical diagnosis of CVD or at high risk for CVD are eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for known CVD risk factors as per current guidelines.

Clinical diagnosis of CVD is defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease (PAD). A diagnosis of CAD has to be documented by any of the following:

- Angiographic evidence of ≥ 50% stenosis of 1 or more major epicardial coronary arteries
- History of myocardial infarction documented by positive enzymes, and either symptoms of myocardial ischemia, or ECG changes (Thygesen et al. 2012)
- History of coronary revascularization

- Evidence of cardiac ischemia on exercise testing, or imaging study

Patients at a high risk for CVD are defined using the following criteria:

- Type 2 Diabetes Mellitus requiring treatment, and
- Age ≥50 years, and
- at least one additional CV risk factor:
    - men ≥55 years of age and women ≥65 years of age, or
    - current cigarette smoker, or stopped smoking within 3 months prior screening, or
    - hypertension requiring antihypertensive treatment

Patients will be evaluated for study eligibility during Screening, which takes place within 4 weeks prior to Day 1 (the first day of Study Drug administration) and will include an at least a 2-week diet stabilization period followed by an up to 2-week qualification period. Patients on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 2-week diet stabilization phase. Patients who are determined to be eligible, based on screening assessments, will be enrolled in the study at Day 1 and randomly assigned to 1 of the 4 parallel dosing cohorts, with each cohort having a 4:1 ratio to receive ISIS 678354 or matching volume of placebo, respectively, by SC injection for up to 52 weeks.

Following the End-of-Treatment, patients will enter the 13-week post-treatment follow-up period.

3.2 Number of Study Centers

This is a multicenter, multinational study.

3.3 Number of Patients

Approximately 100 patients will be randomized in this study, with approximately 25 patients assigned to each of the 4 treatment cohorts.

3.4 Overall Study Duration and Follow-up

The length of patients' participation in the study may be up to approximately 16 months (69 weeks), which includes a 4-week screening period that includes a 2-week diet stabilization/run-in period for patients not already on a stable diet, and a 2-week qualification period, an up to 52-week treatment period, and a 13-week post-treatment follow-up period. The treatment portion of the study will be complete when the last patient reaches 6 months of exposure.

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

3.4.1 Screening

Patient eligibility for the study will be determined within 4 weeks prior to study.

3.4.2 Treatment

For each patient, minimum treatment duration is 6 months and a maximum of 52 weeks.

All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 4 treatment cohorts. On completion of the 6 months, patients will continue treatment within the same randomized cohort until the last patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. The End of Treatment visits for all patients on treatment will be scheduled no later than the End of Treatment visit of the last patient to complete 6 months of exposure.

The End of Treatment visit should be scheduled one dosing interval post last dose of study drug: one week post last dose for weekly dosing (Cohort D), 2 weeks post last dose for every 2-week dosing (Cohort C), and 4 weeks post last dose for every 4-week dosing (Cohorts A-B). The procedures scheduled for the Week 53/ET visit (Appendix A) will be performed at the End of Treatment visit. Following the End of Treatment visit patients will then enter a 13-week post-treatment follow-up period.

Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures in Appendix A. During the Treatment, Study Drug (ISIS 678354 or placebo) will be administered by SC injection once-weekly, every 2 weeks, or every 4 weeks, depending on cohort assignment.

3.4.3 Post-Treatment

Patients, when completed dosing, will enter the 13-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits at 4, 8, and 13 weeks post End of Treatment period as per Appendix A (Follow-up).

The final study visit for each patient will be 13 weeks post End of Treatment period. End of Treatment period is defined as one dosing interval post last dose.

3.5 End-of-Study

The End-of-Study is defined as last patient, last visit.

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

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 678354 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 678354, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and/or Statistical Analysis Plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient directed information and/or recruitment material.

Patients or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Randomization

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

Using an Interactive Web-Response System (IXRS), eligible patients will be randomized in a 1:1:1:1 ratio to 1 of the 4 parallel-dose cohorts (Cohorts A, B, C, or D). Within each dose cohort, patients will be randomized in a 4:1 ratio to receive ISIS 678354 or matching volume of placebo, respectively.

A permuted block schedule will be used. The randomization schedule will be generated and held by an independent vendor.

4.3 Replacement of Patients

Patients who withdraw from the study will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all patients, monitors, and Study Center personnel related to the study will be blinded throughout the study and until all patients have completed the study and the database has been locked. However, if a patient has suffered an SAE (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient using the IXRS. The Sponsor will determine the point at which all treatment assignments will be unblinded. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. In addition, all SUSARs will be unblinded by the Sponsor's or designee's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study, candidates must meet the following eligibility criteria within 4 weeks 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 and ≤ 80 years old at the time of informed consent
3. a. Clinical diagnosis of CVD (defined as documented coronary artery disease, stroke, or peripheral artery disease; refer to Section 3.1), OR
   b. High risk for CVD defined as:
      - Type 2 Diabetes Mellitus requiring treatment, and
      - Age ≥ 50 years, and
      - at least one additional CV risk factor:
        - men ≥ 55 years of age and women ≥ 65 years of age, or
        - current cigarette smoker, or stopped smoking within 3 months prior screening, or
        - hypertension requiring antihypertensive treatment
4. Fasting serum TG ≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥ 5.7 mmol/L) at Screening. If the fasting TG value at Screening is < 200 mg/dL (< 2.3 mmol/L) but ≥ 150 mg/dL (≥ 1.7 mmol/L) one additional test may be performed in order to qualify
5. Fasting TG ≥ 200 mg/dL and ≤ 500 mg/dL at Qualification visit. If fasting TG is < 200 mg/dL but ≥ 150 mg/dL one additional test may be performed in order to qualify
6. Must be on standard-of-care preventative therapy for their known CVD risk factors (e.g., hyperlipidemia, hypertension, diabetes)
7. Patients on the following medications must be on a stable regimen for at least 4 weeks prior to Screening and expected to remain on a stable regimen through the end of the post-treatment follow-up period:
   a. Lipid lowering drugs (statins, ezetimibe, PCSK9 inhibitors, niacin, fibrates, fish oil or other products containing omega-3 fatty acids including OTC preparations)
   b. Antiplatelet drugs
   c. Testosterone, estrogens, progesterone, growth hormone or progestins
8. Females: must be non-pregnant and non-lactating and either:
   a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);
   b. 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 FSH levels in the postmenopausal range for the laboratory involved);

c. Abstinent* or,

d. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 678354 or placebo)

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

9. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 678354

5.2 Exclusion Criteria

1. Within 3 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke/transient ischemic attack
2. Within 3 months of Screening: coronary, carotid, or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis
3. Heart failure NYHA class III and IV
4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
5. History of acute kidney injury within 12 months of Screening
6. Uncontrolled hyper or hypothyroidism
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
10. Patients at high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Hypersensitivity to the active substance or to any of the excipients
13. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
    a. 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
    b. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg.

c. Estimated GFR < 60 mL/min/1.73 m^2 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation

d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN

e. Bilirubin > 1.2 x ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL

f. Alkaline phosphatase (ALP) > 1.5 x ULN

g. Platelet count < LLN

h. LDL-C > 130 mg/dL (> 3.4 mmol/L)

14. Type 1 diabetes mellitus

15. Type 2 diabetes mellitus with any of the following:

a. Newly diagnosed within 12 weeks of Screening

b. HbA1c ≥ 9.0% at Screening

c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Screening [with the exception of ± 10 units of insulin])

d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units for insulin)

e. Current use of GLP-1 agonists, if patient has history of pancreatitis

16. Use of warfarin or other vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors

17. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer

18. Treatment with any non-Akcea/non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Patients that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months has elapsed since dosing

19. BMI > 40 kg/m^2

20. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening

21. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator

22. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study

6. STUDY PROCEDURES

6.1 Study Schedule

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

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. An up to 4-week period is provided for completing screening assessments and determining patient eligibility for the study. Abnormal screening results may be re-tested once for determination of patient eligibility after consultation with the Sponsor Medical Monitor. Patients may be re-screened 1 time in order to determine eligibility.

During the screening period, patients will undergo a medical history and physical examination including vital signs, 12-lead electrocardiogram (ECG) and have blood and urine samples taken for clinical laboratory testing. Patients will be screened for HIV, hepatitis B, and hepatitis C.

As part of the screening period, patients not already on a stable diet will have 2 weeks of diet run-in, followed by a qualification visit, during which final eligibility assessments will be performed. Patients on a stable diet, known to the investigator and followed at the site, may go from Screening to qualification without a 2-week diet run-in. At the qualification visit TGs will be measured.

6.1.2 Treatment Period

Treatment period is defined as the time between the first and the last doses of study drug plus one dosing interval. During the treatment period, patients will report to the study center for clinic visits. Patients will receive 10 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 49 weeks in Cohort A, 50 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 49 weeks in Cohort B, 15 mg doses of Study Drug administered by SC injection once every 2 weeks for up to 51 weeks in Cohort C, or 10 mg doses of Study Drug administered by SC injection once per week (weekly) for up to 52 weeks in Cohort D (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 678354 plasma concentrations, immunogenicity and biomarker samples, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A.

Extensive Pharmacokinetic (PK) Subgroup Only:

Within each cohort, a subgroup of approximately 10 patients, who will consent to extensive PK sampling, will undergo additional PK sampling, in what is referred to as the PK Subgroup in this study. Patients in this subgroup will have additional PK sampling time points in order to evaluate the plasma PK parameters of ISIS 678354. Patients in this subgroup will have additional visits to the clinic during the treatment period in order to collect blood samples for PK assessment (Appendix C).

6.1.3 Post-Treatment Period

Each patient will be followed for safety assessments for 13 weeks post end of treatment period. During the post-treatment follow-up period, patients will return to the Study Center for 3 outpatient visits as outlined in Appendix A for safety and clinical laboratory evaluations and for blood sampling for PK (Appendices A and C).

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

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

Routine blood chemistry and urine samples should be taken after fasting for at least 10 hours and preferably not more than 12 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status, but no later than 7 days after the initial result is obtained. During preparation for fasting samples, the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

If tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood or urine specimen should be re-drawn as soon as possible (ideally within 1 week).

While on treatment, hematology samples will be collected every 14 days (±2 days). Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local samples are unreportable (e.g., due to hemolyzed or clumped blood samples), patient dosing cannot continue until another sample is repeated and determined not to have met a platelet stopping rule.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

While on treatment blood and urine samples for renal function testing will also be collected every 14 days (±2 days) and sent to the central laboratory for analysis for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period per Section 8.5.2.

While on treatment liver function testing will also be collected every 14 days (±2 days) and sent to the central laboratory for analysis for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period per Section 8.5.1.

All lab samples are to be sent to the central laboratory by overnight courier and processed. Lab Alerts issued as per protocol safety monitoring requirements or stopping rules will indicate the applicable protocol section to facilitate review and will be immediately and simultaneously sent by email to the Investigator, the Sponsor and the CRO Medical Monitors, the Sponsor Drug Safety Physician, and the Clinical Trial Manager (CTM), and should be received by them within 2 days from sample collection. Hematology results from the site's local laboratories are received by the study center staff per the local laboratories' standard reporting time, and should be entered as soon as possible into the eCRF to inform the Sponsor and CRO study monitoring teams.

All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3. Any case of a platelet count reduction to levels below 50,000/mm^3 is considered an adverse event of special interest and must be reported in an expedited fashion to the Sponsor as per Sections 9.3.3.1 and 9.4.1.

All liver and renal function tests must also be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the result has not met the stopping rule. Any event meeting renal stopping rules criteria described in Section 8.6.2 is considered an adverse event of special interest and must be reported in an expedited fashion to the Sponsor as per Sections 9.3.3.1 and 9.4.1.

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

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

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure (BP), pulse rate, respiratory rate and body temperature. BP and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. BP should always be measured on the same arm (preferentially on the left arm). Height will be measured at Screening.

6.2.3 Electrocardiography

Electrocardiography (ECG) will be conducted at Screening, Day 1, (prior to the first dose of Study Drug), and again during the treatment period as follows per dosing cohort:

- Cohorts A and B at Weeks 5, 13, 21, 25, 33, 41, 49, and 53
- Cohorts C and D at Weeks 5, 13, 21, 25, 27, 33, 41, 49, and 53

Patients assigned to the PK Subgroup will have additional ECGs conducted as indicated in the Schedule of Procedures (Appendix A). In all cohorts, ECGs will be conducted during the post-treatment follow-up period as outlined in Appendix A.

ECGs will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate.

6.2.4 PK Sampling

Blood samples for the determination of plasma ISIS 678354 concentrations will be collected prior to dosing on Day 1 and at various times throughout the treatment and post-treatment follow-up periods as noted in the tables in Appendix C.

Within each cohort, patients assigned to the PK Subgroup will have additional PK sampling time points and additional visits to the clinic during the treatment period in order to collect blood samples for PK assessment (Appendix C).

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients engaged in sexual relations with a female of child-bearing potential must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the patient's last dose of study treatment.

For the purposes of this study, women of childbearing potential 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, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at Follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug

For female patients and female partners of male patients:

- Using 2 of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository

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

***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 patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 678354 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 678354 or Placebo) will be provided as 0.8 mL deliverable volume in 2 mL stoppered and sealed glass vials as a sterile solution.

The Study Drug is clear to slightly yellow in color, it is for single use, contains no preservatives and must be stored between 2 to 8 °Celsius and be protected from light.

7.1.1 ISIS 678354

ISIS 678354 vials contain 100 mg/mL ISIS 678354 in Water for Injection. Additionally, sodium phosphate buffer and sodium chloride are added to control the measure of the acidity or basicity of the solution (pH) and tonicity, respectively. The target pH is 7.4.

7.1.2 Placebo

Placebo vials contain 0.9% sodium chloride in Water for Injection. 1.6 µg/mL riboflavin is added to ensure color matching of placebo vials to ISIS 678354 vials.

Table 1 Study Drug Characteristics

Study Drug	ISIS 678354	Placebo
Strength	100 mg/mL	Not Applicable
Volume/Formulation	0.8 mL solution per 2.0 mL vial	0.8 mL solution per 2.0 mL vial
Route of Administration	SC	SC

SC = subcutaneous

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 678354 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 of Study Drug (ISIS 678354 or placebo) supplies provided by the Sponsor. The patient must return all used and unused Study Drug to the Study Center for accountability. The Study Center must return all used and unused Study Drug to the Sponsor or designee for destruction. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

ISIS 678354 will be administered to patients by Study Center staff as follows:

Cohort A: a single SC dose of 10 mg once every 4 weeks for up to 49 weeks and a maximum of 13 doses

Cohort B: a single SC dose of 50 mg once every 4 weeks for up to 49 weeks and a maximum of 13 doses

Cohort C: a single SC dose of 15 mg every 2 weeks for up to 51 weeks and a maximum of 26 doses

Cohort D: a single SC dose of 10 mg every week (weekly) for up to 52 weeks and a maximum of 52 doses

Self-administration will be allowed after appropriate training of patient and/or caregiver.

Patients in Cohorts A and B should receive 1 dose every 4 weeks, patients in Cohort C should receive 1 dose every 2 weeks and patients in Cohort D should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example, if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays according to the respective dosing schedule, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 678354 or placebo) preparation and administration.

Table 2 Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 678354
A	10 mg ISIS 678354 or placebo (Every 4 weeks)	0.10 mL	≤ 13	≤ 130 mg
B	50 mg ISIS 678354 or placebo (Every 4 weeks)	0.50 mL	≤ 13	≤ 650 mg
C	15 mg ISIS 678354 or placebo (Every 2 weeks)	0.15 mL	≤ 26	≤ 390 mg
D	10 mg ISIS 678354 or placebo (Every week)	0.10 mL	≤ 52	≤ 520 mg

8.2 Other Protocol-Required Drugs

No other Study Drug treatments are required by the protocol.

8.3 Other Protocol-Required Treatment Procedures

No other treatment procedures are required by the protocol.

8.4 Treatment Precautions

No specific treatment precautions are required.

8.5 Safety Monitoring Rules

Stopping rules are described below in Section 8.6.

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

For the purposes of safety monitoring Baseline is defined as the average of the pre-dose test closest to Day 1 and the Day 1 value itself.

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

In case of discrepancy between the test results from 2 sources, such as between the central and local lab, safety-mandated action must be initiated based on the more critical (lower or higher, as relevant) of the 2 values.

Confirmation Guidance: At any time during the study (treatment or post-treatment follow-up periods), the clinical laboratory results meeting any of 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 prior to administering the next dose of Study Drug (ISIS 678354 or placebo). All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

In addition, as described in Section 6.2.1 hematology labs should be sent in parallel to the central and local laboratory for analysis.

Stopping Rule Guidance: The Investigator may interrupt or permanently discontinue study treatment for any medical reason including changes in clinical laboratory results.

In the event of an initial clinical laboratory result that meets a stopping criterion, study drug must not be administered again until a confirmatory test result has been reviewed by the Study Medical Monitor. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met and are confirmed, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 678354 or placebo), evaluated fully as outlined below and in consultation with the Study Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Study Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate.

Additional Guidance: If possible, a PK sample should be collected as soon as possible after an SAE has occurred (preferably within 2 weeks). In addition, if a patient is asked to return to the clinic for additional evaluations due to an AE, then a PK sample should be taken at the time of the unscheduled visit.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

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

All patients will have liver chemistry tests monitored every 14 days (±2 days) for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period. Upon completion of the study treatment period, liver chemistry tests should be monitored as per visit schedule in Appendix A.

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

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (treatment or post-treatment period), the initial measurement(s) should be confirmed as described in Section 8.5.

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

All results of liver function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.1.

Further Investigation into Liver Chemistry Elevations: For patients 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 (hepatitis A virus [HAV] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, Cytomegalovirus [CMV] IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor and the study DSMB. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

All routine liver function test results will be reviewed on an ongoing basis at the weekly safety review by the Medical Monitor.

All lab alerts for abnormal liver function tests must be promptly reviewed by the Investigator (within 48 hours of receipt) and Medical Monitors (within 24 hours of receipt).

Lab alerts for abnormal liver chemistry tests will be issued for: 1) ALT or AST > 3 x ULN; 2) ALT or AST > 2 x baseline; 3) total bilirubin > ULN; 4) ALP > ULN. These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance referenced in Section 8.5.1.

8.5.2 Safety Monitoring for Renal Function

While on treatment all patients will have renal function tests monitored every 14 days (±2 days) for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period. Upon completion of the study treatment period, urine renal biomarkers will be monitored as per visit schedule in Appendix A.

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

While on treatment during the course of the study, urinary surveillance will include urinalysis to include urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR) and

urinary red blood cells (RBCs), as well as serum creatinine and cystatin-C which will be monitored every 14 days (±2 days). In addition, biomarkers of acute renal injury will also be measured every 14 days (±2 days) (Appendix B).

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than every 14 days will be guided by consultation with a local nephrologist. Any decision taken by the Investigator to discontinue study medication will be made taking into account all available and relevant data. In addition, the decision to discontinue Study Drug may also be based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities. Any decision taken to restart study medication will be made in consultation with the Study Medical Monitor taking into account all available and relevant data.

All renal function test results will be reviewed on an ongoing basis by the Medical Monitor.

All results of renal function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.2.

Lab alerts for abnormal renal tests will be issued for:

- estimated GFR (eGFR) (by CKD-EPI formula) decrease from Baseline > 25%,
- urine albumin/creatinine ratio (UACR) > 250 mg/g,
- urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or
- increase in serum creatinine from Baseline > 0.3 mg/dL

These alert levels are set to anticipate and prevent the risk of a medically significant change in renal function while receiving Study Drug. If any of the above criteria are met, treatment should immediately be interrupted, and the Study Medical Monitor should be informed. In addition, the result should be confirmed as soon as possible (as described in Section 8.5), but no later than 7 days after the initial event. If the confirmatory test is negative (i.e. repeat sample taken within 7 days is within normal limits), the patient may continue treatment upon consultation with the Study Medical Monitor.

The Investigator should also review the patient's concomitant medications for potentially nephrotoxic agents, and, with the results of these evaluations, review any decision to continue or discontinue the patient in consultation with the Study Medical Monitor and the medical area specialist consultant of the DSMB.

Further instruction regarding treatment interruption and/or permanent stopping of study drug can be found in Section 8.6.2.

8.5.3 Safety Monitoring for Platelet Count Results

All patients will have platelet counts monitored every 14 days (±2 days) for the duration of the study treatment period and must not receive Study Drug without an interpretable platelet count result in the prior 14 days. Upon completion of the study treatment period, platelets will be monitored every 14 days (±2 days) for the first 6 weeks and then at 8 and 13 weeks post end of treatment period (as per visit schedule).

As described in Section 6.2.1, all platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3.

Any case of a platelet count reduction to levels below 50,000/mm^3 (Grade 3 or Grade 4) is considered an adverse event of special interest and should be reported in an expedited fashion to the Sponsor. In this case the Investigator should refer the subject to a hematologist to provide diagnostic and therapeutic management.

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm^3, 2) platelet count is ≥ 30% decreased from Baseline, or 3) the hematology sample is unreportable. All these lab alerts, are reviewed promptly by the Medical Monitor and instructions are communicated to the Investigator and the study personnel within 24 hours of receiving an actionable lab alert as described in Section 6.2.1.

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

In the event of a platelet count < 100,000/mm^3 the laboratory tests outlined in Appendix E, should be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

8.5.4 Safety Monitoring for Bleeding Events

Patients will be evaluated for occurrence of bleeding events continuously after the start of Study Drug treatment (Day 1) up to the end of the follow-up period for all cohorts. All bleeding events are considered adverse events and reported on adverse event case report form.

Bleeding events that are either major or clinically-relevant non-major bleeding (as defined below) will need to be monitored and treated, as needed, immediately. Patients with a suspected bleeding event will undergo additional testing if deemed appropriate by the treating physician and an (S)AE case report form will be completed. In addition, if bleeding is considered significant, hemoglobin (Hb), hematocrit (HCT), aPTT, PT, INR, and platelet count are to be obtained. In addition, approximately 2 mL of K2EDTA anticoagulated blood will be collected and resulting plasma must be stored allowing for a centralized assessment of ISIS 678354 concentrations.

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

Major bleeding (MB) is defined as one of the following (Büller et al. 2007):

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome

3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 20 g/L (1.24 mmol/L) or more within 24 hours

Clinically-relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but that resulted, for example, in medical examination, intervention, or had clinical consequences for a subject (Büller et al. 2007).

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

8.5.5 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs or symptoms of fever, constitutional symptoms, rash, arthralgia or joint swelling that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients who experience persistent or increasing symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below

  All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode
  - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit
  - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the respective CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L)
  - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A documented severe hypoglycemic event is defined as one in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level

≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

Instructions should be provided to all patients on the appropriate use of a glucose meter.

8.5.8 Safety Monitoring for Hyperglycemia in Patients with T2DM

If medically appropriate, patients should remain on a stable regimen of anti-hyperglycemic therapy and have either upward dose titration and/or addition of any other anti-hyperglycemic agent(s) only when specific threshold values (listed below) are met and confirmed on subsequent testing (ideally within 1-week of the initial test). Any change to the anti-hyperglycemic therapy should be discussed with the Sponsor Medical Monitor prior to introduction.

Fasting plasma glucose (FPG) and HbA1c are monitored as per visit schedule in Appendix A (approximately every 3 months) throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L) or
- HbA1c > 9% (for patients with baseline HbA1c < 8%) and HbA1c increase of more than 1% from Baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

  In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

  If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken.

8.6 Stopping Rules

Monitoring rules are described above in Section 8.5.

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

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results meeting any of the following criteria, dosing of a patient with Study Drug will be stopped permanently:

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 (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed and total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides

with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event that any of the renal monitoring rules summarized in Section 8.5.2 are met, treatment should immediately be interrupted and the abnormal result should be confirmed as soon as possible, but no later than 7 days after the initial event. In addition, upon consultation with the Study Medical Monitor, site will obtain any additional lab assessments necessary to determine any alternative etiologies that may account for the abnormal result. If results from additional testing confirm the initial abnormal lab result, future treatment of the patient will be determined per the guidelines below:

- An alternative etiology is identified that may account for abnormal results:
  - Patient will have treatment interrupted until either:
    - Lab values have returned to baseline, and/or
    - Alternative etiology has resolved/recovered, AND
    - Study Medical Monitor has approved treatment to resume
- An alternative etiology has not been identified that may account for abnormal results:
  - Patient will be permanently withdrawn from treatment

The follow-up schedule and frequency of renal function monitoring after the initial event will be determined by the Study Medical Monitor in consultation with the Investigator and the medical area specialist on the DSMB. The Investigator should consider consulting a local nephrologist for any change of renal function that presents a concern. If a renal biopsy is performed, a sample specimen should be made available for examination by an independent renal pathologist who has been engaged by the Sponsor to review such specimens.

8.6.3 Stopping Rule for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is already on reduced dose, dosing of the patient with Study Drug will be stopped permanently (Table 3). Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of glucocorticoids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose glucocorticoids. 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 0.52 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral glucocorticoids after methylprednisolone).

In the event of a platelet count < 75,000/mm^3 and ≥ 50,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Büller et al. 2007), dosing of a patient with Study Drug should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. If dosing is continued, it must be at a reduced dose as shown in Table 3. The

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

If, after reintroduction of Study Drug, the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Once a patient commences weekly monitoring this frequency of monitoring should continue until the platelet count returns to the normal range (≥140K/mm^3) for 2 successive values.

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

8.6.4 Stopping Rule for Bleeding

If an event of Major Bleeding or Clinically-Relevant Non-major Bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor (or designee) and the subject should be closely monitored (vital signs, lab tests such as Hb, HCT and platelet count, additional outpatient visits, overnight stays and coagulation tests may be needed) throughout the treatment and during the post-treatment evaluation period.

In the event of Major Bleeding or Clinically-Relevant Non-major Bleeding (see definitions in Section 8.5.4) as assessed by the Investigator, dosing of a subject with Study Drug (ISIS 678354 or placebo) may be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined, including the suitability of the subject for resumption of dosing by the Investigator in consultation with the Sponsor Medical Monitor (or designee).

Table 3 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, ≥140K/mm^3	No action	Monitor every 14 days (±2 days)
≥100K to <140K/mm^3	No action	Closer observation Monitor every week*
≥75K to <100K/mm^3	Permanently reduce as follows: For Cohort A: reduce to 5 mg every 4 weeks For Cohort B: reduce to 25 mg every 4 weeks For Cohort C: reduce to 7.5 mg every 2 weeks For Cohort D: reduce to 5 mg every week	Closer observation Monitor every week*
≥50K to <75K/mm^3	Pause dosing When platelet count returns to ≥ 100K/mm^3 restart dosing as follows **only if approved by Sponsor Medical Monitor:** For Cohort A: reduce to 5 mg every 4 weeks For Cohort B: reduce to 25 mg every 4 weeks For Cohort C: reduce to 7.5 mg every 2 weeks For Cohort D: reduce to 5 mg every week or Permanently discontinue Study Drug if it occurs while on already reduced dose	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/non-steroidal anti-inflammatory drug (NSAIDS)

Platelet Count on Rx	Drug Dose	Monitoring
≥25K to <50K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS while platelet count <50K/mm^3 if possible Refer to hematologist to provide diagnostic and therapeutic management
<25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization Discontinue antiplatelet agents/NSAIDS medication while platelet count <50K/mm^3 if possible Refer to hematologist to provide diagnostic and therapeutic management

* Once a patient commences weekly monitoring this frequency of monitoring should continue until the platelet count returns to the normal range (≥140K/mm^3) for 2 successive values.

** Recovery in platelet count may be accelerated by administration of high dose glucocorticoids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 24 weeks for 1-4 cycles; Prednis(ol-)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone).

8.7 Adjustment of Dose

Dose frequency adjustments for platelet count reduction must be made in accordance with Table 3 (above).

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

Patients may have their dose interrupted in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Drug

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

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.4
- When a platelet count of less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 while the patient is on a reduced dose.

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

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

Any patient who discontinues early from the treatment period or from the post-treatment follow-up period should be strongly encouraged to complete follow-up study visits, procedures and observations as described below.

Any patient who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in Table 3, Section 8.6.3 for the first 6 weeks post end of treatment period and then at 8 and 13 weeks post end of treatment period (as per visit schedule).

If a patient early terminates from the treatment period, an ET visit (Week 53 visit assessments) should be performed at the time of withdrawal, and ideally within 2 weeks from the last dose of Study Drug, and patients should start the 13-week post-treatment follow-up period to collect the study assessments in accordance with the Schedule of Procedures in Appendix A.

If the patient early terminates from the post-treatment follow-up period, a final visit (assessments from the Week 13 of post-treatment follow-up period) should be performed at the time of withdrawal.

8.9 Withdrawal of Patients from the Study

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

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

Other reasons for withdrawal of patients from the study 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 patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET visit (Week 53 visit assessments) and observations at the time of withdrawal (Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the ET visit (Week 53 visit assessments) and observations at the time of withdrawal (Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. 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 from the time the patient has signed the informed consent at Screening to the end of the post-treatment follow-up period.

Allowed Concomitant Therapy

Use of the following is allowed only if the patient has been on a stable regimen for at least 4 weeks prior to screening and is planned to remain on a stable regimen through the end of the post-treatment follow-up period:

- Lipid lowering drugs (statins, ezetimibe, 0 inhibitors, niacin, fibrates, fish oil, other products containing omega-3 fatty acids (including OTC preparations)
    - The timing of PCSK9 inhibitor and study drug administration should be kept consistent with respect to lipid assessments. The first dose of ISIS 678354 (i.e., Study Day 1) will be scheduled for one day ahead of the next planned PCSK9 inhibitor injection to establish a regular time span between the two medications. PCSK9 inhibitors should be administered one day after administration of the study drug for the whole duration of the study treatment.
- Anti-platelet therapies
- Testosterone, estrogens, progesterone, growth hormone, or progestins.

Disallowed Concomitant Therapy

Use of the following is disallowed:

- Warfarin and other vitamin K antagonists, direct thrombin inhibitors or Factor Xa inhibitors
- Other experimental agents during the study including investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. This includes marketed agents at experimental dosages
- Treatment with any non-Ionis oligonucleotide (including siRNA) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Patients that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months has elapsed since dosing

- Lipoprotein apheresis

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

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between screening and the end of the post-treatment follow-up period.

8.11 Treatment Compliance

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

Patients or Study Center Staff will record treatment administered in a dosing diary that will be reviewed by Study Center staff and entered into the eCRF.

8.12 Safety Monitoring Compliance

Compliance with safety monitoring requirements and treatment stopping rules must be documented by the Study Center staff.

Patients and the Study Investigators are required to adhere to a strict program of monitoring requirements and treatment stopping rules as described in Section 6.2.1, Sections 8.5.1-8.5.8, and Sections 8.6.1-8.6.4.

While on treatment patients will be required to have platelet counts every 14 days (±2 days) for the duration of the study and must not receive Study Drug without an interpretable platelet count result in the prior 2 weeks, in which case the Investigator must contact the patient to hold dosing until a new platelet count is obtained and reviewed, and will document this contact.

While on treatment patients will also be required to have renal function testing and assessment of biomarkers of renal damage every 14 days (±2 days) for the first 3 months of the study treatment, and monthly thereafter during the treatment period. In such a case, the Investigator must contact the patient to hold dosing until these or new tests are obtained and reviewed.

Adherence to the program will be closely monitored by the Sponsor, and patients and trial sites that are unable or unwilling to comply with this important risk mitigation program will be discontinued from the study.

Patients should be informed of the possibility and risks of a reduction in platelet count, and of potential hepatic and renal risks, and the importance of adherence to the monitoring program. Any case of a platelet count reduction to levels below 50,000/mm^3, or any event meeting renal stopping rules criteria described in Section 8.6.2 are considered adverse events of special interest and should be reported in an expedited fashion to the Sponsor.

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 Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

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

9.3 Definitions

9.3.1 Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Unexpected Adverse Reaction

Adverse reaction: All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected adverse reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

9.3.3 Serious Adverse Event (SAE)

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

- Results in death

- Is life threatening, that is, poses an immediate risk of death at the time of the event
- An AE or adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.3.3.1 Adverse Events of Special Interest

For the purpose of this study severe reductions in platelet count < 50,000 mm^3 as well as any event meeting renal stopping rules criteria described in Section 8.6.2 are considered as AE of special interest and should be subject to expediting reporting to the Sponsor following the same requirements as for SAE reporting (Section 9.4.1).

9.4 Monitoring and Recording Adverse Events

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

9.4.1 Serious Adverse Events/Adverse Events of Special Interest

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs and AEs of special interest (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period. An Initial Serious Adverse Event Form should be completed and a copy should be emailed or faxed to the Sponsor or designee. The contact information for reporting SAEs is as follows:

Attention: [redacted]

Email: [redacted]

Fax: [redacted]

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

All SAEs considered treatment-related, as defined in Section 9.4.3.1, will be reported by the Sponsor to the DSMB as described in Section 3.6.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 678354 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 patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 678354 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions. For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (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 678354 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 678354 or placebo) administration and dose
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Temporarily Interrupted, Restarted Reduced Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the next lower dose
- **Permanently Discontinued:** Study Drug was discontinued and not restarted

9.4.3.4 Treatment Given for Adverse Event

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

9.4.3.5 Outcome of the Adverse Event

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

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

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious eCRF (the SAE resolution date should be entered as the date of onset of that AE)

- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor that monitoring is no longer necessary. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The 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 and signatures.

All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3.

Any case of a platelet count reduction to levels below 50,000/mm^3 is considered an adverse event of special interest and should be reported in an expedited fashion to the Sponsor as per Sections 9.3.3.1 and 9.4.1).

All results of liver function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.1.

All results of renal function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.2.

Any event meeting renal stopping rules criteria described in Section 8.6.2 is considered an adverse event of special interest and should be reported in an expedited fashion to the Sponsor as per Sections 9.3.3.1 and 9.4.1).

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment. The condition is documented in the patient's medical history
- 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 678354 or placebo) errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event was accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of Study Drug (ISIS 678354 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

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

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

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

Female patients: If a suspected pregnancy occurs while on the study (including during the follow-up period), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient will be encouraged to complete the Post-treatment Follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the Investigator will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks

after birth. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth.** Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

The sections below indicate the overall structure and approach to the analysis of this study. A detailed Statistical Analysis Plan (SAP) incorporating these sections below will be prepared separately. The SAP will outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis.

The study objectives are listed in Section 1.

10.1 Study Endpoints, Subsets, and Covariates

Efficacy and safety endpoints that will be evaluated after the last patient has completed the primary analysis time point are identified in the following sections.

The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A and B) and at Week 27 for patients who received weekly or biweekly dosing (Cohorts C and D). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy and safety analyses will be repeated at the completion of Study Drug treatment.

10.1.1 Primary Endpoint(s)

The primary efficacy analysis for the primary endpoint will be the pairwise comparison of percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354 treated groups and pooled placebo group in the FAS.

The data will be analyzed using an ANCOVA model with the baseline TG level as a covariate.

10.1.2 Secondary Endpoints

The secondary endpoints comprise the effect of ISIS 678354 as compared to placebo at the primary analysis time point on the following:

- Percent change from Baseline in apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I
- Proportion of patients who achieve serum TG ≤ 150 mg/dL (≤ 1.7 mmol/L)
- Proportion of patients achieving TG ≤ 100 mg/dL (≤ 1.13 mmol/L)

10.1.3 Safety Endpoints

The safety analysis will be performed using the following parameters:

- AEs
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Proportion of patients with platelet drop by severity, including platelet drop below lower limit of normal (LLN), platelet drop greater than 30% from Baseline, or any platelet drop meeting stopping rules.
- Proportion of patients with liver adverse events by severity, number of patients meeting liver stopping rules, and change in liver function tests by severity.
- Proportion of patients with renal adverse events by severity, number of patients meeting renal stopping rules, and change in renal function tests by severity.
- ECGs (including serial ECGs in a subgroup of patients undergoing serial PK sampling)
- Use of concomitant medications

10.1.4 Dose Selection

Dose selection for the further development will be based on the following efficacy and safety considerations; more than 1 dose may meet these criteria. An effective dose, or dose regimen, will be one that achieves a clinically-meaningful reduction in serum TG levels. Safety will be evaluated on the basis of incidence of expected and unexpected treatment-related SAEs, and other specific safety considerations including the incidence of platelet reductions.

[redacted]

10.3 Analysis Populations

Full Analysis Set (FAS): All patients who are randomized, received at least 1 dose of Study Drug (ISIS 678354 or placebo), and have a Baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. This population will be used for the primary analysis of efficacy.

Per Protocol Set (PPS): Subset of the FAS who received within 6 months at least 5 monthly doses of Study Drug for patients randomized in Cohorts A and B, or at least 11 every 2-week doses for patients randomized in Cohort C, or at least 22 weekly doses for patients randomized in Cohort D, and who have no major protocol violations that could compromise the interpretation of efficacy. Major violations will be determined prior to unblinding for statistical analysis. This population will be used for supportive inferences concerning efficacy.

Safety Set: All patients who are randomized and receive at least 1 dose of Study Drug. This population will be used for all safety analyses.

PK Population: All patients who are randomized and received at least 1 dose of ISIS 678354, and have at least 1 evaluable concentration result post first dose. This population will be used for analysis of PK data.

10.4 Definition of Baseline

Baseline for TG, apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, apoA-I and other lipid measurements will be defined as the average of the pre-dose measurement on Day 1 and the last measurement closest to Day 1, prior to administration of Study Drug. The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

No interim efficacy analysis will be performed.

10.6 Planned Methods of Analysis

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections. Hypothesis testing will be used for the primary efficacy endpoint and select secondary efficacy endpoints.

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

10.6.1 Demographic and Baseline Characteristics

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

10.6.2 Safety Analysis

10.6.2.1 Adverse Events

Treatment duration and amount of Study Drug (ISIS 678354 or placebo) received will be summarized by treatment group. Patient incidence rates of all AEs will be tabulated by MedDRA system organ class, and by MedDRA preferred term. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug (ISIS 678354 or placebo) will be summarized.

10.6.2.2 Clinical Laboratory Data

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) 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 678354 or placebo) administration, as appropriate. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

10.6.2.3 Vital Signs and Examinations

Vital sign and ECG measures will be tabulated by treatment group.

10.6.3 Efficacy Analysis

10.6.3.1 Analysis of Primary Efficacy Endpoint

The primary efficacy analysis for the primary endpoint will be the pairwise comparison of percent change from Baseline to the primary analysis time point in fasting TG between ISIS 678354 treated groups and pooled placebo group in the FAS. The data will be analyzed using an ANCOVA model with the baseline TG level as a covariate. Missing data may be handled by LOCF or multiple imputation methods (Schafer 1997, Schafer 1999).

The primary efficacy analysis will take place after the last patient has completed the primary analysis time point, and the database has been locked,

The following sensitivity analyses will be conducted:

- The primary analysis will be repeated in the PPS
- The primary efficacy endpoint will be analyzed using a Wilcoxon Rank Sum test on both FAS and PPS, and the treatment effect will be estimated using Hodges-Lehmann estimator

Additional sensitivity analyses may be conducted as appropriate; the details of these analyses will be outlined in the SAP.

10.6.3.2 Analysis of Secondary Efficacy Endpoints

- Percent change from Baseline at the primary analysis time point in fasting apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I will be compared between each ISIS 678354 treatment group and pooled placebo group using an ANCOVA model with baseline as covariate
- Proportion of patients who achieve fasting TG ≤ 150 mg/dL (≤ 1.7 mmol/L) at the primary analysis time point will be compared between each ISIS 678354 treatment group and pooled placebo group using a logistic regression model with Baseline TG as a covariate. Proportion of patients who achieve fasting TG ≤ 100 mg/dL (≤ 1.13 mmol/L) at the primary analysis time point will be analyzed similarly

All analyses of secondary endpoints will be performed on the FAS as primary and PPS as supportive.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

For all patients, trough and post-treatment concentrations of ISIS 678354 in plasma (as total full length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 678354) will be determined and summarized by treatment with and without stratification by subject immunogenicity (IM) status using descriptive statistics. In addition, plasma terminal elimination half-life of ISIS 678354 will be calculated using the post-treatment follow-up data if data permits.

Additionally, for patients in the PK subgroup only, PK parameters will be calculated using non-compartmental methods. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) values will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve (AUC) values after the first dose and steady-state dose will be calculated using the trapezoidal rule. Other PK parameters may be calculated at the discretion of the PK scientist. Plasma PK parameters will be summarized using descriptive statistics with and without stratification by subject IM status.

Exposure-response relationships between selected PD [e.g., TG] and PK measures (e.g., plasma trough concentrations) may be explored (including with and without stratification by IM status) in this study, or in a separate population PK analysis combined with other clinical studies.

The immunogenicity (IM) of ISIS 678354 will be assessed before, during, and after treatment with Study Drug (ISIS 678354 or placebo). The IM incidence (number) and incidence rate (percent) will be summarized at each evaluated study time point and at the patient level by treatment and dose, as the total number of and percent of evaluated patients with antibody negative, positive, and unknown status. Study patients with positive anti-ISIS 678354 antibody status may be further classified (when applicable) as being either ‘persistent’, ‘transient’, or not determinable. Potential relationships of immunogenicity with selected efficacy, safety, and PK measures may be evaluated.

Additional details regarding the PK and immunogenicity analysis will be described in the SAP.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative 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 678354 or placebo) are administered.

Importantly, patients should be informed of the possibility and risks of a reduction in platelet count and other potential risks, in particular hepatic and renal risks, and the importance of strict adherence to the monitoring program. The patient or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient or a legally acceptable representative 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 patient or legally acceptable representative.

The sponsor shall maintain all records referred to in the applicable Regulations for a period of 25 years.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2013 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

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

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The

Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study in accordance with local procedures.

11.4 Patient Confidentiality

The Investigator and Sponsor must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed 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 IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or ET. An Investigator who terminates participate is required to send a copy of the IEC/IRB notification to the Sponsor or designee.

12.3 Study Documentation and Storage

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, 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

Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, 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 for the duration required by GCP or local regulatory requirements, whichever is longer.

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

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 patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the case report forms. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the 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 patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the

clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content in accordance with the general investigational plan.

12.5 Language

Case report forms must be completed in English. Whenever possible, the trade name rather than the generic name for concomitant medications should be recorded and if possible, in English. Generic names are acceptable if the trade name is unknown. Combination medications should be recorded using their trade name in English if possible.

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

Schedule of Procedures for Weekly and Every 2-Week Dosing Cohorts

Schedule of Procedures for Every 4-Week Dosing Cohorts

Appendix A Schedule of Procedures – Weekly and Every 2-Week Dosing

	Screening		Treatment Period																		Follow-up Period		
	Run-in#	Qual*																					
Study Week	-4 to -2	-2 to -1	1	1	5	9	13	17	21	25			26	27[q]	29	33	37	41	45	49	53/ ET	4**	8**	13**
Study Day	-28 to -15	-14 to -7	1	2[a]	29	57	85	113	141	169	170[a]	171[a]	176[a]	183	197	225	253	281	309	337	365	**Weeks from the end of treatment period[p]		
Visit and Testing Window +/- Days	0	0	-3[b]	0	2	2	2	3	3	3	0	0		3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X																							
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X	X																					
Medical History [c]	X																							
Vital Signs	X	X	X		X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X		X		X		X					X		X		X		X	X	X	X	X
Body Weight and Height [d]	X	X												X				X						X
12- lead ECG (triplicate)	X		X[1]	X[2]	X		X		X	X[1]	X[2]	X	X	X		X		X		X	X	X	X	X
Extended Urinalysis [e]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X	X				X	X	X	X	X	X	X	X	X	X	X
Renal Biomarkers [g]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X	X				X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine and Cys-C [i, j]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X	X				X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel [j,k]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X	X				X	X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	X	HEMATOLOGY PERFORMED EVERY 14 DAYS (+/- 2 days) [f, k]																			X[h]	X[h]	X[h]
Coagulation	X		X											X										

Appendix A Schedule of Procedures – Weekly and Every 2-Week Dosing *Continued*

	Screening		Treatment Period																			Follow-up Period		
	Run-in#	Qual *																						
Study Week	-4 to -2	-2 to -1	1	1	5	9	13	17	21	25			26	27[q]	29	33	37	41	45	49	53/ ET	4**	8**	13**
Study Day	-28 to -15	-14 to -7	1	2[a]	29	57	85	113	141	169	170[a]	171[a]	176[a]	183	197	225	253	281	309	337	365	**Weeks from the end of treatment period[p]		
Visit and Testing Window +/- Days	0	0	-3[b]	0	2	2	2	3	3	3	0	0		3	3	3	3	3	3	3	3	3	3	3
Hepatitis B, C, HIV	X																							
HbA1c, HOMA-IR, Fructosamine, Glycated Albumin	X		X				X							X							X			X
Thyroid Panel	X																							
hsCRP			X											X							X			X
Plasma PK - ISIS 678354 [l]			X[1]	X[2]	X	X	X	X	X	X[1]	X[2]	X[3]	X	X[4]	X		X				X	X	X	X
ISIS 678354 Antibodies			X		X	X	X							X							X			X
FSH (women only, if applicable) [j, m]	X																							
Serum Pregnancy Test [m]	X	X	X		X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
Archived Serum & Plasma Samples [j, n]			X			X		X						X			X		X		X	X	X	X
Lipid Panel [j]	X	X	X		X	X	X	X	X					X	X		X		X		X	X	X	X
Study Drug: SC Injection			WEEKLY AND EVERY 2-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 52/Day 358 for Weekly Cohort; Week 1 through Week 51/Day 351 for Every 2-Week Cohort)[o]																					
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Qual = Qualification
Patients on stable diet known to the investigator and followed at the site may go from Screening to qualification without the diet run-in period.

Appendix A Schedule of Procedures – Weekly and Every 2-Week Dosing *Continued*

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

a Visit only required for patients in PK subgroup.

b Day 1/Baseline assessments can be performed up to 3 days (-3 days) prior to the actual Day 1 visit, which is the day of first Study Drug dose.

c Patient charts will be reviewed in order to collect disease associated medical history data such as CVD history.

d Height only required at Screening.

e All tests listed in Appendix B under Extended Urinalysis should be performed, including routine urinalysis, urine microscopy, UACR and UPCR.

f Assessments and procedures to be conducted by either a home healthcare service or the Study Center. Patient Study Center visits must be no more than 4 weeks apart during the treatment period.

g Urine samples for renal biomarkers will be collected. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function.

h During follow-up period, hematology sampling for platelet values are taken every 14 days for 6 weeks after treatment period, then at the Week 8 and Week 13 Follow-up visits.

i Serum Creatinine and Cys-C will be collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone samples at time points when a chemistry panel is not performed.

j Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours, unless tests are repeated for safety reasons.

k 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). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

l Refer to Appendix C for PK Sampling schedule.

m Women who are not surgically sterile or post-menopausal.

n Serum and plasma samples will be collected and stored 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.) and will be retained until completion of the final study report.

o Patients will continue treatment in the study for 12 months, or until the last patient reaches 6 months of exposure. When this milestone is met, all patients still on treatment will have an End of Treatment visit, then enter a 13-week post-treatment follow-up period.

p End of treatment period is defined as one dosing interval post last dose.

q The last patient to reach 6 months of exposure will also be the last patient to complete the End of Treatment (EOT) visit. Therefore, the Week 27 visit will count as the EOT visit for all patient whose EOT visit would have been scheduled to occur later than the EOT visit for the last patient to reach 6 months of exposure. No dose will be administered at this visit.

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

1 Pre-dose for all patients and pre-dose 1, 2, 4, 8 hours post SC injection for patients on PK subgroup only

2 24-hr from previous dose of Study Drug for patients on PK subgroup only

3 48-hr from previous dose of Study Drug for patients on PK subgroup only

4 Pre-dose for Cohort C (every 2-week dosing) patients on PK subgroup only

Appendix A Schedule of Procedures – Every 4-Week Dosing

	Screening		Treatment Period																		Follow-up Period		
	Run-in#	Qual*																					
Study Week	-4 to -2	-2 to -1	1	1	5	9	13	17	21			22	23	25[q]	29	33	37	41	45	49	53/ ET	4**	8**	13**
Study Day	-28 to -15	-14 to -7	1	2[a]	29	57	85	113	141	142[a]	143[a]	148[a]	155[a]	169	197	225	253	281	309	337	365	**Weeks from the end of treatment period[p]		
Visit and Testing Window +/- Days	0	0	-3[b]	0	2	2	2	3	3	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3
Informed Consent	X																							
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X	X																					
Medical History [c]	X																							
Vital Signs	X	X	X		X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X		X		X		X					X		X		X		X	X	X	X	X
Body Weight and Height [d]	X	X												X				X						X
12- lead ECG (triplicate)	X		X[1]	X[2]	X		X		X[1]	X[2]	X	X	X	X		X		X		X	X	X	X	X
Extended Urinalysis [e]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X					X	X	X	X	X	X	X	X	X	X	X
Renal Biomarkers [g]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X					X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine and Cys-C [i, j]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X					X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel [j, k]	X		EVERY 14 DAYS (+/- 2 days) [f]					X	X					X	X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	X	HEMATOLOGY PERFORMED EVERY 14 DAYS (+/- 2 days) [f, k]																			X[h]	X[h]	X[h]
Coagulation	X		X											X										

Appendix A Schedule of Procedures – Every 4-Week Dosing *Continued*

	Screening		Treatment Period																			Follow-up Period		
	Run-in#	Qual*																						
Study Week	-4 to -2	-2 to -1	1	1	5	9	13	17	21			22	23	25[q]	29	33	37	41	45	49	53/ET	4**	8**	13**
Study Day	-28 to -15	-14 to -7	1	2[a]	29	57	85	113	141	142[a]	143[a]	148[a]	155[a]	169	197	225	253	281	309	337	365	**Weeks from the end of treatment period[p]		
Visit and Testing Window +/- Days	0	0	-3[b]	0	2	2	2	3	3	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3
Hepatitis B, C, HIV	X																							
HbA1c, HOMA-IR, Fructosamine, Glycated Albumin	X		X				X							X							X			X
Thyroid Panel	X																							
hsCRP			X											X							X			X
Plasma PK - ISIS 678354 [l]			X[1]	X[2]	X	X	X	X	X[1]	X[2]	X[3]	X	X	X	X		X				X	X	X	X
ISIS 678354 Antibodies			X		X	X	X							X							X			X
FSH (women only, if applicable) [j, m]	X																							
Serum Pregnancy Test [m]	X	X	X		X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X
Archived Serum & Plasma Samples [j, n]			X			X		X						X	X		X		X		X	X	X	X
Lipid Panel [j]	X	X	X		X	X	X	X	X					X	X		X		X		X	X	X	X
Study Drug: SC Injection			EVERY 4-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 49/Day 337)[o]																					
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Qual = Qualification
# Patients on stable diet known to the investigator and followed at the site may go from Screening to qualification without the diet run-in period.

Appendix A Schedule of Procedures – Every 4-Week Dosing *Continued*

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

a Visit only required for patients in PK subgroup.

b Day 1/Baseline assessments can be performed up to 3 days (-3 days) prior to the actual Day 1 visit, which is the day of first Study Drug dose.

c Patient charts will be reviewed in order to collect disease associated medical history data such as CVD history.

d Height only required at Screening.

e All tests listed in Appendix B under Extended Urinalysis should be performed, including routine urinalysis, urine microscopy, UACR and UPCR.

f Assessments and procedures to be conducted by either a home healthcare service or the Study Center. Patient Study Center visits must be no more than 4 weeks apart during the treatment period.

g Urine samples for renal biomarkers will be collected. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function

h During follow-up period, hematology sampling for platelet values are taken every 14 days for 6 weeks post treatment period and then at the Week 8 and 13 Follow-up visits.

i Serum Creatinine and Cys-C will be collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone samples at time points when a chemistry panel is not performed.

j Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours, unless tests are repeated for safety reasons.

k 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). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

l Refer to Appendix C for PK Sampling schedule.

m Women who are not surgically sterile or post-menopausal.

n Serum and plasma samples will be collected and stored 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.) and will be retained until completion of the final study report.

o Patients will continue treatment in the study for 12 months, or until the last patient reaches 6 months of exposure. When this milestone is met, all patients still on treatment will have an End of Treatment visit, then enter a 13-week post-treatment follow-up period.

p End of treatment period is defined as one dosing interval post last dose.

q The last patient to reach 6 months of exposure will also be the last patient to complete the End of Treatment (EOT) visit. Therefore, the Week 25 visit will count as the EOT visit for all patient whose EOT visit would have been scheduled to occur later than the EOT visit for the last patient to reach 6 months of exposure. No dose will be administered at this visit.

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

1 Pre-dose for all patients and pre-dose 1, 2, 4, 8 hours post SC injection for patients on PK subgroup only

2 24-hr from previous dose of Study Drug for patients on PK subgroup only

3 48-hr from previous dose of Study Drug for patients on PK subgroup only

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 678354 or other similar oligonucleotides.

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

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)
- TSH
- Free T4
- HbA1c

Coagulation
- aPTT
- PT
- INR

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL
- ApoC-III
- Non-HDL-C
- ApoA-1
- Lp(a)
- ANGPTL3

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

Pharmacokinetics[1]
- ISIS 678354 (total full length ASO) levels in plasma

Immunogenicity
- Anti-ISIS 678354 antibodies

Other assessments
- HbA1c
- HOMA-IR
- Fructosamine
- Glycated albumin

Inflammatory
- hs-CRP

Extended Urinalysis
- Routine Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Blood
  - Glucose
  - Ketones
  - Bilirubin
  - Urobilinogen
  - Leukocyte esterase
  - Nitrate
- Microscopic examination
- P/C Ratio (UPCR)
- A/C Ratio (UACR)

Renal Urine Biomarkers[2]
- NGAL
- NAG
- KIM-1
- Cys-C

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 678354 with plasma constituents

2 All samples will be collected, handled and stored under the conditions specified for the assays. Please refer to the study Laboratory Manual for details on the appropriate handling and storage methods for biomarker and other samples.

Appendix C PK Sampling Schedule

Sampling Schedule for Weekly and Every 2-Week Dosing Cohorts

Sampling Schedule for Every 4-Week Dosing Cohorts

Appendix C PK Sampling Schedule

Blood samples for the determination of plasma ISIS 678354 concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below. Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation), or to assess other actions of ISIS 678354 with plasma constituents. Extensive PK samples will be collected in PK subgroup only (approximately 10 patients per cohort) (see tables below):

Sampling Schedule for Weekly and Every 2-Week Dosing Cohorts

	Treatment Period														Follow-up Period		
Study Week	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**37**	**53/ET**	**4***	**8***	**13***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**170**	**171**	**176**	**183**	**197**	**253**	**365**	***Weeks from the end of treatment period[4]**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime
PK Sub-group for Weekly Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	48-hr[3]	Pre-dose	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime
PK Sub-group for Every 2-Week Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	48-hr[3]	Any-time	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime

1 8-hr from previous dose of Study Drug. Window of (-) 2 hrs
2 24-hr from previous dose of Study Drug. Window of (+/-) 4 hours
3 48-hr from previous dose of Study Drug. Window of (+/-) 6 hours
4 End of treatment period is defined as one dosing interval post last dose

Appendix C PK Sampling Schedule *Continued*

Sampling Schedule for Every 4-Week Dosing Cohorts

	Treatment Period														Follow-up Period		
Study Week	**1**	**1**	**5**	**9**	**13**	**17**	**21**			**22**	**23**	**25**	**29**	**37**	**53/ET**	**4***	**8***	**13***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**142**	**143**	**148**	**155**	**169**	**197**	**253**	**365**	***Weeks from the end of treatment period[4]**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	NA	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime
PK Sub-group only	Pre-dose, 1, 2, 4, and 8-hr[1]	24-hr[2]	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 1, 2, 4, and 8-hr[1]	24-hr[2]	48-hr[3]	Anytime	Anytime	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime

1 8-hr from previous dose of Study Drug. Window of (-) 2 hours allowed
2 24-hr from previous dose of Study Drug. Window of (+/-) 4 hours allowed
3 48-hr from previous dose of Study Drug. Window of (+/-) 6 hours allowed
4 End of treatment period is defined as one dosing interval post last dose

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥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 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<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	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
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 Adverse Events 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	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
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 >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>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	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) 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	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; 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	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

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

Appendix E Additional Laboratory Tests for Patients with Platelet Count < 100,000/mm^3

Appendix E Laboratory Tests to Be Performed in the Event of a Platelet Count < 100,000/mm3

*Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.

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

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
Folate (folic acid)
Vitamin B12
Fibrinogen
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
von Willebrand factor (vWF) Antigen
Helicobacter pylori
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
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

Official Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

NCT Number: NCT03385239

Document Date: SAP Version 1: 17 December 2019

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Statistical Analysis Plan

ISIS 678354–CS2

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

Date: December 17, 2019

Final Version: 1.0

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Akcea Therapeutics, Inc.

22 Boston Wharf Road, 9th Floor, Boston, MA 02210

Compound Name: ISIS 678354 (AKCEA-APOCIII-L_{Rx})

Protocol: ISIS 678354–CS2

Study Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 678354 Administered Subcutaneously to Patients with Hypertriglyceridemia and Established Cardiovascular Disease (CVD) or at High Risk for CVD

Protocol Issue Date: Amendment 3 – June 12, 2019

Signature: _____ Date: _____

MS

Akcea Therapeutics, Inc.

Signature: _____ Date: _____

MD, PhD

Akcea Therapeutics, Inc.

Signature: _____ Date: _____

Ph.D

Akcea Therapeutics, Inc.

PAREXEL SIGNATURE PAGE

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

	Signatory
Author	[redacted] Project Role: [redacted]

Table of Contents

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	17Dec2019	New document

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANGPTL3	Angiopoietin-Like 3
apoA-I	Apolipoprotein A-I
apoB	Apolipoprotein B
apoC-III	Apolipoprotein C-III
aPTT	Activated Partial Thromboplastin Time
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
CVD	Cardiovascular Disease
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Agency
FLR	Flu-Like Reaction
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HbA1c	Glycated Hemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hsCRP	C-Reactive Protein Measured by High Sensitivity Assay
ICH	International Council on Harmonisation
INR	International Normalized Ratio
ISR	Injection Site Reaction
LCRIS	Local Cutaneous Reactions at Injection Site
LDL-C	Low-Density Lipoprotein Cholesterol
LLN	Lower Limit of Normal
Lp(a)	Lipoprotein(a)

LSM	Least Squares Mean
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MRL	Medpace Reference Laboratories
OTC	Over-The-Counter
PAT	Primary Analysis Time Point
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Set
TC	Total Cholesterol
TEAE	Treatment-Emergent Adverse Events
TSH	Thyroid Stimulating Hormone
UACR	Urine Albumin/Creatinine Ratio
UAT	User Acceptance Testing
ULN	Upper Limit of Normality
ULQ	Upper Limit of Quantification
UPCR	Urine Protein/Creatinine Ratio
VLDL-C	Very Low-Density Lipoprotein Cholesterol
WBC	White Blood Cells
WHODD	World Health Organization Drug Dictionary
βhCG	Serum Beta-Subunit of Human Chorionic Gonadotropin

1 INTRODUCTION

Hypertriglyceridemia is associated with increased risk of first or secondary cardiovascular (CV) events even in patients with well controlled LDL-C levels. Elevated triglyceride levels are thought to play an important role in development of atherosclerosis and subsequently CV disease (CVD) due to accumulation of triglyceride-rich lipoproteins (TRL) and their remnant cholesterol in the arterial wall (Nordestgaard and Varbo, 2014).

Apolipoprotein C-III (apoC-III), a 79 amino acid glycoprotein synthesized principally in the liver, is a key regulator of plasma triglyceride-rich lipoprotein (TRL) metabolism. ApoC-III determines serum triglyceride levels by two main mechanisms, by inhibiting lipoprotein lipase (LPL) activity as well as by directly inhibiting hepatic uptake of TRL, thus leading to increased levels of chylomicrons and TRLs (Norata et al. 2015). Genome wide significance studies have shown that individuals with loss of function mutations in *APOC3* gene exhibited reduced serum triglyceride levels, reduced coronary heart disease, and increased longevity, thus providing the evidence for *APOC3* gene as a target for CVD risk reduction (Jorgensen et al. 2014).

AKCEA-APOCIII-L_{Rx} (ISIS 678354) is a second-generation antisense oligonucleotide (ASO) drug targeted to apoC-III that has been covalently bonded to triantennary N-acetyl galactosamine ($GalNAc_3$), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor to form an ASO-$GalNAc_3$ conjugate. This $GalNAc_3$-conjugate approach results in enhanced ASO delivery to hepatocytes vs. non-parenchymal cells, therefore increases ASO potency and allows to achieve a therapeutic benefit at a lower dose (Crooke et al. 2019). In the Phase 1 study in subjects with hypertriglyceridemia treatment with AKCEA-APOCIII-L_{Rx} significantly decreased plasma apoC-III protein levels and triglyceride levels by over 90% and over 70%, respectively at the highest dose used.

Therefore, the present study was designed to evaluate this new approach to lowering triglycerides by reducing apoC-III levels, specifically in high-risk patients, those with established CVD or at high risk for CVD, whose LDL-C levels are controlled by standard therapeutic strategies but whose elevated triglyceride levels place them at continued risk of CV events.

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Akcea Therapeutics, Inc. study with Protocol Number ISIS 678354-CS2. The analyses described in this statistical analysis plan (SAP) are based upon the following study documents:

- Study Protocol, Amendment 3 (June 12, 2019)
- electronic Case Report Form (eCRF), Version 6.0 (March 06, 2019)

Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; and, Section 3 provides the detailed plan for the statistical analyses. Any deviations from the final version of this Statistical Analysis Plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

1.1 Study Overview

The study ISIS 678354-CS2 is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-ranging study being conducted at approximately 32 sites in the United States and Canada.

Patients ≥ 18 and ≤ 80 years old with elevated plasma triglyceride levels (≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥ 5.7 mmol/L)) and a clinical diagnosis of established CVD, or at high risk for CVD (as defined in the study protocol), will be eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for known CVD risk factors as per current guidelines. The study is comprised of the following periods:

- **Screening:** An up to 4 week Screening Period, including an up to 2-week qualification period following an at least 2-week diet stabilization period, where appropriate. Patients on a stable diet known to the investigator and clinically followed at the site may go from Screening to the qualification visit without a 2-week diet stabilization phase.

- **Treatment Period:** Following qualification, up to approximately 100 eligible patients will be randomized in a 1:1:1:1 ratio to one of the 4 dosing cohorts as shown in Table 1, with each cohort having a 4:1 ratio to receive ISIS 678354 or matching volume of placebo, respectively, by SC injection.

Table 1: Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 678354
A	10 mg ISIS 678354 or placebo (Every 4 weeks)	0.10 mL	≤ 13	≤ 130 mg
B	50 mg ISIS 678354 or placebo (Every 4 weeks)	0.50 mL	≤ 13	≤ 650 mg
C	15 mg ISIS 678354 or placebo (Every 2 weeks)	0.15 mL	≤ 26	≤ 390 mg
D	10 mg ISIS 678354 or placebo (Every week)	0.10 mL	≤ 52	≤ 520 mg

The minimum treatment duration for all patients is 6 months and the maximum is 12 months. The treatment portion of the study will be complete when the last patient reaches 6 months of exposure, at which time patients still receiving Study Drug (ISIS 678354 or placebo) will transition to the Post-Treatment Follow-up Period.

The End of Treatment (EoT) visit for all patients should be scheduled no later than the EoT visit of the last patient to reach 6 months of exposure. The EoT visit should be scheduled to occur at one dosing interval post last dose of Study Drug: one week post last dose for weekly treatment (Cohort D), 2 weeks post last dose for every 2-week treatment (Cohort C), and 4 weeks post last dose for every 4-week treatment (Cohorts A-B). For any patient whose EoT visit would occur later than the EoT visit for the last patient to reach 6 months of exposure, the primary endpoint visit (Week 25 or Week 27 depending on Cohort) will count as the EoT visit.

- **Post-Treatment Follow-up Period:** After the EoT visit has been completed, patients will enter the 13-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits at 4, 8, and 13 weeks post EoT visit.

1.2 Objectives

1.2.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 678354 and to assess the efficacy of different doses and dosing regimens of ISIS 678354 for reduction of serum triglyceride levels in patients with hypertriglyceridemia and established CVD or at a high risk for CVD.

1.2.2 Secondary Objectives

To evaluate the efficacy of ISIS 678354 on serum levels of apolipoprotein C-3 (apoC-III), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein B100 (apoB) and apolipoprotein A-1 (apoA-I).

To evaluate pharmacokinetics (PK) of ISIS 678354 across different doses and dose regimens in patients with hypertriglyceridemia and established CVD or at a high risk for CVD.

1.2.3 Exploratory Objectives

To evaluate the efficacy of ISIS 678354 on serum levels of lipoprotein(a) [Lp(a)], remnant cholesterol, and angiopoietin-like 3 (ANGPTL3).

1.3 Hypotheses

The study hypothesis is that ISIS 678354 can significantly reduce the serum triglyceride levels and is well-tolerated for patients with established CVD or at a high risk for CVD.

1.4 Endpoints

The primary analysis time point (PAT) is at Week 25 for patients who received every 4-week dosing (Cohorts A and B) and at Week 27 for patients who received weekly or biweekly dosing (Cohorts C

and D). For patients continuing treatment beyond the PAT additional supportive efficacy and safety analyses will be repeated at the completion of Study Drug treatment. A final analysis will be conducted after all patients have completed their post-treatment follow-up visits.

1.4.1 Primary Efficacy Endpoint

Percent change in fasting triglyceride level from Baseline to the PAT.

1.4.2 Secondary Efficacy Endpoints

The secondary endpoints are the following at the PAT:

- Percent change from Baseline in apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I
- Proportion of patients who achieve serum triglycerides ≤ 150 mg/dL (≤ 1.7 mmol/L)
- Proportion of patients who achieve triglycerides ≤ 100 mg/dL (≤ 1.13 mmol/L)

1.4.3 Exploratory Endpoints

Percent change in Lp(a), remnant cholesterol, and ANGPTL3 from Baseline to the PAT.

Remnant cholesterol will be calculated using the following formula:

Remnant cholesterol = TC – (LDL-C+HDL-C)

1.4.4 Safety Endpoints

The safety analysis will be performed using the following parameters:

- Adverse events (AEs)
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Proportion of patients with platelet drop by severity, including platelet drop below lower limit of normal (LLN), platelet drop greater than 30% from baseline, or any platelet drop meeting stopping rules.
- Proportion of patients with liver adverse events by severity, number of patients meeting liver stopping rules, and change in liver function tests by severity.
- Proportion of patients with renal adverse events by severity, number of patients meeting renal stopping rules, and change in renal function tests by severity.
- Electrocardiograms (ECGs) (including serial ECGs in a subgroup of patients undergoing serial PK sampling)
- Use of concomitant medications

2 PROCEDURES

The study for an individual patient will generally consist of the following periods (see also Section 1.1):

- A Screening Period (up to 4 weeks), including an up to 2-week qualification period following an at least 2-week diet stabilization phase, where appropriate
- A Treatment Period (up to 52 weeks) during which Study Drug will be administered per assigned cohort by SC injection
- A Post-treatment Follow-up Period (13 weeks)

2.1 General Overview of Procedures

2.1.1 Screening Period

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. An up to 4-week period is provided for completing screening assessments and determining patient eligibility for the study. Abnormal screening results may be re-tested once for determination of patient eligibility after consultation with the Sponsor Medical Monitor. Patients may be re-screened 1 time in order to determine eligibility. During the screening period, patients will undergo a medical history and physical examination including vital signs, 12-lead ECG and have blood and urine samples taken for clinical laboratory testing. Patients will be screened for Human Immunodeficiency Virus (HIV), hepatitis B, and hepatitis C.

2.1.2 Treatment Period

Patients will receive the Study Drug (ISIS 678354 or placebo) administered by SC injection as shown in Table 1. Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters, ISIS 678354 plasma concentrations, anti-drug antibody (ADA) and biomarker samples, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Protocol Appendix A. A list of laboratory analytes required for the study is contained in Protocol Appendix B. Protocol Appendix C details the PK sampling schedules. Within each cohort, a subgroup of approximately 10 patients, who will consent to extensive PK sampling, will undergo additional PK sampling, in what is referred to as the PK Subgroup in this study. Patients in this subgroup will have additional PK sampling time points, additional ECG assessments, and additional clinic visits during the treatment period according to the PK Sampling Schedule in Protocol Appendix C.

2.1.3 Post-Treatment Follow-Up Period

Following the end of the treatment period, patients will enter a 13-week Post-Treatment Follow-up Period and return to the Study Center for 3 outpatient visits outlined in the Schedule of Procedures in Protocol Appendix A and C.

2.2 Randomization and Treatment Allocation

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

Using an Interactive Web-Response System (IWRS), eligible patients will be randomized in a 1:1:1:1 ratio to 1 of the 4 parallel-dose cohorts (Cohorts A, B, C or D). Within each dose cohort, patients will be randomized in a 4:1 ratio to receive ISIS 678354 or matching volume of placebo, respectively.

A permuted block schedule will be used. The randomization schedule will be generated and held by an independent vendor. Patients who withdraw from the study will not be replaced. The study is planned to randomize approximately 100 patients.

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 Agency (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

In order to ensure maintenance of the study blind, the results of efficacy parameters consisting of lipid panel results including apoA-I, apoB, apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, triglycerides, ANGPTL3 and Lp(a) will be blinded to the Akcea study team, Clinical Research Organization (CRO) study team, Investigators, Study Center personnel and patients until after database lock for EoT. After Sponsor's unblinding post completion of treatment period, blinded study personnel will continue to oversee the study until all patients completed the study.

2.4.1 Safety Data Monitoring

Safety information will be collected, reviewed, and evaluated by Akcea (or designee) in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

In addition to the standard monitoring of clinical safety parameters, there are individual monitoring rules for the selected parameters related to renal, liver function, platelet count, bleeding events, constitutional symptoms, and glycemic control, described in the Protocol Section 8.5. The stopping rules and adjustment of dose are specified in protocol Sections 8.6 and 8.7

Akcea (or designee) is responsible for regulatory submissions and reporting to the Investigators of suspected unexpected serious adverse reactions (SUSARs) per ICH guidelines. Processing of serious adverse events (SAEs) is delegated to a third-party vendor although Akcea remains accountable for this activity and process. AEs and SAEs are reviewed according to standard operating procedures.

The Study Medical Monitor will review all AEs and SAEs on an ongoing basis throughout the study. Monitoring of AEs are outlined in the Protocol section 9.4

2.4.2 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 678354 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 678354, the DSMB will provide recommendations to Akcea for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter.

2.5 Data Management

2.5.1 Case Report Form (CRF) Data

Bioclinica® is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by the Sponsor (or designee).

Trennic Data Services, a data management vendor contracted by Akcea, is responsible for creating CRF Completion Guidelines (CCGs) and will oversee the development of the Electronic Data Capture (EDC) system by the EDC hosting vendor. Akcea (or designee) is responsible for the review, querying, and locking of the database.

2.5.2 Laboratory Data

Trennic Data Services is responsible for the format of the laboratory electronic data transfers and the transfer schedule. Akcea is responsible for the review of the clinical laboratory data. Central lab data managed by Medpace Reference Laboratories (MRL) are not stored in the EDC system but will be transferred to Trennic Data Services. Investigator sites have access to this data via lab reports sent directly from MRL.

2.5.3 Pharmacokinetics and Anti-drug Antibody Data

PPD and Charles River Laboratories are responsible for the production of PK and anti-drug antibody (ADA) data respectively. Akcea is responsible for the review of the data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK and ADA results are not stored in the EDC system but will be transferred to Akcea Therapeutics, Inc. or designee as external data.

2.5.4 Other Data

Almac manages and produces randomization code. The User Acceptance Testing (UAT) data will be delivered prior to the database lock for pre-programming. The actual data will be delivered after database lock. Data will not be stored in the EDC system, but will be transferred to Parexel as external data.

3 ANALYSIS PLANS

3.1 Statistical Design Summary

This is a multi-center, randomized, double blind, placebo-controlled study.

The study hypotheses will be formally evaluated at the planned EoT analysis on data obtained through the data cut-off date, defined as the date of the last EoT visit. The database will be queried, and data cleaning performed on all data, with database interim lock of all data, at which point the treatment code is unblinded and the EoT analysis is performed.

The primary analysis model will be an Analysis of Covariance (ANCOVA) model for percent change from baseline to the PAT in fasting triglycerides. Missing data will be imputed by a multiple imputation method as the primary analysis and will be supported by various sensitivity analyses.

The treatment groups proposed in this analysis are defined as follows:

- ISIS 678354 10 mg every 4 weeks (Q4W)
- ISIS 678354 50 mg every 4 weeks (Q4W)
- ISIS 678354 15 mg every 2 weeks (Q2W)
- ISIS 678354 10 mg every week (QW)
- Pooled Placebo, defined as the combined group of placebo patients from the 4 randomized cohorts

A final analysis will be performed after all data from the 13-week post treatment follow-up period are collected and locked.

3.2 General Overview of Analyses

This analysis plan describes the reporting of data at 1) all patients completed the primary analysis time point 2) all patients completed the study.

3.2.1 General Conventions

All reporting will be performed in SAS version 9.3 or higher.

All eCRF data and lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study, and will be sorted by treatment group, patient ID, visit, and time point (where appropriate).

3.2.2 Reporting Conventions

Efficacy results will be summarized under the treatment to which patients were randomized. Safety and PK results will be summarized under the treatment which patients actually received. Should there be any cases after unblinding in which a patient received treatment other than what the patient was

randomized to, such cases will be discussed in the study report and noted in footnotes where applicable.

All tables will present the population frequencies in each treatment group and/or subgroup (where appropriate) and will indicate the number of patients with non-missing data and the denominators for percentages.

Descriptive summary statistics including n, mean, median, standard error, standard deviation SD, interquartile range (25th percentile, 75th percentile), range (minimum, maximum), mean 95% confidence interval (CI) for continuous variables, and counts and percentages for categorical variables, will be used to summarize data by treatment group. Summaries of PK concentrations and parameters will also include coefficient of variation (CV%), geometric mean, and geometric CV%. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

Except summaries for PK parameters, precision for displays will use the following conventions. Means, percentiles (e.g., median, 25th and 75th percentile), least squares means, difference in least squares means will be displayed to one more decimal place than measured values. Standard deviations and standard errors will be displayed to two more decimal places than measured values. The minimum, maximum and confidence intervals will be displayed using the same number of decimal places as the recorded values. All raw values presented in listings will be displayed to the measured precision. Percentages will be displayed to one decimal place. For PK concentrations and parameters, mean, standard deviation, standard error, geometric mean, median, minimum, and maximum values will be presented to 3 significant digits and CV% and geometric CV% will be presented to one decimal place. p-value will be displayed to 4 decimal places. p-value less than 0.0001 will be presented as "<0.0001". p-value greater than 0.9999 will be displayed as ">0.9999". Confidence intervals will be presented using a comma separator rather than a dash.

Age will be presented in years. Weight will be presented in kg. Height will be presented in cm. Temperature will be presented in °C. Laboratory listings will be presented using original unit. Summary tables of lab results will be based on original unit. For multiple original units within the parameters, the results will be converted to the majority of units as reported. Lab shift tables and abnormalities tables will be based on mock shell displays.

The lab data will be reported using central lab and/or local lab depending on the type of outputs or values. Table 2 and Table 3 outline which data source, lab unit and visits should be used for the specific outputs and values.

Table 2: Summary of Lab Data Source per Type of outputs

	Type of Outputs	**Data source**	**Unit**	**Visits**

Listings	Listings of lab data	Central and local lab in separate listings	Original Unit	SCH + USCH visits
Tables, Figures	All efficacy endpoints (primary, secondary, exploratory)	Central lab	Original Unit	analysis SCH + USCH within visit window
	Descriptive summary of platelet count data	Central and local lab, separate tables and figures	Original Unit (cells/mm^3)	nominal SCH visits
	Descriptive summary safety lab data other than platelet counts	Central lab	Original Unit	nominal SCH visits
	Safety shift tables	Central and local lab	Per mock shells	nominal SCH + USCH visits
	Abnormalities lab tables	Central and local lab	Per mock shells	nominal SCH + USCH visits

SCH: scheduled; USCH: unscheduled

Table 3: Summary of Lab Data Source per Type of Values

Type of values	Data source	Unit	Visits
Baseline for platelet count	Central and local lab	Original Unit (cells/mm^3)	SCH + USCH visits prior to the first dose of Study Drug
Baseline for other safety labs	Central lab	Original Unit	nominal based on SCH + USCH visits; selected as last non missing prior to first dose of Study Drug
Confirmed lab value	Central and local lab	Per mock shells	nominal SCH + USCH visits

SCH: scheduled; USCH: unscheduled

Efficacy assessments (i.e. lipid panel) will be mapped to an analysis visit per the analysis visit windows as specified in Appendix A and summarized by analysis visit. The selection rule of analysis visits is specified in Appendix A as well.

Safety assessments will be summarized by nominal visit as collected in CRF. For summary tables by nominal visit, only scheduled visits will be used. For multiple records at the nominal (scheduled) visit, the average will be used for continuous values, or the worst will be used for categorical values.

For summary tables of platelet counts by nominal visit, scheduled visits from central lab data and separately, from local lab data will be used. For multiple records at the nominal (scheduled) visit, the average will be used for continuous values, or the worst will be used for categorical values.

3.2.2 Patient Population Analyzed

The following analysis sets will be used for the analysis of data as described within each analysis set.

Screened Patients are defined as the patients who sign an informed consent form.

Randomized Patients are defined as the patients who receive a randomization assignment.

Full Analysis Set (FAS): All patients who are randomized and received at least 1 dose of Study Drug (ISIS 678354 or placebo). The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in International Conference on Harmonisation (ICH) Guideline E9. This population will be used for the analysis of efficacy.

Per Protocol Set (PPS): Subset of the FAS who received prior to the Primary Analysis Timepoint at least 5 monthly doses of Study Drug for patients randomized in Cohorts A and B, or at least 11 every 2-week doses for patients randomized in Cohort C, or at least 22 weekly doses for patients randomized in Cohort D, and who have no major protocol deviations that could compromise the interpretation of efficacy. Major deviations will be determined prior to unblinding for statistical analysis. This population will be used for supportive inferences concerning efficacy.

Safety Set (SS): All patients who are randomized and received at least 1 dose of Study Drug. This population will be used for all safety analyses.

PK Population: All patients who are randomized and received at least 1 dose of ISIS 678354, and have at least 1 evaluable concentration result post first dose. This population will be used for analysis of PK data.

PK Subgroup: A subset of PK population who will undergo additional PK sampling after dose administration on Day 1 and Week 21 (Cohorts A and B) / Week 25 (Cohorts C and D) to evaluate the plasma PK parameters of ISIS 678354.

Patients in PK subgroup will also have additional ECGs conducted as indicated in Table 4.

Table 4: Additional PK Sampling and ECG Schedule for PK Subgroup

Cohort	Additional PK Sampling	Additional ECGs

Cohort A and B	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 21 (1, 2, 4, 8, 24, 48 hr post-dose), Week 22 (Anytime), Week 23 (Anytime)	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 21 (1, 2, 4, 8, 24 hr post-dose)
Cohort C	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 25 (1, 2, 4, 8, 24, 48 hr post-dose), Week 26 (Anytime), Week 27 (pre-dose)	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 25 (1, 2, 4, 8, 24 hr post-dose)
Cohort D	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 25 (1, 2, 4, 8, 24, 48 hr post-dose), Week 26 (pre-dose)	Week 1 (1, 2, 4, 8, 24 hr post-dose), Week 25 (1, 2, 4, 8, 24 hr post-dose)

PK-ECG Set: All patients who provide baseline ECG data and at least one post-baseline matched PK before onset of anti-drug antibody and ECG record. This population will be used to analyze the exposure-QTcF relationship. Patients determined to have a pacemaker rhythm will be excluded from the PK-ECG Set.

All primary and secondary efficacy endpoints will be assessed in the FAS and PPS, with the former being the basis for the primary efficacy analysis. All exploratory efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the SS. PK endpoints will be assessed in the PK Population and PK Subgroup as applicable.

Patients in randomization populations, FAS and PPS will be analyzed in the treatment group to which they were randomized. Patients in SS, PK Population, PK Subgroup, and PK-ECG Set will be analyzed in the group with actual treatment they received.

[redacted]

[redacted]

3.2.4 Baseline and Endpoint Definition

For platelet count data, central and local lab will be used in baseline derivation. For other lab data, only central lab will be used in baseline derivation.

Baseline for lipid panel is defined as the average of Day 1 fasting pre-dose assessment and the last non-missing fasting measurement prior to Day 1 pre-dose assessment. If 1 of the 2 measurements is missing, then the other measurement will be assigned as the baseline value. If both are missing, then the baseline will be set as missing. Note that if on Day 1, there are multiple pre-dose assessments, then the last assessment with non-missing value will be used as the Day 1 pre-dose assessment.

Baseline for platelet is defined as the average of all assessments prior to the first dose of Study Drug.

Baseline for ECG is the average of the triplicate taken on Day 1 pre-dose for ECG summary over time and abnormal ECG parameters tables. If only one or two assessments are available, the single assessment or average of the two assessments will be used. If ECG results on Day 1 pre-dose is missing, results at screening visit will be used as baseline.

Baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug.

3.2.5 Patient Characteristics

Disposition and Analysis Population

The number of patients screened, randomized, dosed, number of patients included in each analysis set, the number of patients who completed treatment, discontinued treatment along with reasons for discontinuing treatment, entered post-treatment follow-up, completed post-treatment follow-up, and discontinued post-treatment follow-up, along with reasons for early terminating post-treatment follow-up, will be presented in screened patients by treatment group to which they were randomized, and overall.

Listings of patient disposition will also be provided for all randomized patients.

Protocol Deviation

Major protocol deviations will be summarized by deviation category for randomized patients. Reasons for excluding patients from PPS will be summarized for randomized patients. All protocol deviations (major and minor) will be provided in a data listing for randomized patients.

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall in FAS, including age, sex, race, ethnicity. Baseline characteristics include number of patients with established CVD vs. high risk for CVD, weight, height, body mass index (BMI), triglycerides, apoA-I, apoB, apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, ANGPTL3, remnant cholesterol, and Lp(a).

Medical History

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 20.1 and will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall for the FAS. Medical history will also be provided in a data listing.

Cardiovascular history will be tabulated by ISIS 678354 treatment group and pooled placebo group. A by-patient data listing will also be provided.

Prior/Concomitant Medications

All medications will be coded by World Health Organization Drug Dictionary (WHODD) Version DEC2017. The start and stop dates of medications that are recorded on the Concomitant Medications CRF will be used to determine whether the medications are prior or concomitant to the treatment period. Missing or partial dates will be imputed as outlined in Section 3.7.1. Prior medications include medications that started prior to the first dose of Study Drug from the time the patient has signed the informed consent, regardless whether continued while on treatment or not. A concomitant medication is any drug or substance (including over-the-counter (OTC) medications, herbal medications and vitamin supplements) administered between first administration of study drug and the end of the post-treatment follow-up period. A prior medication with an imputed stop date that is missing or on or after date of first dose of Study Drug will also be considered as a concomitant medication. Medications will be classified based on imputed start and imputed stop dates as follows:

1) Prior Medication

Start Date	**End Date**
< FDD	≥ Inform Consent Date
	Missing

FDD = Date of First Dose of Study Drug

2) Concomitant Medication

Start Date	**End Date**
< FDD	≥ FDD
	Missing
≥ FDD	Any non-missing stop date
	Missing

FDD = Date of First Dose of Study Drug

Prior or concomitant medications will be summarized separately for all Safety Set by Anatomical Therapeutic Chemical (ATC) class, Preferred Term, treatment group and overall with counts and percentages, sorting by decreasing frequency of all patients. The concomitant medications in on-treatment and on-study period will be summarized respectively.

Prior or concomitant medications will be displayed in patient listings for all Randomized Patients. A listing of ancillary procedures will also be provided. Note that imputed dates will be used for prior and concomitant medications classification. Originally reported dates will be used for listings.

Treatment Exposure and Compliance

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall in Safety Set. Compliance to Study Drug will be summarized by descriptive statistics by treatment group and overall.

Compliance (%) will be calculated as follows:

> 100 x (total volume of Study Drug) / (total volume of Study Drug scheduled during the treatment period).

For early withdrawals/terminations, the volume of Study Drug will be calculated for the period up to their withdrawal/termination.

3.3 Primary Analyses

3.3.1 Primary Endpoint Definition

The primary endpoint is the percent change in fasting triglycerides from baseline to the primary analysis time point. The primary analysis time point is Week 25 for patients in Cohort A and B, and Week 27 for Cohort C and D.

3.3.2 Primary Efficacy Analysis

The primary efficacy analysis for the primary endpoint will be the pairwise comparison of percent change from baseline to the primary analysis time point in fasting triglycerides between ISIS 678354 treated groups and pooled placebo group in the FAS.

The percent change from baseline in triglycerides will be analyzed using an ANCOVA model with treatment group as a fixed factor and log-transformed baseline triglycerides as a covariate. The ANCOVA model will use log(Y/X) as dependent variable, where Y is the post-baseline value of triglycerides and X is the baseline value of the triglyceride. The model will provide an estimate of the log ratio, which will then be converted back to the original ratio scale. The percent change from baseline will then be estimated based on the estimated ratio. Patients with missing primary endpoint will have their fasting triglyceride value imputed using the multiple imputation method described below.

Missing data for the primary efficacy endpoint will be handled by a multiple imputation model that contains the following variables: log-transformed baseline fasting triglyceride value, log-transformed fasting post-baseline triglyceride values, stratified by treatment (Schafer 1997; Schafer 1999). Imputation of missing data will be conducted under a working assumption of missing at random (MAR), meaning that the propensity for a data point to be missing is not related to the missing data, but it is related to some of the observed data.

The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing primary endpoint by treatment group (ISIS 678354 treatment group or pooled placebo treatment group). In order to be compliant with the normality assumption, baseline and post-baseline triglyceride data will be log-transformed prior to the imputation process and will be reverted when creating the imputed dataset. The MCMC method will impute 100 datasets in order to estimate the treatment effect, where the median value across the imputed datasets will be used for patients with missing endpoint.

The primary endpoint will be compared between each ISIS 678354 treatment group and the pooled placebo group for each of the 100 imputed datasets. The estimates from the 100 fitted models will be combined to provide an overall estimate, with corresponding CIs and p-value (Little and Rubin, 2002). Results from the ANCOVA model will be tabulated by ISIS 678354 treatment groups compared to the pooled placebo group.

For fasting triglycerides, observed value, change from baseline and percentage of change will be summarized by analysis visit using descriptive statistics in FAS.

Mean (SD) percent change over time in fasting triglycerides will be plotted by ISIS 678354 treatment group and pooled placebo group, until there are fewer than 10% of the FAS/PPS population at a given visit. Waterfall plots of by-patient percent changes from baseline to the primary analysis time point will also be provided.

The primary efficacy analysis will take place after the last patient has completed the primary analysis time point, and the database has been locked.

All primary efficacy data will be provided in data listings.

The sample SAS code for the ANCOVA model can be found below: where the baseline and post-baseline values will be log-transformed first. Log (post-baseline/baseline) calculated as log (post-baseline) – log (baseline) will be subjected to the ANCOVA model.

```
**********************************************************************
* Note:
*  Base= baseline
*  Y=Post-baseline
*  TRTP = Treatment group: Pooled Placebo, 10 mg Q4W, 50 mg Q4W, 15 mg Q2W, 10 mg QW
**********************************************************************
ods output lsmeans=lsm diffs=diff;
proc mixed data = dataset;
        class TRTP (ref='pooled placebo') ;
        model log (Y/base) = TRTP  log(Base) /solution cl;
        lsmeans TRTP/ diff cl;
run;
```

3.3.3 Sensitivity Analyses of Primary Endpoint

In addition to the primary efficacy analysis, the following sensitivity analyses will be conducted on the FAS.

Sensitivity Analysis 1 (Per Protocol Set): The primary efficacy analysis will be repeated, using the PPS population.

Sensitivity Analysis 2 and 3 (Non-Parametric Analyses): The primary efficacy endpoint will be analyzed using a non-parametric Wilcoxon Rank Sum test using both the FAS and the PPS. Missing data will be handled using the same MCMC multiple imputation method as the primary analysis. The

treatment effect will be estimated using the Hodges-Lehmann estimator of the location shift between ISIS 678354 treatment groups and the pooled placebo group. Asymptotic 95% CI and corresponding p-values will be provided.

Sensitivity Analysis 4 (FAS) Using controlled imputations (pattern mixture models [PMM] with ANCOVA) will be conducted to assess the robustness of the missing at random assumption. With this approach, missing not at random (MNAR) is assumed, and the mean function for the missing data from patients treated with ISIS 678354 who discontinue the study is pre-specified. Missing triglycerides for placebo patients will be imputed using the same MCMC multiple imputation method as the primary analysis. Patients treated with ISIS 678354 who discontinue the study due to AE or lack of efficacy will have their post-discontinuation triglyceride values imputed using estimates from the placebo patients using the copy increment from reference (CIR) approach, detailed in (Carpenter et al. 2013). The assumption is based on the premise that when a patient discontinues treatment due to informative missing data, at the time of discontinuation they would progress in a similar manner as placebo-treated patients. Otherwise, non-informative missing data will be imputed using the same MCMC method as the primary analysis, since it is assumed that those patients would have continued in a similar manner to similar patients in their own treatment group who remained on the study. Therefore, the missing data for these patients is expected to be missing at random.

Sensitivity Analysis 5 (FAS) An ANCOVA will be performed on the primary efficacy endpoint without applying any imputation for missing data.

Sensitivity Analysis 6 (FAS) A repeated measures analyses will be performed on the fasting triglyceride endpoint. The percent change from baseline in triglycerides will be analyzed using an MMRM model with treatment group as a fixed factor, log-transformed baseline triglycerides and timepoint as covariates. If log transformation is applied, the analysis will carry the same conditions as the primary efficacy analysis for back transformation. No imputation of data is applied to this analysis. Analysis visits beyond PAT (Week 29, 37, 45, and 53) will be included only if the total n at the analysis visit is at least 10% of the overall FAS. Visit mapping is provided in Appendix A and SAS code is outlined in Appendix B.

3.3.4 Subgroup Analyses of Primary Endpoint

Subgroup analyses (with log-transformation and imputation method) for the primary endpoint are planned as follow:

- Gender: Male, Female
- Age: <65 and ≥65 years old
- CV history: established CVD (All patients enrolled in original protocol and protocol amendment 1, and Patients enrolled in protocol amendment 2 per Inclusion Criteria 3a), at risk for CVD (Patients enrolled in protocol amendment 2 per Inclusion Criteria 3b)

- Concomitant drugs used in diabetes: yes, no (ATC code: A10, ATC2 text: Drugs Used in Diabetes)

- Concomitant use of insulin and insulin analogues: yes, no (ATC code: A10A, ATC3 text: Insulins and Analogues)

- Concomitant use of triglyceride lowering drugs (fibrates, omega-3 fatty acids): yes, no to include ATC code: C10AB, ATC4 text: Fibrates, and ATC code: C10AX, ATC4 Text: Other Lipid Modifying Agents, Preferred Term: EICOSAPENTAENOIC ACID ETHYL ESTER, FISH OIL, FISH OIL;OMEGA-3 FATTY ACIDS, FISH OIL;TOCOPHEROL, OMEGA-3 FATTY ACIDS, OMEGA-3-ACID ETHYL ESTER.

3.4 Secondary Efficacy Analyses

All analyses of secondary endpoints will be performed on the FAS as primary and PPS as supportive. Secondary efficacy analyses are based on the data collected at the primary analysis time point.

- Percent change from baseline at the primary analysis time point in fasting apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I will be compared between each ISIS 678354 group and pooled placebo group using an ANCOVA model with log-transformed baseline as covariate. The ANCOVA model without applying any imputation for missing data will use log(Y/X) as dependent variable, where Y is the post-baseline lipid value and X is the baseline lipid value.
- Proportion of patients who achieve fasting triglycerides ≤ 150 mg/dL (≤ 1.7 mmol/L) at the primary analysis time point with MCMC imputation will be compared between each ISIS 678354 treatment group and pooled placebo group using a logistic regression model with baseline triglycerides as a covariate.
- Proportion of patients who achieve fasting triglycerides ≤ 100 mg/dL (≤ 1.13 mmol/L) at the primary analysis time point with MCMC imputation will be compared between each ISIS 678354 treatment group and pooled placebo group using a logistic regression model with baseline triglycerides as a covariate.

Summary statistics of the observed value, change and percent change from baseline by analysis visit will be performed for fasting apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and apoA-I on FAS.

3.5 Exploratory Efficacy Analyses

All analyses of exploratory endpoints will be performed on the FAS. Percent change from baseline at the primary analysis time point in fasting Lp(a), remnant cholesterol, and ANGPTL3 as log-transformed ratio of post-baseline to baseline value will be compared between each ISIS 678354 group and pooled placebo group using an ANCOVA model with log-transformed baseline as covariate. Summary statistics including observed value, change and percent change from baseline by analysis visit will also be performed.

Table 5 outlines the analysis methods used in each efficacy analysis.

Table 5 Summary of Analysis Methods in Efficacy Analyses

Endpoint	Analysis Type	Log-Transformed Data	MCMC imputation	Population	Model
Primary Endpoint	Primary Analysis	Yes	Yes, assume MAR	FAS	ANCOVA
	Sensitivity Analysis 1	Yes	Yes, assume MAR	PPS	ANCOVA
	Sensitivity Analysis 2	Yes	Yes, assume MAR	FAS	non-parametric Wilcoxon Rank Sum test
	Sensitivity Analysis 3	Yes	Yes, assume MAR	PPS	non-parametric Wilcoxon Rank Sum test
	Sensitivity Analysis 4	Yes	Yes, Placebo: assume MAR. ISIS 678354: missing before discontinuation, assume MAR; missing after discontinuation assume CIR	FAS	ANCOVA
	Sensitivity Analysis 5	Yes	No	FAS	ANCOVA
	Sensitivity Analysis 6	Yes	No	FAS	MMRM
	Subgroup Analysis	Yes	Yes	FAS	ANCOVA
Secondary Endpoints	Secondary Analysis	Yes	Yes for triglycerides; No for other endpoints	FAS and PPS	ANCOVA
Exploratory Endpoint	Exploratory Analyses	Yes	No	FAS	ANCOVA

3.6 Pharmacokinetic and Anti-Drug Antibody analysis

3.6.1 Pharmacokinetic Data Analysis

All PK data analysis will be conducted using the PK Population except the listing of PK concentrations which will be conducted on the Safety Set.

The concentrations of ISIS 678354 in plasma expressed as ISIS 678354-equivalent (as total full-length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 678354) will be summarized by nominal visit by treatment group with and without stratification by patient ADA status using descriptive statistics. In addition, plasma terminal elimination half-life of ISIS 678354 will be calculated using the post-treatment follow-up data if data permits.

Additionally, for patients in the PK subgroup only, PK parameters will be calculated using non-compartmental methods. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) values will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve (AUC) values after the first dose ($AUC_{0\text{-}24h}$) and steady-state dose ($AUC_{0\text{-}24h}$ and AUC_{tau}) will be calculated using the linear trapezoidal rule. Other PK parameters may be calculated at the discretion of the Sponsor. Plasma PK parameters will be summarized using descriptive statistics with and without stratification by patient ADA status.

Exposure-response relationships between selected lipid and PK measures (e.g., plasma trough concentrations) may be explored in a separate population PK/PD analysis combined with other clinical studies.

3.6.2 Anti-Drug Antibody Data Analysis

All ADA data analysis will be conducted using the Safety Set.

The ADA of ISIS 678354 will be assessed before, during, and after treatment with Study Drug (ISIS 678354 or placebo). The ADA incidence will be summarized by nominal visit and at the patient level by treatment group, as the total number of and percent of evaluated patients with ADA negative, positive, and unknown status. Patient ADA status (positive, negative or unknown) for all evaluable patients, along with the study day associated with the first emergence of ADA positivity (i.e., onset of ADA), the last positive ADA status observed, and peak ADA titer will be listed by treatment group. Potential relationships of ADA with selected efficacy, safety, and PK measures may be evaluated.

3.7 Safety Analyses

All safety analyses will use the Safety Set unless otherwise specified. Unless noted otherwise, denominators for all tables will be number of patients in the SS. Safety endpoints including laboratory assessments and vital signs will be analyzed by nominal visit collected on CRF.

Adverse events, concomitant medications, safety shift tables, and all tables related to safety monitoring/stopping rules will be summarized by 2 periods: on-treatment and on-study. On-treatment assessment is defined as the assessment from the first dose to the last dose of Study Drug plus one dosing interval. For Cohorts A and B, on-treatment period spans time from first dose to the last dose + 28 days; For Cohort C, on-treatment period spans time from first dose to the last dose + 14 days;

For Cohort D, on-treatment period spans time from first dose to the last dose + 7 days. On-study assessment is defined as the assessment from the first dose to the last visit in post-treatment follow-up period.

3.7.1 Imputation of Missing/Partial Dates

3.7.1.1 Adverse Events

For AEs, the following imputation rules will be applied to impute start dates under conservative principles:

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

Imputation will be performed for the end date only if the day or month is missing (i.e., year is present) for a resolved AE as follows:

- If month and day are missing, and year is
  - the same as the year of the last dose of Study Drug then assign the month-day of the last dose of Study Drug
  - otherwise, assign December 31
- If only day is missing, then assign the last day of the month

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

Analysis period (on-treatment and on-study) will be assigned by comparing the imputed AE start date with the period start/end date.

3.7.1.2 Prior/Concomitant Medications

For prior/concomitant medications, the following imputation rules will be applied to impute start dates under conservative principles:

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

Imputation will be performed for the end date only if the day or month is missing (i.e., year is present) for a stopped prior/concomitant medication as follows:

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

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

Analysis period will be assigned by comparing the imputed medication start/end date with the period start/end date.

3.7.2 Adverse Events

All AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Missing or partial dates will be imputed as outlined in Section 3.7.1.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that occurred after the first dose of Study Drug. If the imputed onset date/time is the same as or after the date/time of the first dose of Study Drug, then the event is treatment emergent. An AE with a completely missing start date will be assumed to be treatment emergent.

In the situation where change in severity (but no change in seriousness) occurs for an AE, study sites are instructed to enter an end date for the original AE and start a new record for the AE with a new severity reported. In the new record, the changed severity is to be recorded and the start date will be set to be the end date of the previous record.

When counting the total number of treatment-emergent events for table display, events reporting an increase in severity will be counted as separate events.

AE summary tables by treatment group and overall will be presented in 2 periods separately: on-treatment and on-study. The frequency of patients with any incidence of AEs and the number of events will be summarized by SOC and PT for:

- TEAEs
- TEAEs related to Study Drug. Related is defined as "Related", "Possible", or missing relationship to Study Drug
- TEAEs by severity. At each level of patient summarization, a patient with multiple events is counted only once according to the worst reported severity. Adverse events with missing severity will be categorized as "Missing" for this summary.
- TEAEs related to Study Drug by severity
- Most common TEAEs. Most Common TEAE is defined as treatment-emergent adverse events with an incidence of 10% or more within any treatment groups at PT level.
- Treatment Emergent SAEs
- Treatment Emergent SAEs related to Study Drug
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death.

Summary tables will be sorted by decreasing frequency of SOC and then by decreasing frequency of PT within SOC in pooled ISIS 678354 group. If the frequency is the same for multiple PTs, sort alphabetically.

An overview of AEs will be provided for all TEAEs. Treatment-emergent AEs, treatment-emergent SAEs, TEAEs related to Study Drug, treatment-emergent SAEs related to Study Drug, TEAEs that lead to Study Drug discontinuation, TEAEs that lead to Study Drug interruption, TEAEs that lead to dose reduction, and TEAEs leading to death will be listed. Note that imputed dates will be used for defining TEAEs and classification of TEAEs into analysis periods.

Listings of all AEs, TEAEs related to Study and Treatment Emergent SAEs related to Study will be presented. Originally reported dates will be used in listings.

3.7.2.1 Treatment Emergent Adverse Events at Injection Site

Treatment Emergent AEs at injection site will follow two definitions:

Definition 1: Local cutaneous reactions at injection site (LCRIS) are defined as injection site erythema, injection site swelling, injection site pruritus, injection site pain, or injection site tenderness that started on the day of injection and persisted for at least two days (i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after injection) will be included. Events on the day of the injection with a missing resolution date will also be included.

Definition 2: Injection Site Reactions (ISR) are defined as any AE with PT or verbatim term containing 'Injection Site' that persisted for at least two days (i.e. event onset date on the day of

injection and resolution date not on the day of injection or the day after injection) will be included. Events with a missing resolution date will also be included.

Treatment Emergent LCRIS will be summarized by SOC and PT and by severity in on-treatment period only. Treatment Emergent ISRs will be summarized by SOC and PT and by severity in on-treatment and on-study periods.

Additionally, the following will be summarized using Definition 2 (i.e., ISRs):

- Percentage of injections leading to ISR for overall and preferred term will be summarized using descriptive statistics for on-study period only. Percentage of injections leading to ISR will be calculated as follows for each patient: (A/B) *100, where A = number of injections leading to ISR, and B = total number of injections.
- ISRs by injection location for on-study period only
- Incidence of ISR and time to first ISR for on-study period only
- ISRs by treatment time interval (<=13 weeks, >13-26 weeks, >26-39 weeks, and >39-52 weeks) for on-treatment period only

An additional table summarizing ISRs (definition 2) on-treatment by SOC and PT and by severity within cohort will be presented.

3.7.2.2 Treatment Emergent Flu-Like Reactions

Treatment Emergent Flu-Like Reactions (FLRs) will follow two definitions:

- Definition 1: TEAEs with either (i) influenza like illness or (ii) at least one of following PTs: pyrexia, feeling hot, or body temperature increased, plus at least two of the following PTs: chills, myalgia, and arthralgia, starting on the day of injection or the next day.

- Definition 2: TEAEs with following PTs or verbatim: influenza like illness, chills, myalgia, arthralgia, pyrexia, feeling hot, or body temperature increased, starting on the day of injection or the next day.

Note that imputed dates will be used for defining.

Treatment Emergent FLRs defined in definition 1 will be summarized by category (i) or (ii). Treatment Emergent FLRs defined in definition 2 will be summarized by SOC and PT. Both definitions will be presented in on-treatment period.

Percentage of injections leading to FLRs (definition 2) for overall and by preferred term will also be summarized using descriptive statistics. Percentage of injections leading to FLRs will be calculated for each patient as (A/B)*100, where A is the number of injections associated with FLRs, and B is the total number of injections.

3.7.2.3 Adverse Events of Special Interest

The TEAEs of bleeding based on the Haemorrhages (SMQ) Export from MedDRA version 20.1 will be summarized by SOC and PT and by severity in on-treatment and on-study period respectively.

The TEAEs of bleeding in presence or absence of concomitant antithrombotic medication (ATC3 Text: Antithrombotic agents) will be summarized by SOC and PT in on-treatment period. The TEAEs of bleeding in presence or absence of concomitant antithrombotic medication will be listed as well.

An additional table summarizing treatment-emergent bleeding AEs on-treatment by SOC and PT within cohort will be presented.

3.7.3 Vital Signs Measurements

Vital signs include weight, BMI, body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure. Vital signs will be summarized using the descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, maximum, and mean 95% CI) for observed values, change from baseline and percent change from baseline at each nominal study visit. Scheduled visits will be used for summary table. A listing of vital signs with scheduled and unscheduled visits will also be provided.

3.7.4 Laboratory Measurements

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

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, glomerular filtration rate, uric acid, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatine kinase, GGT, Cystatin-C
- Hematology: red blood cells, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelets, white blood cells (WBCs), and WBC differential (percentage and absolute count), neutrophils, eosinophils, basophils, lymphocytes, and monocytes
- Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR)
- Inflammatory Panel: C-reactive protein measured by high sensitivity assay (hsCRP)
- Test Performed at Screening Only: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, follicle-stimulating hormone (FSH) (women only), serum beta-subunit of human chorionic gonadotropin (βhCG) (women only), thyroid stimulating hormone (TSH), free T4. The screening test data will only be displayed in patient listings
- Urinalysis: color, appearance, specific gravity, pH, protein, red blood cell, ketones, glucose, urobilinogen, bilirubin, leukocytes esterase, nitrate. For expanded urinalysis at certain visits,

additional measurements will be performed including: microscopic examination, urine protein/creatinine ratio (UPCR), urine albumin/creatinine ratio (UACR).

- Renal Urine Biomarkers: NGAL, NAG, KIM-1, Cystatin-C
- Other assessments (glycemic control): plasma insulin, fasting plasma glucose, homeostatic model assessment of insulin resistance (HOMA-IR) as provided in the central laboratory data, fructosamine, glycated albumin, and glycated hemoglobin (HbA1c)

Missing WBC differential absolute counts and percentages will be derived: If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophil counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Quantitative laboratory measurements reported as '< X', i.e. below the lower limit of quantification (BLQ), or '> X', i.e. above the upper limit of quantification (ULQ), i.e. outside the limit of quantification, will be converted to X (or limit of quantification) for the purpose of quantitative summaries. If urine albumin/creatine ratio (UACR) or urine protein/creatinine ratio (UPCR) is 'Cannot calc' indicating urine albumin or urine protein in the below quantification range, UACR and UPCR will be calculated as the ratio of urine albumin or urine protein to urine creatinine after converting urine albumin or urine protein to the limit of quantification.

Estimated Glomerular Filtration Rate (eGFR) is based on the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation and is provided as a parameter in the central laboratory data.

Chemistry, hematology, inflammatory panel, coagulation, other assessments, renal biomarkers, and quantitative urinalysis (observed value, absolute and percent change from baseline) will be summarized using descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, and maximum, mean 95% CI) by scheduled nominal visit. HOMA-IR and plasma insulin will be summarized only in patients not treated with insulins or insulin analogues. Qualitative urinalysis will be summarized using counts and percentages by scheduled nominal visit. Lab summary table except for platelet count will be based on the scheduled visits in central lab data only with the results in original unit. The summary table of platelet count will be based on the scheduled visits in central and separately in local lab data with the results in original unit.

All laboratory test results will be listed separately for local and central labs at scheduled and unscheduled visits with results in original unit.

A confirmed laboratory value is based on consecutive lab values performed on a different day to, but within 7 days (no matter central lab data or local lab data). If consecutive value is same or worse, then the initial value is confirmed. If the consecutive value is better, then the initial value is confirmed using consecutive value. 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 central lab data or local lab data), then the worst value will be utilized in the analysis.

The following lab results will be graded based on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Number and proportion of patients with shift from baseline to worst post-baseline values by toxicity grade will be tabulated for on-treatment and on-study periods. Post-baseline lab results are defined as any assessment taken after the first dose no matter central lab or local lab data. If a patient has no baseline value but has a post-baseline value, then the baseline assessment will be labeled as "unknown". Likewise, if a patient has a baseline value but has no post-baseline value, then the worst value will be labeled as "unknown". Shift tables for eGFR, ALT, AST and total bilirubin will be provided using original and confirmed values.

- Hemoglobin: shift from Baseline to minimum post-baseline value
- WBCs: shift from Baseline to minimum post-baseline value
- Platelets: shift from Baseline to minimum post-baseline value
- BUN: shift from Baseline to maximum post baseline value
- Creatinine: shift from Baseline to maximum post-baseline value
- eGFR: shift from Baseline to minimum post-baseline value
- Proteinuria: shift from Baseline to worst post-baseline value
- ALT: shift from Baseline to maximum post-baseline value
- AST: shift from Baseline to maximum post-baseline value
- Alkaline phosphatase: shift from Baseline to maximum post-baseline value
- Total bilirubin: shift from Baseline to maximum post-baseline value

eGFR will be graded using the following criteria:

- $\geq$ 90 mL/min/1.73m^2
- $\geq$ 60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2
- $\geq$ 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2
- $\geq$ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2
- < 15 mL/min/1.73m^2

The number and percent of patients who stopped treatment because they met a protocol-defined safety monitoring rule(s) and stopping rule(s) (see Protocol Section 8.6 for details) will be tabulated by treatment group. A listing will be provided for patients who met protocol-defined safety monitoring rules and for patients who terminated treatment due to a protocol-defined stopping rule as well.

Additional investigation of abnormalities in liver chemistry, platelet counts, and renal functions will be performed for on-treatment and on-study periods as below.

Abnormalities in liver chemistry: The number and percent of patients falling in each of the following categories (using available central and local laboratory assessments) will be tabulated based on worst post-baseline assessments by treatment group and for pooled ISIS 678354.

- The higher of ALT > 3 x upper limit of normality (ULN) or ALT > 2 x Baseline
- ALT/AST > 3 x ULN
- ALT/AST > 5 x ULN
- ALT/AST > 8 x ULN
- ALT > 3 x ULN - ≤ 5 x ULN
- ALT > 5 x ULN - ≤ 8 x ULN
- Total bilirubin > 2 x ULN
- ALP > 2 x ULN and (baseline ALP < 2 x ULN or baseline ALP missing)

The number and percent of patients falling in each of the following categories based on confirmed worst post-baseline assessments will be tabulated by treatment group and for pooled ISIS 678354.

- ALT/AST > 8 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed and persist for at least 2 weeks
- ALT/AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed and either:
    - Total bilirubin > 2 x ULN, or
    - INR > 1.5, or
    - Temporal association with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness (PT: abdominal pain or abdominal pain upper), fever, rash, or eosinophilia (PT: Eosinophilia and the corresponding lab value >ULN within the interval of associated Eosinophilia start and end date); and where temporal will be defined as the report date of the confirmed laboratory parameter occurring within the interval of the associated adverse event start and stop dates

For patients having confirmed 3-fold or greater elevations above the ULN for ALT or AST, a listing of all ALT, AST, total bilirubin, INR, and alkaline phosphatase records will be provided.

Abnormalities of platelet counts: The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments) based on worst post-baseline assessments will be provided:

- Any 2 occurrences of platelet count < 140,000 cells/mm^3
- Any single occurrence of platelet count < 100,000 cells/mm^3
- Any 2 occurrences of platelet count < 140,000 cells/mm^3 or any single occurrence of value < 100,000 cells/mm^3

The nadir platelet count will be summarized by following categories:

- Decrease ≥ 30% from baseline
- Decrease ≥ 50% from baseline
- 100,000 cells/mm^3 to < 140,000 cells/mm^3
- 75,000 cells/mm^3 to < 100,000 cells/mm^3
- 50,000 cells/mm^3 to < 75,000 cells/mm^3
- 25,000 cells/mm^3 to < 50,000 cells/mm^3
- 0 to < 25,000 cells/mm^3

All categories of abnormalities in platelet count will be summarized based on confirmed values for on-study period as well.

Abnormalities of renal function: The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments) based on confirmed worst post-baseline assessments will be provided:

- eGFR by CKD-EPI > 25% decrease from baseline
- UACR > 250 mg/g
- UPCR > 0.5 g/g
- Serum creatinine increase of > 0.3 mg/dL from baseline

3.7.5 12-Lead Electrocardiogram

ECGs will be performed in triplicate at the visits indicated in the Protocol Appendix A. Patients in PK Subgroup will have additional ECG conducted during the treatment period. Patients determined to have a pacemaker rhythm will be excluded from summary tables.

The ECG data include ventricular rate, PR interval, QRS duration, QT and corrected QT intervals. For the continuous variables, the average of measurements at a given visit will be used for analysis. For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, P25, P75, minimum, maximum, and mean 95% CI) of the observed values, as well as the change from baseline to each nominal study visit, will be presented by treatment group and for pooled placebo in summary tables. The summary table will be presented in SS and in PK Subgroup separately. Scheduled visits will be used for all summary tables.

The number and percent of patients who have the following reported events will be tabulated by treatment group and for pooled ISIS 678354.

- Absolute QT/QTcF/QTcB >450 msec
- Absolute QT/QTcF/QTcB >480 msec

- Absolute QT/QTcF/QTcB >500 msec
- Increase from baseline in QT/QTcF/QTcB >30 msec
- Increase from baseline in QT/QTcF/QTcB >60 msec
- Increase from baseline in PR ≥50% (if absolute baseline <200 msec)
- Increase from baseline in PR ≥25% (if absolute baseline >200 msec)
- Increase from baseline in QRS ≥50% (if absolute baseline <100 msec)
- Increase from baseline in QRS ≥25% (if absolute baseline >100 msec)

QTcB (msec) = QT (msec) / $(RR)^{1/2}$; if RR is missing, use QT (msec) * $(HR(bpm)/60)^{1/2}$

QTcF (msec) = QT (msec) / $(RR)^{1/3}$; if RR is missing, use QT (msec) * $(HR(bpm)/60)^{1/3}$

All the ECG data with scheduled and unscheduled visits will be listed.

An exploratory exposure-response analysis will be performed in PK-ECG Set to evaluate the relationship between QTcF and plasma concentration of ISIS 678354. The relationship between ISIS 678354 concentration and change from baseline QTcF (ΔQTcF) and placebo-corrected change from baseline QTcF (ΔΔQTcF) will be investigated using a linear mixed-effects modeling approach on time-matched ECG and ISIS 678354 concentration data.

ΔQTcF or ΔΔQTcF = α + β1 x [ISIS 678354 concentration] + β2 x [baseline QTcF] + γ x [patient effect]

ΔΔQTcF = (ΔQTcF for ISIS 678354 treated patient) − (mean of ΔQTcF for pooled placebo group).

Matching of ECG and ISIS 678354 concentration (PK) data will be based on the following algorithm, in the sequence provided:

1. Time of ECG and PK must be within 60 minutes (±60 minutes) of each other.
2. If there are multiple records within the 60 minutes range, the closest match will be chosen.
3. If there is more than one closest match identified in the previous step, the recorded pair with the ECG time point after the PK time point will be chosen.

Plots of ΔQTcF or ΔΔQTcF versus ISIS 678354 concentration including all patients in PK-ECG Set will be generated.

3.8 Interim Analysis

There is no interim analysis planned for the study.

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5 APPENDICES

Appendix A – Efficacy Measurement Analysis Visit Window and Selection Rules

- Primary Efficacy: Fasting triglycerides
- Second Efficacy: Fasting apoA-I, apoB, apoC-III, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C
- Exploratory Efficacy: Fasting ANGPTL3, Lp(a) and remnant cholesterol (per TC, HDL-C and LDL-C)

Cohort A/B

Period	Study Week	Target Day	Study Day Window
Screening	Run-in	-28 to -15	≤ -15
	Qualification	-14 to -7	-14 to < 1
Treatment	Week 1	1	1
	Week 5	29	2 to 43
	Week 9	57	44 to 71
	Week 13	85	72 to 99
	Week 17	113	100 to 127
	Week 21	141	128 to 155
	Week 25 (PAT)	169	156 to 183
	Week 29	197	184 to 211
	Week 37	253	240 to 267
	Week 45	309	296 to 323
	Week 53	365	352 to 379

Data collected under visit labels containing follow up will not be mapped to analysis week.

Cohort C/D

Period	Study Week	Target Day	Study Day Window
Screening	Run-in	-28 to -15	≤ -15
	Qualification	-14 to -1	-14 to < 1
Treatment	Week 1	1	1
	Week 5	29	2 to 43
	Week 9	57	44 to 71
	Week 13	85	72 to 99
	Week 17	113	100 to 127
	Week 21	141	128 to 155
	Week 27 (PAT)	183	156 to 190
	Week 29	197	191 to 211
	Week 37	253	240 to 267
	Week 45	309	296 to 323
	Week 53	365	352 to 379

Data collected under visit labels containing follow up will not be mapped to analysis week.

Record selection rules to identify analysis visit will be based on the following algorithm, in the sequence provided:

1. Records must be fasting
2. If there are multiple records with fasting, the closest record to target day will be chosen.
3. If there are multiple records within same range to target day, the record prior to the target day will be chosen.
4. If there is more than one record on the same day prior to the target day, the average of these records will be chosen.

Appendix B – Repeated Measures Efficacy Visit Mapping Instructions for Sensitivity Analysis 6 and Model

For the MMRM analysis of triglycerides, we will map the visits per Appendix A for assignment to the analysis visits. For the MMRM we should only include the following analysis visit timepoints in the model: Week 5, 9, 13, 17, 21, 25/27 (PAT). Also include Week 29, 37, 45, and 53 only if total n at the analysis visit is at least 10% of the overall FAS.

In order to use the same visit number in the model for primary analysis time point, Week 25 in cohort A and B will be re-numbered to Week 27.

The sample SAS code for the repeated measures analysis can be found below:

```
**********************************************************************

* Note:

* Base represents baseline triglycerides value

* Y represents post-baseline triglycerides value

* TRTP represents treatment group (pooled placebo, 10 mg Q4W, 50 mg Q4W, 15 mg Q2W, 10 mg QW)

*AVISIT represents the visit variable (Week 5, 9, 13, 17, 21, PAT, and potentially 29, 37, 45, and 53)

*SUBJID represents the variable identifying the patients

**********************************************************************

ods output lsmeans=lsm diffs=diff;

proc mixed data = dataset;

        class TRTP AVISIT SUBJID;

        model log(Y/base) = TRTP log(BASE) AVISIT TRTP*AVISIT;

        repeated AVISIT / subject=SUBJID (TRTP) type=un;

        lsmeans TRTP*AVISIT/E CL DIFF=CONTROL ("pooled placebo" "Week xx");

run;

ods output close;
```