Official Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

NCT Number: NCT03070782

Document Date(s): Protocol Amendment Version 6: 25-January-2018

Protocol Amendment Version 5: 30-May-2017

Protocol Amendment Version 4: 5-January-2017

Protocol Amendment Version 3: 9-December-2016

Sponsor:
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2855 Gazelle Court
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AKCEA THERAPEUTICS

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 6 – 25 January 2018

EudraCT No: 2016-003373-18

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 6 – 25 January 2018

Protocol History:

Original Protocol:	15 August 2016
Protocol Amendment 1:	12 October 2016
Protocol Amendment 2:	29 November 2016
Protocol Amendment 3:	30 December 2016
Protocol Amendment 4:	5 January 2017
Protocol Amendment 5:	30 May 2017

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ISIS 681257-CS6

Ionis Protocol Number ISIS 681257-CS6

Protocol Amendment 6

EudraCT No: 2016-003373-18

Clinical Phase: 2

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

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Date: 25 January 2018

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment: Amendment 6

Date: 25 January 2018

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 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)," dated 25 January 2018, 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.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENTS

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 6

Amendment Date: 25 January 2018

The following table summarizes the history and nature of amendments to the protocol ISIS 681257-CS6.

None of the antecedent versions of the study protocol has been enacted clinically and therefore no patients have been enrolled prior to issuance of Amendment 4.

Protocol Version	Date	Rationale for Amendments
Original Protocol	15 August 2016	
Amendment 1	6 October 2016	Regulatory advice on inclusion of more detailed description of processes for platelet monitoring, and more frequent monitoring of liver function.
Amendment 2	29 November 2016	Regulatory advice on inclusion of biomarkers of renal damage and increased frequency of renal monitoring. Addition of a DSMB.
Amendment 3	30 December 2016	Adjustment of the frequency, and alert and intervention limits, for renal safety and adjustment of the frequency of liver safety testing.
Amendment 4	5 January 2017	The study population was increased to 270 patients (54 per cohort) to support a statistical assessment of risk of platelet reduction in this population. In addition, the 10 mg weekly treatment cohort has been modified to 20 mg every 2 weeks (biweekly).
Amendment 5	30 May 2017	Regulatory advice on addition of exclusion criteria, reduced permitted timeframe for identifying critical laboratory results by the investigator and replacement of the AE definition. In addition, Section 8.6.2 was edited for consistency.
Amendment 6	25 January 2018	Updated platelet monitoring to allow for potential to return to every 2-week monitoring, clarified definition and scheduling of the follow-up period and End of Treatment visit for last patient to complete primary endpoint visit.

PROTOCOL SUMMARY OF CHANGES

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 6

Amendment Date: 25 January 2018

The following modifications to Protocol ISIS 681257-CS6 Amendment 5 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 Amendment 5 of the protocol:

Protocol Section	Description of Change	Rationale
Throughout	Updated Sponsor to Akcea Therapeutics and Collaborator to Ionis Pharmaceuticals, Inc.	Sponsorship has been transferred from Ionis Pharmaceuticals, Inc. to Akcea Therapeutics
Section 3.4.2	Added detail around definition and scheduling of End of Treatment Visit	Clarification and detail added to ensure definition of Treatment Period is clear. Additional clarification was also added around scheduling of the End of Treatment Visit for all patients once last patient is enrolled.
Section 6.2.1 Laboratory Assessments	Added “should” to samples being collected and analyzed in parallel at the central and local lab.	The word “should” was inadvertently left out of the sentence in a prior amendment.
Section 8.5.3 Safety Monitoring for Platelet Count Results	Updated reference to Appendix from D to E for platelet counts < 100,000/mm^3	Correct Appendix is E

Protocol Section	Description of Change	Rationale
Section 8.6.3 Stopping Rule for Platelet Count Results Table 3 Actions in Patients with Low Platelet Count	Changed language around weekly monitoring requirement to allow for return to every 2-week monitoring if 2 successive platelet values fall within the normal range.	Given the episodic transient nature of mild platelet drops recorded to date, weekly platelet monitoring for the entire duration of the study even when the platelet count returns to the normal range is medically unjustified.
Section 8.6.3 Stopping Rule for Platelet Count Results Table 3 Actions in Patients with Low Platelet Count	Clarified platelet ranges and updated Section 8.6.3 accordingly.	Clarification to ensure no overlap in actions to be taken based on platelet value
Appendix A Schedule of Procedures	Clarified that follow-up visits should be timed to correspond with last visit of the treatment period	Clarification to ensure alignment among sites in scheduling of follow up visits in relation to the last visit of the treatment period rather than the last dose.
Appendix A Schedule of Procedures	Added “(optional)” to genetic testing assessment	This test is only required for patients who sign separate consent
Appendix A Schedule of Procedures	Clarified timing of study drug administration for weekly and every 2-week dosing	Clarification to account for last dose variation between weekly and every 2-week cohorts.
Appendix A Schedule of Procedures	Added footnote stating the last patient to reach 6 months of exposure will complete all assessments for primary endpoint visit (Week 25 or Week 27 based on cohort) and for End of Treatment visit (Week53/ET), and will not receive a dose at that visit.	Clarification that the last patient’s primary endpoint visit will count as Week 25/Week 27 and End of Treatment visit (Week53/ET)

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)
Study Phase	2
Indication	Patients with hyperlipoproteinemia(a) and established CVD.
Investigational Drug	ISIS 681257 is a second generation 2'-MOE modified, $GalNAc_3$–conjugated antisense oligonucleotide inhibitor of apolipoprotein (a) [apo(a)].
Primary Objective	To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.
Secondary Objective(s)	To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B100 (apoB), oxidized phospholipids (OxPL) on apo(a) [OxPL-apo(a)], and OxPL on apoB (OxPL-apoB). To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in patients with hyperlipoproteinemia(a) and established CVD.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio to receive ISIS 681257 or placebo. This number was chosen to provide statistical power for both efficacy and safety assessments. Study Drug (ISIS 681257 or placebo) will be administered SC 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 will then enter a 16-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-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, 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 (as needed) data collected on ISIS 681257 during this study, both individual events and aggregate data.
Number of Subjects	Approximately 270

PROTOCOL SYNOPSIS *Continued*

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. Clinical diagnosis of CVD defined as documented coronary artery disease, stroke, or peripheral artery disease 4. Lp(a) plasma level ≥ 60 mg/dL 5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors 6. 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 7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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 8. 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 16 weeks after the last dose of ISIS 681257

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria 1. Within 6 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 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 with a history of major bleed or high-risk of bleeding diathesis 11. Recent history of, or current drug or alcohol abuse 12. Known history or presence of systemic allergic or pseudoallergic (drug) reactions 13. Hypersensitivity to the active substance or to any of the excipients 14. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following: a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr c. Estimated GFR < 60 mL/min as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL f. Alkaline phosphatase (ALP) > ULN g. Platelet count < LLN 15. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors 16. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Study Population
Continued</td><td>Exclusion Criteria
17. Treatment with any 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
18. BMI > 40 kg/m^2
19. Blood donation of 50-499 mL within 30 days of screening or of > 499 mL within 8 weeks of Screening
20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
21. 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 5 parallel cohorts:
Cohort A (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.
Cohort B (n = 54): Patients will be randomized 5:1 to receive 40 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.
Cohort C (n = 54): Patients will be randomized 5:1 to receive 60 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.
Cohort D (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every 2 weeks for up to 26 doses.
Cohort E (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every week for up to 52 doses.
<table>
<tr><th>Cohort</th><th>Treatment</th><th># Doses</th><th>Total ISIS 681257</th></tr>
<tr><td>A</td><td>20 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 260 mg</td></tr>
<tr><td>B</td><td>40 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 520 mg</td></tr>
<tr><td>C</td><td>60 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 780 mg</td></tr>
<tr><td>D</td><td>20 mg ISIS 681257 or placebo (Every 2 weeks)</td><td>≤ 26</td><td>≤ 520 mg</td></tr>
<tr><td>E</td><td>20 mg ISIS 681257 or placebo (Every week)</td><td>≤ 52</td><td>≤ 1040 mg</td></tr>
</table>
</td></tr>
</table>

PROTOCOL SYNOPSIS *Continued*

Study Drug Dosage and Administration	The Sponsor will provide ISIS 681257 in a concentration of 100 mg/mL and matching volume placebo: Cohort A: 20 mg every 4 weeks ISIS 681257 or placebo (0.2 mL) Cohort B: 40 mg every 4 weeks ISIS 681257 or placebo (0.4 mL) Cohort C: 60 mg every 4 weeks ISIS 681257 or placebo (0.6 mL) Cohort D: 20 mg every 2 weeks ISIS 681257 or placebo (0.2 mL) Cohort E: 20 mg every week ISIS 681257 or placebo (0.2 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 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a). The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state. The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) ≤ 30 mg/dL).
Rationale for Dose and Schedule Selection *Continued*	The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.
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.

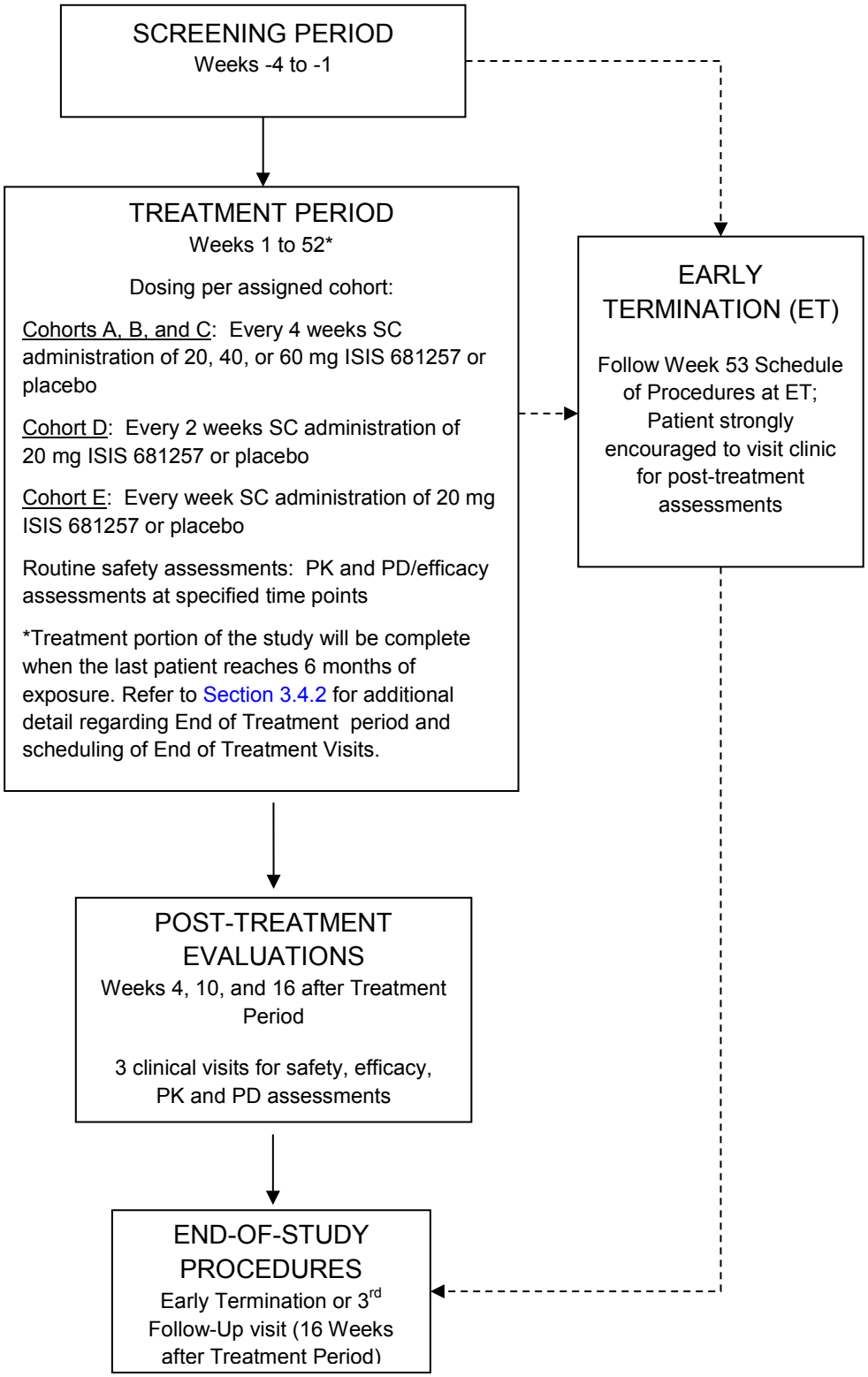
PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures	Detailed information regarding the study procedures are outlined in Section 6, Appendices A and C. All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may 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 • An up to 52-week treatment period during which Study Drug will be administered per assigned cohort by SC injection • A 16-week post-treatment follow-up period Patients in Cohorts A through C will receive up to 13 SC doses of ISIS 681257 or placebo every 4 weeks. Patients in Cohort D will receive up to 26 SC doses of ISIS 681257 or placebo every 2 weeks and patients in Cohort E will receive up to 52 SC doses of ISIS 681257 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). 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 and use of concomitant medications. Safety and tolerability results in patients dosed with ISIS 681257 will be compared with those dosed with placebo.
Efficacy Evaluations	The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). The primary endpoint is the percent change in plasma Lp(a) from baseline at the primary analysis time point for ISIS 681257 treatment groups compared to placebo. The secondary endpoints comprise the effect of ISIS 681257 as compared to placebo at the primary analysis time point on the following: • Percent change from baseline in LDL-C • Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL (≤ 125 nmol/L) • Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL (≤ 75 nmol/L) • Percent change from baseline in apoB • Percent change from baseline in OxPL-apo(a) • Percent change from baseline in OxPL-apoB

PROTOCOL SYNOPSIS *Continued*

Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 681257 plasma trough levels throughout treatment and during the post-treatment follow-up period. In addition, in a subset of patients (approximately 12 patients per cohort), more frequent plasma samples will be taken following the first and Day 169 (for Cohorts A, B, and C) or Day 183 (for Cohorts D and E) dose to determine PK parameters. Plasma sample collection time points are detailed in Appendices A and C. The plasma ISIS 681257 levels over time will be descriptively summarized by treatment with stratification by subject immunogenicity status. Apparent terminal elimination half-life will be calculated in patients who received ISIS 681257 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 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 Lp(a) between ISIS 681257 treated groups and placebo group in the Full Analysis Set. The data will be analyzed using an ANCOVA model with the baseline Lp(a) 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 plasma Lp(a) 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. Sample Size Considerations: <u>Efficacy:</u> Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients. <u>Safety:</u> Based upon prior clinical trial experience with ISIS ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event. A total of approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.
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
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
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
CVD	cardiovascular disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
Cys C	Cystatin C
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
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL-1β	interleukin-1 beta
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 681257	antisense inhibitor of apolipoprotein (a)
IV	intravenous(ly)
IXRS	interactive voice/internet response system
KIM-1	kidney injury molecule 1
kg	kilogram

STUDY GLOSSARY *Continued*

Abbreviation	Definition
L	liter
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MI	myocardial infarction
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
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OxPL	oxidized phospholipids
PAD	peripheral arterial disease
PBS	phosphate buffered saline
PCSK9	proprotein convertase subtilisin/kexin type 9
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLA_2	Lp(a)-associated Lp-phospholipase A_2
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

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
SC	subcutaneous(ly)
Study Drug	ISIS 681257 or placebo
SUSAR	suspected unexpected serious adverse reaction
Tg	transgenic
T_{max}	time to maximal concentration
UACR	urine albumin -creatinine ratio
ULN	upper limit of normal
UPCR	urine protein- creatinine ratio
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established cardiovascular disease (CVD).

1.2 Secondary Objective(s)

To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), oxidized phospholipids (OxPL) on apolipoprotein (a) [apo(a)] [OxPL-apo(a)] and OxPL on apoB (OxPL-apoB).

To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in in patients with hyperlipoproteinemia(a) and established CVD.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Lipoprotein (a)

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein (Figure 1, Koschinsky and Marcovina 2004) in which the apoB component of LDL is linked by a disulfide bond to apolipoprotein(a) [apo(a)], the distinct protein component of Lp(a) that is mainly responsible for its signature structural and functional properties (Dubé et al. 2012; Kronenberg and Utermann 2013). Lp(a) is now recognized as an independent, genetic, causal risk factor for coronary artery disease (CAD), stroke, peripheral arterial disease (PAD), and calcific aortic stenosis (Erquo et al. 2009; Nordestgaard et al. 2010; Thanassoulis et al. 2013).

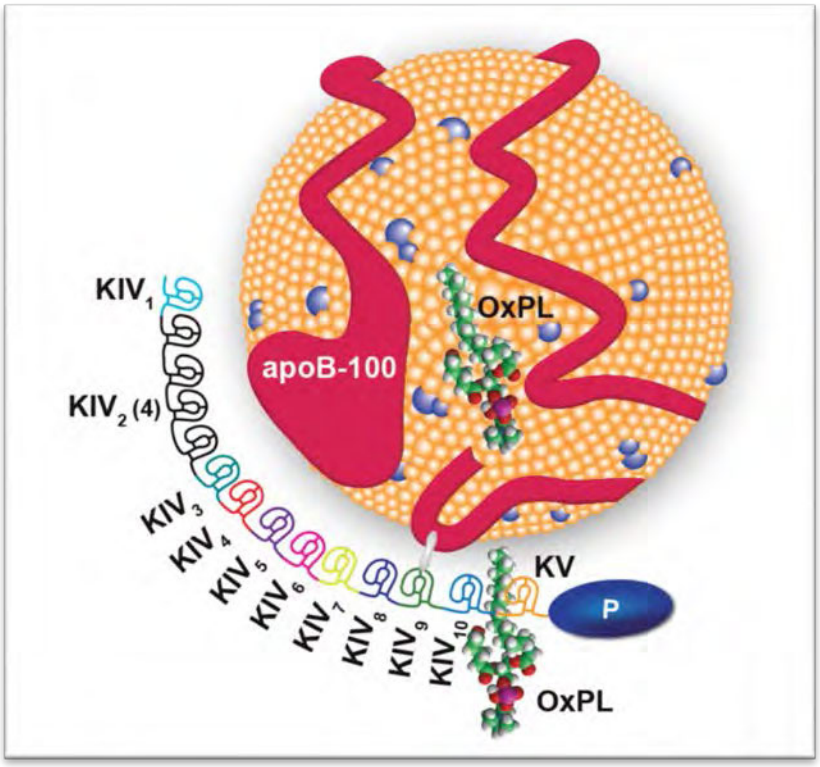


Figure 1 Schematic Representation of the Lp(a) Particle. Lp(a) is Composed of apo(a) Covalently Bound to apoB

Apo(a) contains 10 unique units of kringle IV repeats, of which KIV2 are present in variable copies (1 to > 40) conferring structural heterogeneity to Lp(a). Apo(a) also contains kringle V and an inactive protease-like (P) domain. In this model, 4 KIV2 repeats are shown. Lp(a) also contains OxPL in the lipid phase of apoB as well as covalently bound to apo(a).

Plasma levels of Lp(a) vary substantially among individuals, and most of this variation reflects the effects of genetic variation in the *LPA* gene which encodes the apo(a) protein.

A second contributor to plasma-level variability are LPA single nucleotide polymorphisms (SNPs) that can be associated with either higher or lower Lp(a) levels (Clarke et al. 2009; Li et al. 2011). Significant associations exist between 2 particular LPA variants, rs10455872 and rs3798220, increased Lp(a) levels, CVD, and aortic stenosis, with the CVD risk primarily mediated by Lp(a) plasma levels rather than an independent effect of the SNPs (Clarke et al. 2009; Li et al. 2011).

Lp(a) plasma levels are generally inversely associated with apo(a) size, and can vary by > 1,000-fold (0.1 to > 250 mg/dL or < 0.25 to > 625 nmol/L) between individuals (Merki et al. 2011). Despite this inter-individual variation, intra-individual Lp(a) levels are thought to be generally stable over time along a pre-set genetically determined levels without significant impact from dietary or environmental factors, mediating CVD risk throughout the patient's lifetime.

2.1.2 Pathophysiology

Lp(a) adheres to plaque sites and is retained in the artery wall and has proatherogenic and pro-inflammatory properties due to its LDL and apo(a) components (Spence and Koschinsky 2012). In addition, Lp(a) may be prothrombotic by inhibiting fibrinolysis because of its structural similarity to plasminogen and its enhancement of platelet aggregation (Rand et al. 1998). In vitro studies have provided evidence for both of these pathogenic mechanisms, but in vivo data are not definitive (Dubé et al. 2012). In humans, Lp(a) is the main lipoprotein carrier of OxPL, which may drive the risk associated with Lp(a) (Bergmark et al. 2008; Leibundgut et al. 2013; Tsimikas et al. 2014). In fact, OxPL measured on apoB (OxPL-apoB), which largely reflect the OxPL on Lp(a), have been shown to be a prognostic indicator for future CV events (Tsimikas et al. 2010; Tsimikas et al. 2012; Tsimikas et al. 2014). OxPL associated with Lp(a) can be subjected to degradation by the Lp(a)-associated Lp-phospholipase A2 (PLA2), implicating Lp(a) in novel proinflammatory and atherogenic pathways (Kiechl et al. 2007).

Hyperlipoproteinemia(a) in humans is associated with increased risk of cardiac death, myocardial infarction (MI), stroke, aortic stenosis, and peripheral arterial disease (PAD), particularly in subjects with small apo(a) isoforms (Bennett 2008; Erqou et al. 2009; Erqou et al. 2010; Bertoia et al. 2013; Thanassoulis et al. 2013). Although prospective, randomized, controlled outcomes studies have not been conducted, epidemiological, genome-wide association and Mendelian randomized controlled study data to date provide supporting evidence for a role of Lp(a) as a risk factor for CVD (Kamstrup et al. 2009). For example, in the Copenhagen City Heart Studies of 42,000 subjects with a 15-year follow-up (Kamstrup et al. 2009) using a Mendelian randomization approach, higher Lp(a) levels were related to risk of MI.

2.1.3 Current Treatment Options

In 2010, the European Atherosclerosis Society (EAS) Consensus Panel recommended screening for elevated Lp(a) in people at moderate to high risk of CVD to reach a treatment goal of < 50 mg/dL (125 nmol/L), after therapeutic management of LDL-C (Nordestgaard et al. 2010). Approximately 20% of people are estimated to have plasma Lp(a) levels over 50 mg/dL (125 nmol/L) and approximately 0.3% to have levels over 175 mg/dL (438 nmol/L). There are no gender differences in Lp(a) concentrations but racial differences have been observed, with whites and Asians having lower levels while blacks and Hispanics generally have somewhat higher levels (Nordestgaard et al. 2010).

Lifestyle and diet are thought to have little impact on an individual's Lp(a) level. Current treatment recommendations from the EAS Consensus Panel are limited to the use of 1 to 3 g of niacin (nicotinic acid) daily which could result in an up to 30% reduction in Lp(a). However, niacin is associated with side effects (e.g., flushing) that reduce patient tolerability and compliance (Parker et al. 2006; Guyton 2007).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are neither indicated nor formally recommended for treatment of hyperlipoproteinemia(a) but have been reported to reduce Lp(a) levels by ~20%-35% in patients with hypercholesterolemia (Desai et al. 2013; Raal et al. 2015).

The other current option for patients with significantly elevated Lp(a) levels (≥ 60 mg/dL) is lipoprotein apheresis, either general lipoprotein apheresis (Jaeger et al. 2009; Leebmann et al. 2013; Rosada et al. 2014) or Lp(a)-specific apheresis (Safarova 2012). While very effective at acutely lowering Lp(a) (acute

and interval Lp(a) reductions of > 60% and > 30% respectively), this treatment option is expensive, burdensome for patients, and unavailable/not reimbursed in many countries and regions.

2.2 Therapeutic Rationale

Therapeutic modalities to reduce Lp(a) levels in humans are few, and there are no drugs currently available that specifically target Lp(a) alone. Antisense oligonucleotides (ASOs) are emerging as viable therapeutic agents to treat disorders where overexpression of proteins is associated with a disease process. Apo(a) is synthesized primarily in the liver, a target organ for ASOs, where it is subsequently covalently linked to the apoB-100 component of LDL to form the Lp(a) lipoprotein. The goal of treatment with ISIS 681257 is to reduce the production of apo(a) in the liver and thus, the level of Lp(a) lipoprotein by using an ASO directed against the messenger ribonucleic acid (mRNA) of apo(a). It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse CVD by reducing thrombotic, atherogenic, or inflammatory events in patients with elevated Lp(a) levels (Nordestgaard et al. 2010).

Importantly, there is no evidence that lowering Lp(a) will result in adverse consequences in individuals, and there are no reports linking very low Lp(a) to any deleterious effects.

2.3 ISIS 681257

Please refer to the ISIS 681257 Investigator's Brochure for more details on ISIS 681257 mechanism of action, chemistry, pre-clinical and clinical experience. The summary is provided below.

2.3.1 Mechanism of Action

ISIS 681257 is a second-generation ASO drug targeted to apo(a) that has been covalently bonded to triantennary *N*-acetyl galactosamine ($GalNAc_3$), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-$GalNAc_3$ conjugate. This $GalNAc_3$-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold compared to unconjugated ASOs in mice (Prakash et al. 2014).

The ASO portion of ISIS 681257 is complementary to a region spanning the Exon 24-25 splice site at position 3901 of apo(a) transcript sequence (NM_005577.2) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 681257 to the cognate mRNA results in the Ribonuclease H1 (a non-specific endonuclease that catalyzes the cleavage of RNA via hydrolytic mechanism RNase H1-mediated degradation of the apo(a) mRNA, thus preventing production of the apo(a) protein). Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

ISIS 681257 does not have any complementary homology to plasminogen mRNA (Graham et al. 2016).

2.3.2 Chemistry

Chemically, ISIS 681257 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed

backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and further enhances potency of $GalNAc_3$ conjugated ASOs.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities, thereby resulting in an improved safety profile compared to first-generation antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 681257 employs this chimeric structure to enable use of the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). The fourth region is composed of a triantennary cluster of $GalNAc_3$ sugars that is linked to the 5′ end of ISIS 681257 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 681257 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the $GalNAc_3$ cluster is metabolized to release “free ASO” inside the cell (Prakash et al. 2014).

2.3.3 Preclinical Experience

The pharmacology of ISIS 681257 has been examined in apo(a) transgenic (Tg) mice which express the entire human apo(a) genomic sequence (Frazer et al. 1995) and nonhuman primates.

Administration of ISIS 681257, a human apo(a) antisense inhibitor, to mice containing the human apo(a) transgene produced dose-dependent reductions in human apo(a) liver mRNA and apo(a) plasma protein after 6 weeks of ASO administration at 0.3, 1, 3, and 10 mg/kg/wk.

When ISIS 681257 was administered to normal chow fed cynomolgus monkeys for 4 weeks at the dose of 12 mg/kg/wk, it significantly reduced hepatic apo(a) mRNA by 90% relative to the cohort administered phosphate buffered saline (PBS). As there is an 80% sequence conservation between apo(a) and plasminogen nucleotide sequences, plasminogen mRNA levels were also measured, and no change compared to the PBS cohort was observed.

Findings from the chronic studies with ISIS 681257 (the 26-week mice and 39-week monkey studies) were similar to those observed in the 4- and 6-week studies and were not considered adverse. The plasma and tissue concentrations observed for ISIS 681257 in mice and monkeys were generally similar to those observed for other unconjugated 20-mer 2′-MOE ASOs in this chemical class with and without $GalNAc_3$-conjugation. However, the proportion of drug in hepatocytes compare to nonparenchymal liver cells was greater for ISIS 681257, compared to the parent drug ISIS 494372 (without $GalNAc_3$-conjugation), which is the basis for increased potency of ISIS 681257 (unpublished results; Geary et al. 2003; Yu et al. 2007; Prakash et al. 2016).

The most noteworthy safety finding in the chronic monkey study was a marked platelet reduction that, occurred in 2 male monkeys in the high-dose group (20 mg/kg/wk) and 1 animal (1 female) in the mid-dose (10 mg/kg/wk) group beginning on Days 44-135, which led to the subsequent early termination (ET) of these 3 animals. An additional male monkey in the 10 mg/kg/wk dose group had a moderate decrease in platelets that was successfully treated with steroid, and was terminated at the scheduled 6-month interim sacrifice. There were no platelet reductions or other toxicologically significant findings in monkeys treated with 2 mg/kg/wk for up to 39 weeks. There were no marked platelet reductions in mice at doses up to 70 mg/kg/wk for 26 weeks. However, mice exposed to ISIS 681257 at doses of ≥ 10 mg/kg/wk for up to 26 weeks showed evidence of hepatobiliary effects in both sexes as indicated by increases in ALT (up to + 10.3x), AST (up to + 10.4x), and/or ALP (+ 2.5x).

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 681257 can be found in the Investigator's Brochure. A summary of the study that has been conducted with ISIS 681257 is included below.

ISIS 681257-CS1 was a Phase 1 double-blind, placebo-controlled, dose-escalation study designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple doses of ISIS 681257 administered subcutaneously (SC) to 45 healthy subjects with Lp(a) ≥ the upper limit of normal (ULN) (30 mg/dL). Twenty one (21) subjects received 10 to 120 mg SC (10, 20, 40, 80, and 120 mg) as a single-dose, and 24 subjects received 10, 20, and 40 mg as multiple doses (6 doses in 21 days: 3 loading doses during the first week on alternate days (Days 1, 3, and 5), and then once a week for the next 3 weeks (Days 8, 15, and 22).

There were no serious adverse events (SAEs), or clinically-relevant changes in laboratory assessments and all subjects completed the treatment and post-treatment follow-up periods.

Constitutional symptoms such as fever, chills, increase in body temperature and arthralgias have been observed following parenteral administration of ASOs, primarily during the initial dosing period. Following SC administration of ISIS 681257 constitutional symptoms were observed in 4 of the 6 subjects who received a single-dose of 120 mg. The symptoms were mild in severity and resolved spontaneously with or without treatment with acetaminophen.

Fluctuations in platelet counts to below the lower limit of normal were observed in 5 study subjects on active drug and across doses. These changes were not considered adverse or clinically-significant by the Investigator and did not appear to be dose related.

Two (2) mild AEs of redness at the site of injection occurred 48 to 72 hours after administration in 1 subject who received ISIS 681257 in the 20 mg multiple-dose cohort. Both AEs resolved by the time of the subject's next visit.

Following SC administration, ISIS 681257 was absorbed rapidly into the systemic circulation, with median time to maximum plasma concentrations (T_{max}) ranging from 1 to 4 hours. Similar T_{max} values were observed at all dose levels. Maximum observed plasma concentrations (C_{max}) and $AUC_{0\text{-}24hr}$ were dose-dependent over the studied SC dose range. The mean peak (C_{max}) and total exposure ($AUC_{0\text{-}24hr}$)

increased proportionally with dose at dose levels ranging from 10 to 40 mg, and greater than dose proportionally at dose levels ranging from 40 to 120 mg.

After reaching C_{max}, mean plasma concentrations of ISIS 681257 declined in a biphasic fashion over time, with an initial, relatively fast distribution phase that dominated the plasma clearance followed by a slower elimination phase. Characterization of the terminal elimination phase yielded an apparent terminal elimination half-life of approximately 3 to 4 weeks over a dose range of 10 to 120 mg (either single- or multiple-dose), and appeared to be independent of dose. This result is consistent with the slow elimination of ISIS 681257 observed from monkey tissues, and the comparatively long elimination half-lives observed for this chemical class.

Plasma trough concentrations (168 hours or 7 days from previous dose) monitored during the treatment period in the multiple-dose cohorts increased with increasing dose, consistent with expectations (based on preclinical assessments and experience with other compounds of this chemical class) that trough plasma concentrations reflect exposure in tissues. Plasma trough concentrations did not increase greatly after the loading period (Day 15), suggesting that accumulation in major tissues of distribution had approached steady-state after the loading period.

Overall, the human PK of ISIS 681257 are consistent with the expected PK for compounds within this chemical class.

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a).

The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) $\leq$ 30 mg/dL).

The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio (225 ISIS 681257 and 45 placebo) to receive ISIS 681257 or placebo. Study Drug (ISIS 681257 or placebo) will be administered SC every week, every 2 weeks (biweekly), 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.

The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy analysis (to evaluate whether the treatment effect is maintained) and safety analysis (for the purpose of dose(s) selection) will be repeated at the completion of Study Drug treatment.

The treatment portion of the study will be complete when the last patient reaches 6 months of exposure. All patients will then enter a 16-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.

Patients ≥ 18 and ≤ 80 years old with elevated plasma Lp(a) levels (≥ 60 mg/dL) and a clinical diagnosis of CVD are eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for other than elevated Lp(a) 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 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). 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 5 parallel dosing cohorts, with each cohort having a 5:1 ratio to receive ISIS 681257 or matching volume of placebo, respectively, by SC injection for up to 52 weeks.

Following the End-of-Treatment, patients will enter the 16-week post-treatment follow-up period.

3.2 Number of Study Centers

This is a multicenter, multinational study.

3.3 Number of Patients

Approximately 270 patients will be randomized in this study, with approximately 54 patients assigned to each of the 5 treatment cohorts.

3.4 Overall Study Duration and Follow-up

The length of patients' participation in the study may be up to 18 months (72 weeks), which includes a 4-week screening period, an up to 52-week treatment period with Study Drug (ISIS 681257 or placebo), and a 16-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 maximum is 52 weeks.

All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may 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. 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 E), 2 weeks post last dose for every 2-week dosing (Cohort D), and 4 weeks post last dose for every 4-week dosing (Cohort A-C). 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 16-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 681257 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 16-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits 4, 10, and 16 weeks after the treatment period as per Appendix A (Follow-up).

The final study visit for each patient will be 16 weeks after the treatment period.

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 681257 during this study. The DSMB will be constituted to include expertise in medical specialties relevant to the safety of antisense drugs (nephrology, hepatology, hematology and cardiology). Specialist members of the DSMB will be informed and consulted on all treatment-related SAEs relevant to their expertise and all changes of relevant laboratory parameters that trigger stopping rules (Section 8.6), within 24 hours of receipt of such results. In addition, all accrued safety data relevant to each of medical area specialist will be forwarded monthly for review.

The full DSMB review of all accumulated data will be performed quarterly. Based on its ongoing assessment of the safety and tolerability of ISIS 681257, 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 1:1:1:1:1 ratio to 1 of the 5 parallel-dose cohorts (Cohorts A, B, C, D, or E). Within each dose cohort, patients will be randomized in a 5:1 ratio to receive ISIS 681257 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 a 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 at within 4 weeks of Study Day 1or 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. Clinical diagnosis of CVD defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease
4. Lp(a) plasma level ≥ 60 mg/dL
5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors
6. 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, proprotein convertase subtilisin/kexin type 9 [PCSK9s] 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
7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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

8. 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 16 weeks after the last dose of ISIS 681257

5.2 Exclusion Criteria

1. Within 6 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 New York Heart Association (NYHA) class 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 with a history of major bleed or high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Known history or presence of systemic allergic or pseudoallergic (drug) reactions

13. Hypersensitivity to the active substance or to any of the excipients
14. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
    a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr
    b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr
    c. Estimated GFR < 60 mL/min (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance
    d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN
    e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
    f. Alkaline phosphatase (ALP) > ULN
    g. Platelet count < LLN
15. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors
16. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
17. Treatment with any 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
18. BMI > 40 kg/m^2
19. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
21. 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. A 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.

On confirmation of eligibility and prior to randomization, patients will also undergo a 24 hr urine collection for creatinine, albumin, and protein as a baseline assessment.

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 20 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 49 weeks in Cohort A, 40 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 49 weeks in Cohort B, 60 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 49 weeks in Cohort C, 20 mg doses of Study Drug administered by SC injection once every 2 weeks for up to 51 weeks in Cohort D, or 20 mg doses of Study Drug administered by SC injection once per week (weekly) for up to 52 weeks in Cohort E (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 681257 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 12 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 681257. 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 16 weeks after the treatment period. During the post-treatment follow-up period, patients will return to the Study Center for 3 outpatient visits at Weeks 4, 10, and 16 after the treatment period 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 (excluding 24-hour urine collection) should be taken after fasting for at least 10 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status. 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. 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 and sent to the central laboratory for analysis, per Section 8.5.2. If there are no test results available within 14 days of the last set of results for parameters considered critical to patient safety, the Investigator will contact the patient to hold dosing until a new test set is obtained and reviewed.

While on treatment liver function testing will also be collected every 14 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 sent to the central laboratory are received on the next day 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 on the day of sample collection, 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 24 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/mm3 (Grade 3 or

Grade 4) 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 24 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 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, B, and C at Weeks 5, 13, 21, 25, 33, 41, 49, and 53
- Cohorts D and E at Weeks 5, 13, 21, 27, 33, 41, 49, and 53

In all cohorts, ECGs will be conducted during the post-treatment follow-up period at 4, 10, and 16 weeks after the treatment period.

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 681257 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 16 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 16 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 before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 681257 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 681257 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 681257

ISIS 681257 vials contains 100 mg/mL ISIS 681257 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 681257 vials.

Table 1 Study Drug Characteristics

Study Drug	ISIS 681257	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 681257 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 681257 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 681257 will be administered to patients by Study Center staff as follows:

Cohort A: a single SC dose of 20 mg once every 4 weeks for up to 49 weeks and a maximum of 13 doses

Cohort B: a single SC dose of 40 mg once every 4 weeks for up to 49 weeks and a maximum of 13 doses

Cohort C: a single SC dose of 60 mg once every 4 weeks for up to 49 weeks and a maximum of 13 doses

Cohort D: a single SC dose of 20 mg every 2 weeks for up to 51 weeks and a maximum of 26 doses

Cohort E: a single SC dose of 20 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, B, and C should receive 1 dose every 4 weeks, patients in Cohort D should receive 1 dose every 2 weeks and Cohort E 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 681257 or placebo) preparation and administration.

Table 2 Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 681257
A	20 mg ISIS 681257 or placebo (Every 4 weeks)	0.2 mL	≤ 13	≤ 260 mg
B	40 mg ISIS 681257 or placebo (Every 4 weeks)	0.4 mL	≤ 13	≤ 520 mg
C	60 mg ISIS 681257 or placebo (Every 4 weeks)	0.6 mL	≤ 13	≤ 780 mg
D	20 mg ISIS 681257 or placebo (Every 2 weeks)	0.2 mL	≤ 26	≤ 520 mg
E	20 mg ISIS 681257 or placebo (Every week)	0.2 mL	≤ 52	≤ 1040 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

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 681257 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, patients must not be re-dosed 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 681257 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 2 weeks for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period.

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 24 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 (within 24 hours of receipt) reviewed by the Investigator and Medical Monitors.

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 2 weeks throughout the study. Upon completion of the study treatment period, urine renal biomarkers should be monitored every 2 weeks for the first 6 weeks and then at 10 and 16 weeks post treatment period (as per visit schedule).

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 to estimate glomerular filtration rate (eGFR), which will be monitored every 2 weeks. In addition, biomarkers of acute renal injury will also be measured every 2 weeks (Appendix B).

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than every 2 weeks 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 at the weekly safety review by the Medical Monitor.

All results of renal function tests must be reviewed promptly (within 24 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: Creatinine clearance (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 an 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.

In the event of a confirmed (as described in Section 8.5) laboratory result meeting one or more of the above criteria, dosing with the Study Drug should be interrupted and the Study Medical Monitor informed. In addition, the following supplemental renal tests should be immediately obtained:

> Serum creatinine, urine culture, 24-hour urine sample for creatinine clearance, urine albumin and urine protein, urine microscopy sample with inspection of sediment.

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.

8.5.3 Safety Monitoring for Platelet Count Results

All patients will have platelet counts monitored every 2 weeks for the duration of the study treatment period and must not receive Study Drug without an interpretable platelet count result in the prior 2 weeks.

Upon completion of the study treatment period, platelets should be monitored every 2 weeks for the first 6 weeks and then at 10 and 16 weeks post treatment period (as per visit schedule). In addition, platelet function will be evaluated by aggregometry, using an approved point-of-care diagnostic device, in all patients at each study site visit; additional functional testing may be performed at selected study centers.

As described in Section 6.2.1, all platelet count results must be reviewed promptly (within 24 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.

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm^3; 2) when platelet count is ≥ 30% decreased from baseline, or 3) when 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 Minor Bleeding Events

Patients will be instructed to promptly report any signs or symptoms of bleeding. Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, or gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, hepatic enzymes, bilirubin and platelet count should be performed.

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 symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.6 Stopping Rules

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 of an estimated creatinine clearance (by CKD-EPI formula) meeting any of the following criteria, or any change in renal biomarkers deemed by the nephrologist on the DSMB to require further evaluation, a serum creatinine, urine culture, 24-hour urine sample for creatinine clearance and protein, and urine microscopy sample with inspection of sediment should be immediately obtained:

1. CKD-EPI decrease of > 40% from Baseline
2. CKD-EPI value < 45 mL/min/1.73 m^2

Dosing of a patient with Study Drug (ISIS 681257 or placebo) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

1. Urine protein is > 1.0 g
2. Creatinine clearance decrease of > 40% from baseline
3. Creatinine clearance < 45 mL/min/1.73 m^2

Irrespective of whether the stopping rule is confirmed or not, 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

Stopping Rules 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 steroids 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 steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days
(**note:** may require continuation with oral steroids 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; Schulman et al. 2005), 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.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)

5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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 2 weeks
≥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 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 weeks For Cohort E: reduce to 10 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 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 week For Cohort E: reduce to 10 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)/ anticoagulant medication
≥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/anticoagulant medication while platelet count < 50K/mm^3 if possible

Platelet Count on Rx	Drug Dose	Monitoring
< 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 and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* 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 steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: 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 Section 8.6.3 and 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 8.6.3
- 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 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 treatment period. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), platelets should be tested 10 and 16 weeks post 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 16-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 16 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, PCSK9 inhibitors, niacin, fibrates, fish oil, other products containing omega-3 fatty acids (including OTC preparations)
- Anti-platelet therapies
- Testosterone, estrogens, progesterone, growth hormone, or progestins.

Disallowed Concomitant Therapy

Use of the following is disallowed:

- Warfarin, 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 of platelet count, and liver and renal function as described in Section 6.2.1, Sections 8.5.1-8.5.3, and Sections 8.6.1-8.6.3.

While on treatment patients will be required to have platelet counts every 2 weeks 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 2 weeks, and must not receive Study Drug if there are no test results for parameters considered critical to patient safety available within the prior 2 weeks. 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 (Grade 3 or Grade 4), 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. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. 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 681257 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 681257 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 681257 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 681257 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 24 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 as per Sections 9.3.3.1 and 9.4.1).

All results of liver function tests must be reviewed promptly (within 24 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 24 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 681257 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 681257 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-C) and at Week 27 for patients who received weekly or biweekly dosing (Cohorts D and E). 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 endpoint is the percent change in Lp(a) from baseline at the primary analysis time point achieved by ISIS 681257 compared to pooled placebo.

Lp(a) levels will be analyzed from patient blood samples taken at specified time points throughout the study.

10.1.2 Secondary Endpoints

The secondary endpoints include the following parameters from baseline at the primary analysis time point for ISIS 681257 compared to placebo:

- Percent change from baseline in LDL-C
- Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL (≤ 125 nmol/L)
- Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL (≤ 75 nmol/L)
- Percent change from baseline in apoB
- Percent change from baseline in OxPL-apo(a)
- Percent change from baseline in OxPL-apoB

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
- 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 clinically-meaningful reduction in plasma Lp(a) 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, and renal or hepatic injury.

10.2 Sample Size Considerations

Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients.

Based upon prior clinical trial experience with Ionis ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event.

Therefore, approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.

10.3 Analysis Populations

Full Analysis Set (FAS): All patients who are randomized, received at least 1 dose of Study Drug (ISIS 681257 or placebo), and have a Baseline Lp(a) 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, B, and C or at least 11 biweekly doses for patients randomized in Cohort D or at least 22 weekly doses for patients randomized in Cohort E, 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 Study Drug, and have sufficient data for the analysis of PK parameters. This population will be used for analysis of PK data.

10.4 Definition of Baseline

Baseline for Lp(a), LDL-C, apoB, OxPL-apo(a), OxPL-apoB, and other lipid measurements will be defined the pre-dose measurement on Day 1 or 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 681257 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 681257 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 681257 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 analysis of the primary endpoint will be the pairwise comparison of percent change from baseline to primary analysis time point in fasting Lp(a) between ISIS 681257 treatment groups and pooled placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the Baseline Lp(a) 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 LDL-C will be compared between each ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate

- Proportion of patients who achieve ≤ 50 mg/dL (≤ 125 nmol/L) in fasting Lp(a) at the primary analysis time point will be compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with Baseline Lp(a) as a covariate. Proportion of patients who achieve ≤ 30 mg/dL (≤ 75 nmol/L) in fasting Lp(a) at the primary analysis time point will be analyzed similarly
- Percent change from baseline at the primary analysis time point in fasting apoB, OxPL-apo(a) and OxPL-apoB will be compared between ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate

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 681257 in plasma (as total full length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 681257) will be determined and summarized by treatment with stratification by subject immunogenicity status using descriptive statistics.

In addition, non-compartmental PK analysis of ISIS 681257 concentrations will be carried out on each individual patient data set in patients who received ISIS 681257 treatment, and the plasma disposition half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate, using available data at the End-of-Treatment and the post-treatment follow-up period from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, where λz is the rate constant associated with the apparent terminal elimination phase.

For patients in the PK subgroup only, non-compartmental PK analysis of ISIS 681257 will be carried out on each individual patient data set in patients who received ISIS 681257 treatment. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Following single dosing (Day 1), area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours after the dose ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Following multiple dosing, $AUC_{0\text{-}24hr}$ and area under the plasma concentration-time curve during the time of each sampled dosing interval (tau,τ) at steady-state (AUC_{τ}) will be calculated using the linear trapezoidal rule.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Plasma PK parameters will be summarized using descriptive statistics with stratification by subject immunogenicity status. Exposure-response relationships between selected PD [e.g., Lp(a)] and PK measures (including but may not be limited to plasma trough concentrations) may be explored (including with and without stratification by IM status) in this study, or in a separate population PK analysis with all clinical studies combined.

The immunogenicity (IM) of ISIS 681257 will be assessed before, during, and after treatment with Study Drug (ISIS 681257 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 681257 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 681257 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.

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27[p]**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Treatment Period**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
12- lead ECG (triplicate)	X	X		X		X		X		X				X		X		X	X	X	X	X
24-Hour Urine for Creatinine Clearance and Protein	X																					
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																		X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																		X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																		X	X	X
Genetic Testing (optional)		X																				
Chemistry Panel [j,k]	X	EVERY 14 DAYS [f]				X	X	X	X				X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																		X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Coagulation	X	X								X												
Hepatitis B, C, HIV	X																					
Thyroid Panel	X																					
hsCRP		X								X									X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X	X[3]	X[1]	X[2]	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X				X									X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27[p]**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Treatment Period**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
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
Archived Serum & Plasma Samples [j, n]		X			X		X			X					X		X		X	X	X	X
PD Panel [j]	X	X		X	X	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
Lp(a) Characterization		X																				
Study Drug: SC Injection		WEEKLY SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 52/Day 358)[o] EVERY 2-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 51/Day 351)[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
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks post treatment period, then at Week 10 and Week 16 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.

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

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 24 hours of receipt) by the Investigator as per Section 6.2.1. 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 16-week post-treatment follow-up period.

p For the last patient to reach 6 months of exposure ONLY, the Week 27 visit will count as the End of Treatment Visit, therefore all Week 53/ET assessments will be included in this visit. No dose will be administered at this visit.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8 hours post SC injection

Appendix A Schedule of Procedures – Every 4-Week Dosing

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25[p]**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Treatment Period**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
Physical Examination	X	X		X		X		X	X						X		X		X	X	X	X	X
Body Weight and Height [d]	X								X								X						X
12- lead ECG (triplicate)	X	X		X		X		X	X						X		X		X	X	X	X	X
24-hour Urine for Creatinine Clearance and Protein	X																						
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																			X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																			X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																			X	X	X
Genetic Testing (optional)		X																					
Chemistry Panel [j, k]	X	EVERY 14 DAYS [f]					X	X	X					X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																			X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X														
Hepatitis B, C, HIV	X																						
Thyroid Panel	X																						
hsCRP		X							X											X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X[3]	X[1]	X[2]	X	X	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X			X											X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25[p]**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Treatment Period**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
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
Archived Serum & Plasma Samples [j, n]		X			X		X		X					X		X		X		X	X	X	X
PD Panel [j]	X	X		X	X	X	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	X
Lp(a) Characterization		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
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

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks post treatment period, then at Week 10 and Week 16 Follow-up visits.

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

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 24 hours of receipt) by the Investigator as per Section 6.2.1. 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 16-week post-treatment follow-up period.

p For the last patient to reach 6 months of exposure ONLY, the Week 25 visit will count as the End of Treatment Visit, therefore all Week 53/ET assessments will be included in this visit. No dose will be administered at this visit.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8, hrs post SC injection

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 681257 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
- Free T3

Coagulation
- aPTT
- PT
- INR
- Fibrinogen
- Plasminogen

PD Panel
- Lp(a)
- OxPL-apoB
- OxPL-apo(a)

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL

Lp(a) Characterization
- Apo(a) isoforms

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 681257 (total full length ASO) levels in plasma

Immunogenicity
- Anti-ISIS 681257 antibodies

Genetic Testing
- LPA SNPs associated with elevated Lp(a)

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

24 Hour Urine Test[3]
- Creatinine clearance
- Protein
- Albumin

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 681257 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.

3 To be performed during Screening upon confirmation of eligibility

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 681257 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 681257 with plasma constituents. Extensive PK samples will be collected in PK subgroup only (12 subjects 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**	**27**			**29**	**37**	**53/ET**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184**	**185**	**197**	**253**	**365**	***Post Treatment Period**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime
PK Sub-group Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	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	Pre-dose	Anytime	Anytime	Anytime	Anytime

1 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

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**	**25**			**26**	**27**	**29**	**37**	**53/ET**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**170**	**171**	**176**	**183**	**197**	**253**	**365**	***Post Treatment Period**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose,	NA	NA	NA	NA	NA	Pre-dose	Pre-dose	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	Pre-dose, 1, 2, 4, and 8-hr[1]	24-hr[2]	48-hr[3]	Anytime	Anytime	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime

1 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

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/mm^{3*}

*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
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
Platelet Antibody Bead Array (PABA)

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

Collaborator:
Akcea Therapeutics
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IONIS PHARMACEUTICALS, INC.

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 5 – 30 May 2017

EudraCT No: 2016-003373-18

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 5 – 30 May 2017

Protocol History:

Original Protocol:	15 August 2016
Protocol Amendment 1:	12 October 2016
Protocol Amendment 2:	29 November 2016
Protocol Amendment 3:	30 December 2016
Protocol Amendment 4:	5 January 2017

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ISIS 681257-CS6

Ionis Protocol Number ISIS 681257-CS6

Protocol Amendment 5

EudraCT No: 2016-003373-18

Clinical Phase: 2

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

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Mobile: [redacted]
E-mail: [redacted]

Date: 30 May 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment: Amendment 5

Date: 30 May 2017

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 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)," dated 30 May 2017, 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.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENTS

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 5

Amendment Date: 30 May 2017

The following table summarizes the history and nature of amendments to the protocol ISIS 681257-CS6.

None of the antecedent versions of the study protocol has been enacted clinically and therefore no patients have been enrolled prior to issuance of Amendment 5.

Protocol Version	Date	Rationale for Amendments
Original Protocol	15 August 2016	
Amendment 1	6 October 2016	Regulatory advice on inclusion of more detailed description of processes for platelet monitoring, and more frequent monitoring of liver function.
Amendment 2	29 November 2016	Regulatory advice on inclusion of biomarkers of renal damage and increased frequency of renal monitoring. Addition of a DSMB.
Amendment 3	30 December 2016	Adjustment of the frequency, and alert and intervention limits, for renal safety and adjustment of the frequency of liver safety testing.
Amendment 4	5 January 2017	The study population was increased to 270 patients (54 per cohort) to support a statistical assessment of risk of platelet reduction in this population. In addition, the 10 mg weekly treatment cohort has been modified to 20 mg every 2 weeks (biweekly).
Amendment 5	30 May 2017	Regulatory advice on addition of exclusion criteria, reduced permitted timeframe for identifying critical laboratory results by the investigator and replacement of the AE definition. In addition, Section 8.6.2 was edited for consistency.

PROTOCOL SUMMARY OF CHANGES

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 5

Amendment Date: 30 May 2017

The following modifications to Protocol ISIS 681257-CS6 Amendment 4 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 Amendment 4 of the protocol:

Protocol Section	Description of Change	Rationale
Protocol Synopsis (Exclusion Criteria), 5.2 Exclusion Criteria	Addition of new exclusion criteria, placed at Exclusion Number 12 and 13, and shifting subsequent exclusion criteria to sequentially increased number.	Adding exclusion criteria to exclude patients with known allergic or pseudo allergic drug reactions and those with hypersensitivity to the active drug substance.
Protocol Synopsis (Efficacy Evaluations), 10.1.2 Secondary Endpoints, 10.6.3.2 Analysis of Secondary Efficacy Endpoints	Provided Lp(a) values in additional alternate unit of measure	Laboratories will measure and report Lp(a) values in either mg/dL or nmol/L, so both units will be provided in protocol for clarity. Efficacy data will be provided only in nmol/L.
6.2.1 Laboratory Assessments 8.5.1 Safety Monitoring Rules for Liver Chemistry Tests, 8.5.2 Safety Monitoring for Renal Function, 8.5.3 Safety Monitoring for Platelet Count Results	Revision of window allowed for review of key safety laboratory results to within 24 hours by Investigator or designee.	To ensure more timely review of key safety laboratory results while patients are on Study Drug.

Protocol Section	Description of Change	Rationale
6.2.1 Laboratory Assessments, 9.3.3.1 Adverse Events of Special Interest	Adding additional AE of special interest – when patient meets renal stopping rules.	To enhance importance of strict monitoring of renal function.
6.3.1 Contraception Requirements	To clarify acceptable use of contraception methods.	Clarification.
8.5.2 Safety Monitoring for Renal Function, 8.5.3 Safety Monitoring for Platelet Count Results, 8.8.1 Follow-up Visits for Early Termination from Treatment Period or from Post-Treatment Follow-up Period	Addition of text to clarify frequency and timing of assessments and platelet monitoring and urine renal biomarkers in post Treatment Follow-up period to be consistent with the landmark study visits after Study Drug dosing has ended.	Clarification of time points for platelet monitoring post last Study Drug dose.
8.6.2 Stopping Rules for Renal Function Test Results	Addition of urine culture and urine microscopic sample inspection to follow-up testing for renal stopping rules	Additional laboratory tests added for analysis of renal function to match follow-up testing for renal monitoring and stopping rules.
8.8.1 Follow-up Visits for Early Termination from Treatment Period or from Post-Treatment Follow-up Period	Clarification for timing of final visit assessment for treatment period and final visit for follow-up period for patients who discontinue early from treatment or during the post-treatment follow-up period.	Clarification.
9.3.2 Adverse Reaction and Unexpected Adverse Reaction	Correction of definition of Adverse Drug Reaction and adding definition of Unexpected Adverse Reaction.	Clarification of definition to be consistent with ICH.

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)
Study Phase	2
Indication	Patients with hyperlipoproteinemia(a) and established CVD.
Investigational Drug	ISIS 681257 is a second generation 2'-MOE modified, $GalNAc_3$–conjugated antisense oligonucleotide inhibitor of apolipoprotein (a) [apo(a)].
Primary Objective	To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.
Secondary Objective(s)	To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B100 (apoB), oxidized phospholipids (OxPL) on apo(a) [OxPL-apo(a)], and OxPL on apoB (OxPL-apoB). To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in patients with hyperlipoproteinemia(a) and established CVD.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio to receive ISIS 681257 or placebo. This number was chosen to provide statistical power for both efficacy and safety assessments. Study Drug (ISIS 681257 or placebo) will be administered SC 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 enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period. The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, 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 (as needed) data collected on ISIS 681257 during this study, both individual events and aggregate data.
Number of Subjects	Approximately 270
Study Population	<u>Inclusion Criteria</u> 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. Clinical diagnosis of CVD defined as documented coronary artery disease, stroke, or peripheral artery disease 4. Lp(a) plasma level ≥ 60 mg/dL 5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Inclusion Criteria 6. 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 7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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 8. 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 16 weeks after the last dose of ISIS 681257 Exclusion Criteria 1. Within 6 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 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

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria 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 with a history of major bleed or high-risk of bleeding diathesis 11. Recent history of, or current drug or alcohol abuse 12. Known history or presence of systemic allergic or pseudoallergic (drug) reactions 13. Hypersensitivity to the active substance or to any of the excipients 14. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following: a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr c. Estimated GFR < 60 mL/min as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL f. Alkaline phosphatase (ALP) > ULN g. Platelet count < LLN 15. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors 16. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 17. Treatment with any 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 18. BMI > 40 kg/m^2 19. Blood donation of 50-499 mL within 30 days of screening or of > 499 mL within 8 weeks of Screening 20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 21. 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

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Treatment Groups</td><td>Patients will be randomized to 5 parallel cohorts:

Cohort A (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort B (n = 54): Patients will be randomized 5:1 to receive 40 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort C (n = 54): Patients will be randomized 5:1 to receive 60 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort D (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every 2 weeks for up to 26 doses.

Cohort E (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every week for up to 52 doses.

<table>
<tr><th>Cohort</th><th>Treatment</th><th># Doses</th><th>Total ISIS 681257</th></tr>
<tr><td>A</td><td>20 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 260 mg</td></tr>
<tr><td>B</td><td>40 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 520 mg</td></tr>
<tr><td>C</td><td>60 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 780 mg</td></tr>
<tr><td>D</td><td>20 mg ISIS 681257 or placebo (Every 2 weeks)</td><td>≤ 26</td><td>≤ 520 mg</td></tr>
<tr><td>E</td><td>20 mg ISIS 681257 or placebo (Every week)</td><td>≤ 52</td><td>≤ 1040 mg</td></tr>
</table>
</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>The Sponsor will provide ISIS 681257 in a concentration of 100 mg/mL and matching volume placebo:

Cohort A: 20 mg every 4 weeks ISIS 681257 or placebo (0.2 mL)

Cohort B: 40 mg every 4 weeks ISIS 681257 or placebo (0.4 mL)

Cohort C: 60 mg every 4 weeks ISIS 681257 or placebo (0.6 mL)

Cohort D: 20 mg every 2 weeks ISIS 681257 or placebo (0.2 mL)

Cohort E: 20 mg every week ISIS 681257 or placebo (0.2 mL)

All doses will be given by SC injection. Self-administration will be allowed after appropriate training of patient and/or caregiver.</td></tr>
<tr><td>Rationale for Dose and Schedule Selection</td><td>The Phase 1 program evaluated ISIS 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a). The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) ≤ 30 mg/dL).</td></tr>
</table>

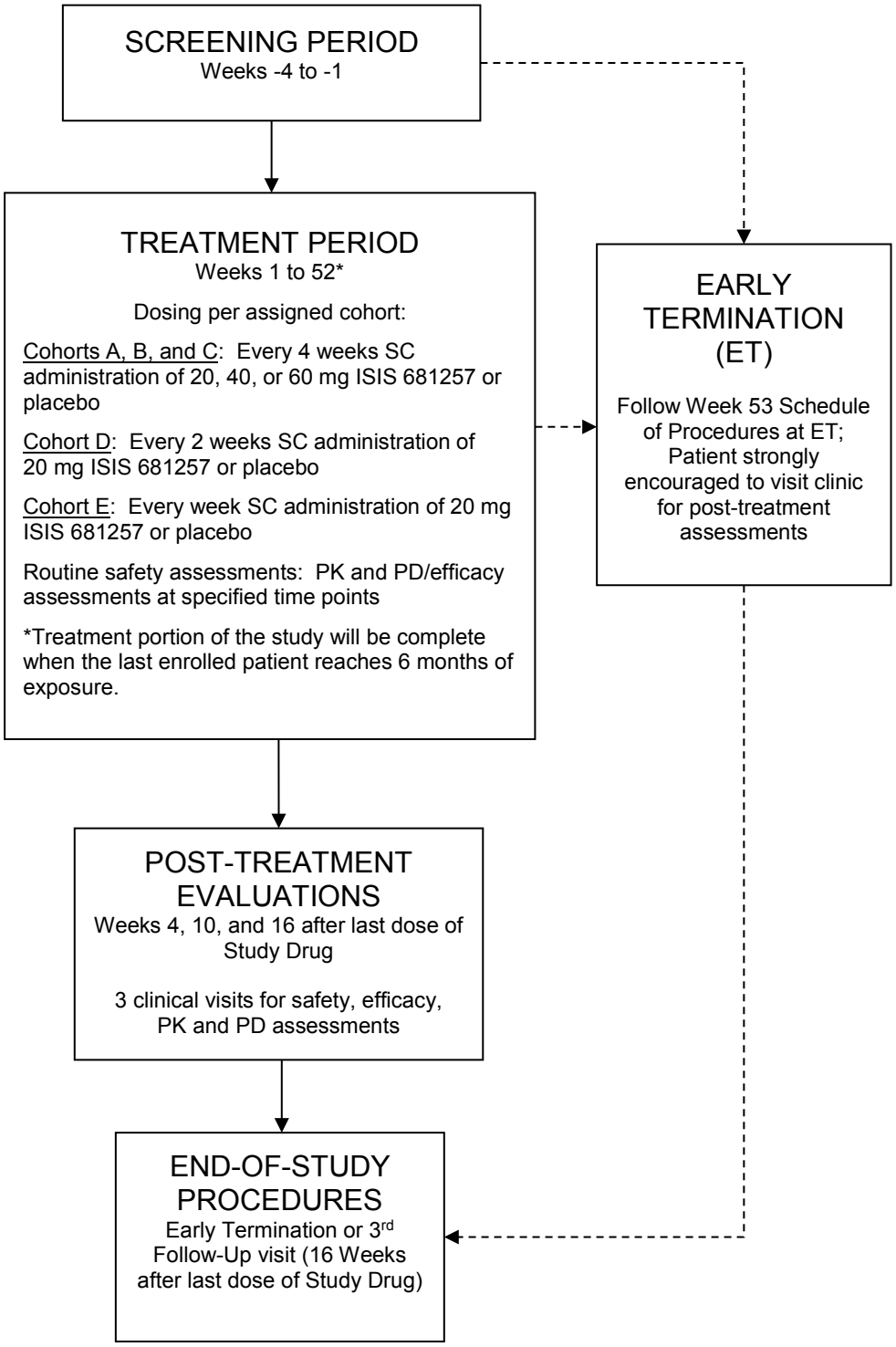
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection ***Continued***	The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.
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 are outlined in Section 6, Appendices A and C. All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may continue treatment within the same randomized cohort until the last enrolled patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. The study for an individual patient will generally consist of the following periods: • An up to 4-week screening period • An up to 52-week treatment period during which Study Drug will be administered per assigned cohort by SC injection • A 16-week post-treatment follow-up period Patients in Cohorts A through C will receive up to 13 SC doses of ISIS 681257 or placebo every 4 weeks. Patients in Cohort D will receive up to 26 SC doses of ISIS 681257 or placebo every 2 weeks and patients in Cohort E will receive up to 52 SC doses of ISIS 681257 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). 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 and use of concomitant medications. Safety and tolerability results in patients dosed with ISIS 681257 will be compared with those dosed with placebo.
Efficacy Evaluations	The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). The primary endpoint is the percent change in plasma Lp(a) from baseline at the primary analysis time point for ISIS 681257 treatment groups compared to placebo. The secondary endpoints comprise the effect of ISIS 681257 as compared to placebo at the primary analysis time point on the following: • Percent change from baseline in LDL-C • Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL (≤ 125 nmol/L) • Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL (≤ 75 nmol/L) • Percent change from baseline in apoB • Percent change from baseline in OxPL-apo(a) • Percent change from baseline in OxPL-apoB

PROTOCOL SYNOPSIS *Continued*

Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 681257 plasma trough levels throughout treatment and during the post-treatment follow-up period. In addition, in a subset of patients (approximately 12 patients per cohort), more frequent plasma samples will be taken following the first and Day 169 (for Cohorts A, B, and C) or Day 183 (for Cohorts D and E) dose to determine PK parameters. Plasma sample collection time points are detailed in Appendices A and C. The plasma ISIS 681257 levels over time will be descriptively summarized by treatment with stratification by subject immunogenicity status. Apparent terminal elimination half-life will be calculated in patients who received ISIS 681257 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 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 Lp(a) between ISIS 681257 treated groups and placebo group in the Full Analysis Set. The data will be analyzed using an ANCOVA model with the baseline Lp(a) 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 plasma Lp(a) 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. Sample Size Considerations: <u>Efficacy:</u> Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients. <u>Safety:</u> Based upon prior clinical trial experience with ISIS ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event. A total of approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.
Sponsor/Collaborator	Ionis Pharmaceuticals/Akcea Therapeutics

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
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
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
CVD	cardiovascular disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
Cys C	Cystatin C
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
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL-1β	interleukin-1 beta
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 681257	antisense inhibitor of apolipoprotein (a)
IV	intravenous(ly)
IXRS	interactive voice/internet response system
KIM-1	kidney injury molecule 1
kg	kilogram

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
L	liter
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MI	myocardial infarction
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
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OxPL	oxidized phospholipids
PAD	peripheral arterial disease
PBS	phosphate buffered saline
PCSK9	proprotein convertase subtilisin/kexin type 9
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLA_2	Lp(a)-associated Lp-phospholipase A_2
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

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
SC	subcutaneous(ly)
Study Drug	ISIS 681257 or placebo
SUSAR	suspected unexpected serious adverse reaction
Tg	transgenic
T_{max}	time to maximal concentration
UACR	urine albumin -creatinine ratio
ULN	upper limit of normal
UPCR	urine protein- creatinine ratio
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established cardiovascular disease (CVD).

1.2 Secondary Objective(s)

To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), oxidized phospholipids (OxPL) on apolipoprotein (a) [apo(a)] [OxPL-apo(a)] and OxPL on apoB (OxPL-apoB).

To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in in patients with hyperlipoproteinemia(a) and established CVD.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Lipoprotein (a)

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein (Figure 1, Koschinsky and Marcovina 2004) in which the apoB component of LDL is linked by a disulfide bond to apolipoprotein(a) [apo(a)], the distinct protein component of Lp(a) that is mainly responsible for its signature structural and functional properties (Dubé et al. 2012; Kronenberg and Utermann 2013). Lp(a) is now recognized as an independent, genetic, causal risk factor for coronary artery disease (CAD), stroke, peripheral arterial disease (PAD), and calcific aortic stenosis (Erquo et al. 2009; Nordestgaard et al. 2010; Thanassoulis et al. 2013).

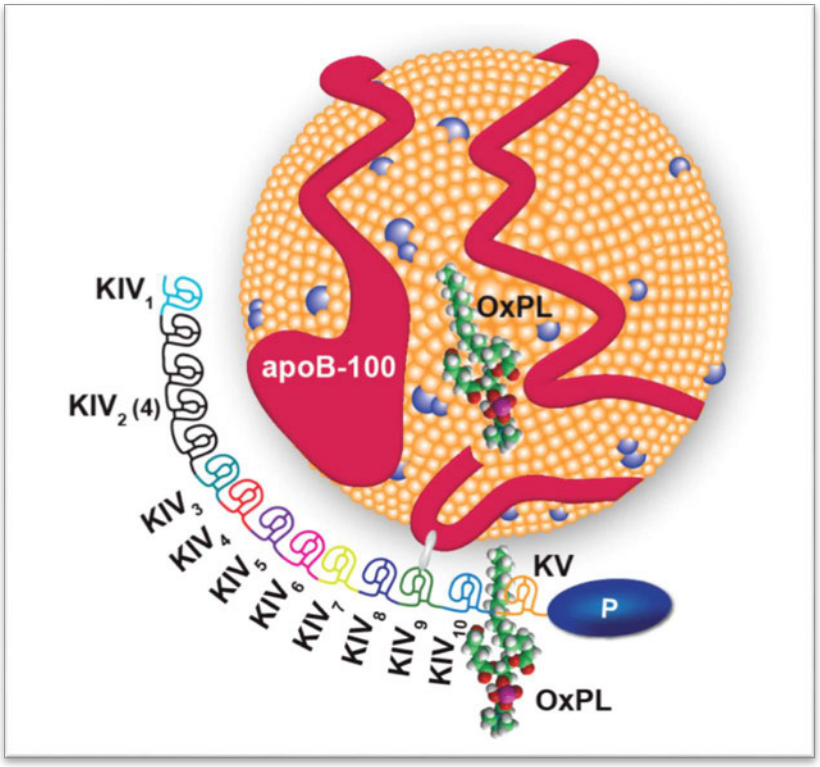


Figure 1 Schematic Representation of the Lp(a) Particle. Lp(a) is Composed of apo(a) Covalently Bound to apoB

Apo(a) contains 10 unique units of kringle IV repeats, of which KIV2 are present in variable copies (1 to > 40) conferring structural heterogeneity to Lp(a). Apo(a) also contains kringle V and an inactive protease-like (P) domain. In this model, 4 KIV2 repeats are shown. Lp(a) also contains OxPL in the lipid phase of apoB as well as covalently bound to apo(a).

Plasma levels of Lp(a) vary substantially among individuals, and most of this variation reflects the effects of genetic variation in the *LPA* gene which encodes the apo(a) protein.

A second contributor to plasma-level variability are LPA single nucleotide polymorphisms (SNPs) that can be associated with either higher or lower Lp(a) levels (Clarke et al. 2009; Li et al. 2011). Significant associations exist between 2 particular LPA variants, rs10455872 and rs3798220, increased Lp(a) levels, CVD, and aortic stenosis, with the CVD risk primarily mediated by Lp(a) plasma levels rather than an independent effect of the SNPs (Clarke et al. 2009; Li et al. 2011).

Lp(a) plasma levels are generally inversely associated with apo(a) size, and can vary by > 1,000-fold (0.1 to > 250 mg/dL or < 0.25 to > 625 nmol/L) between individuals (Merki et al. 2011). Despite this inter-individual variation, intra-individual Lp(a) levels are thought to be generally stable over time along a pre-set genetically determined levels without significant impact from dietary or environmental factors, mediating CVD risk throughout the patient's lifetime.

2.1.2 Pathophysiology

Lp(a) adheres to plaque sites and is retained in the artery wall and has proatherogenic and pro-inflammatory properties due to its LDL and apo(a) components (Spence and Koschinsky 2012). In addition, Lp(a) may be prothrombotic by inhibiting fibrinolysis because of its structural similarity to plasminogen and its enhancement of platelet aggregation (Rand et al. 1998). *In vitro* studies have provided evidence for both of these pathogenic mechanisms, but *in vivo* data are not definitive (Dubé et al. 2012). In humans, Lp(a) is the main lipoprotein carrier of OxPL, which may drive the risk associated with Lp(a) (Bergmark et al. 2008; Leibundgut et al. 2013; Tsimikas et al. 2014). In fact, OxPL measured on apoB (OxPL-apoB), which largely reflect the OxPL on Lp(a), have been shown to be a prognostic indicator for future CV events (Tsimikas et al. 2010; Tsimikas et al. 2012; Tsimikas et al. 2014). OxPL associated with Lp(a) can be subjected to degradation by the Lp(a)-associated Lp-phospholipase A_2 (PLA_2), implicating Lp(a) in novel proinflammatory and atherogenic pathways (Kiechl et al. 2007).

Hyperlipoproteinemia(a) in humans is associated with increased risk of cardiac death, myocardial infarction (MI), stroke, aortic stenosis, and peripheral arterial disease (PAD), particularly in subjects with small apo(a) isoforms (Bennett 2008; Erqou et al. 2009; Erqou et al. 2010; Bertoia et al. 2013; Thanassoulis et al. 2013). Although prospective, randomized, controlled outcomes studies have not been conducted, epidemiological, genome-wide association and Mendelian randomized controlled study data to date provide supporting evidence for a role of Lp(a) as a risk factor for CVD (Kamstrup et al. 2009). For example, in the Copenhagen City Heart Studies of 42,000 subjects with a 15-year follow-up (Kamstrup et al. 2009) using a Mendelian randomization approach, higher Lp(a) levels were related to risk of MI.

2.1.3 Current Treatment Options

In 2010, the European Atherosclerosis Society (EAS) Consensus Panel recommended screening for elevated Lp(a) in people at moderate to high risk of CVD to reach a treatment goal of < 50 mg/dL (125 nmol/L), after therapeutic management of LDL-C (Nordestgaard et al. 2010). Approximately 20% of people are estimated to have plasma Lp(a) levels over 50 mg/dL (125 nmol/L) and approximately 0.3% to have levels over 175 mg/dL (438 nmol/L). There are no gender differences in Lp(a) concentrations but racial differences have been observed, with whites and Asians having lower levels while blacks and Hispanics generally have somewhat higher levels (Nordestgaard et al. 2010).

Lifestyle and diet are thought to have little impact on an individual's Lp(a) level. Current treatment recommendations from the EAS Consensus Panel are limited to the use of 1 to 3 g of niacin (nicotinic acid) daily which could result in an up to 30% reduction in Lp(a). However, niacin is associated with side effects (e.g., flushing) that reduce patient tolerability and compliance (Parker et al. 2006; Guyton 2007).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are neither indicated nor formally recommended for treatment of hyperlipoproteinemia(a) but have been reported to reduce Lp(a) levels by ~20%-35% in patients with hypercholesterolemia (Desai et al. 2013; Raal et al. 2015).

The other current option for patients with significantly elevated Lp(a) levels (≥ 60 mg/dL) is lipoprotein apheresis, either general lipoprotein apheresis (Jaeger et al. 2009; Leebmann et al. 2013; Rosada et al. 2014) or Lp(a)-specific apheresis (Safarova 2012). While very effective at acutely lowering Lp(a) (acute and interval Lp(a) reductions of > 60% and > 30% respectively), this treatment option is expensive, burdensome for patients, and unavailable/not reimbursed in many countries and regions.

2.2 Therapeutic Rationale

Therapeutic modalities to reduce Lp(a) levels in humans are few, and there are no drugs currently available that specifically target Lp(a) alone. Antisense oligonucleotides (ASOs) are emerging as viable therapeutic agents to treat disorders where overexpression of proteins is associated with a disease process. Apo(a) is synthesized primarily in the liver, a target organ for ASOs, where it is subsequently covalently linked to the apoB-100 component of LDL to form the Lp(a) lipoprotein. The goal of treatment with ISIS 681257 is to reduce the production of apo(a) in the liver and thus, the level of Lp(a) lipoprotein by using an ASO directed against the messenger ribonucleic acid (mRNA) of apo(a). It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse CVD by reducing thrombotic, atherogenic, or inflammatory events in patients with elevated Lp(a) levels (Nordestgaard et al. 2010).

Importantly, there is no evidence that lowering Lp(a) will result in adverse consequences in individuals, and there are no reports linking very low Lp(a) to any deleterious effects.

2.3 ISIS 681257

Please refer to the ISIS 681257 Investigator's Brochure for more details on ISIS 681257 mechanism of action, chemistry, pre-clinical and clinical experience. The summary is provided below.

2.3.1 Mechanism of Action

ISIS 681257 is a second-generation ASO drug targeted to apo(a) that has been covalently bonded to triantennary *N*-acetyl galactosamine ($GalNAc_3$), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-$GalNAc_3$ conjugate. This $GalNAc_3$-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold compared to unconjugated ASOs in mice (Prakash et al. 2014).

The ASO portion of ISIS 681257 is complementary to a region spanning the Exon 24-25 splice site at position 3901 of apo(a) transcript sequence (NM_005577.2) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 681257 to the cognate mRNA results in the Ribonuclease H1 (a non-specific endonuclease that catalyzes the cleavage of RNA via hydrolytic mechanism RNase H1-mediated degradation of the apo(a) mRNA, thus preventing production of the apo(a) protein). Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

ISIS 681257 does not have any complementary homology to plasminogen mRNA (Graham et al. 2016).

2.3.2 Chemistry

Chemically, ISIS 681257 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and further enhances potency of $GalNAc_3$ conjugated ASOs.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities, thereby resulting in an improved safety profile compared to first-generation antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 681257 employs this chimeric structure to enable use of the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). The fourth region is composed of a triantennary cluster of $GalNAc_3$ sugars that is linked to the 5′ end of ISIS 681257 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 681257 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the $GalNAc_3$ cluster is metabolized to release "free ASO" inside the cell (Prakash et al. 2014).

2.3.3 Preclinical Experience

The pharmacology of ISIS 681257 has been examined in apo(a) transgenic (Tg) mice which express the entire human apo(a) genomic sequence (Frazer et al. 1995) and nonhuman primates.

Administration of ISIS 681257, a human apo(a) antisense inhibitor, to mice containing the human apo(a) transgene produced dose-dependent reductions in human apo(a) liver mRNA and apo(a) plasma protein after 6 weeks of ASO administration at 0.3, 1, 3, and 10 mg/kg/wk.

When ISIS 681257 was administered to normal chow fed cynomolgus monkeys for 4 weeks at the dose of 12 mg/kg/wk, it significantly reduced hepatic apo(a) mRNA by 90% relative to the cohort administered phosphate buffered saline (PBS). As there is an 80% sequence conservation between apo(a) and plasminogen nucleotide sequences, plasminogen mRNA levels were also measured, and no change compared to the PBS cohort was observed.

Findings from the chronic studies with ISIS 681257 (the 26-week mice and 39-week monkey studies) were similar to those observed in the 4- and 6-week studies and were not considered adverse. The plasma and tissue concentrations observed for ISIS 681257 in mice and monkeys were generally similar to those observed for other unconjugated 20-mer 2′-MOE ASOs in this chemical class with and without $GalNAc_3$-conjugation. However, the proportion of drug in

hepatocytes compare to nonparenchymal liver cells was greater for ISIS 681257, compared to the parent drug ISIS 494372 (without $GalNAc_3$-conjugation), which is the basis for increased potency of ISIS 681257 (unpublished results; Geary et al. 2003; Yu et al. 2007; Prakash et al. 2016).

The most noteworthy safety finding in the chronic monkey study was a marked platelet reduction that, occurred in 2 male monkeys in the high-dose group (20 mg/kg/wk) and 1 animal (1 female) in the mid-dose (10 mg/kg/wk) group beginning on Days 44-135, which led to the subsequent early termination (ET) of these 3 animals. An additional male monkey in the 10 mg/kg/wk dose group had a moderate decrease in platelets that was successfully treated with steroid, and was terminated at the scheduled 6-month interim sacrifice. There were no platelet reductions or other toxicologically significant findings in monkeys treated with 2 mg/kg/wk for up to 39 weeks. There were no marked platelet reductions in mice at doses up to 70 mg/kg/wk for 26 weeks. However, mice exposed to ISIS 681257 at doses of ≥ 10 mg/kg/wk for up to 26 weeks showed evidence of hepatobiliary effects in both sexes as indicated by increases in ALT (up to + 10.3x), AST (up to + 10.4x), and/or ALP (+ 2.5x).

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 681257 can be found in the Investigator's Brochure. A summary of the study that has been conducted with ISIS 681257 is included below.

ISIS 681257-CS1 was a Phase 1 double-blind, placebo-controlled, dose-escalation study designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple doses of ISIS 681257 administered subcutaneously (SC) to 45 healthy subjects with Lp(a) ≥ the upper limit of normal (ULN) (30 mg/dL). Twenty one (21) subjects received 10 to 120 mg SC (10, 20, 40, 80, and 120 mg) as a single-dose, and 24 subjects received 10, 20, and 40 mg as multiple doses (6 doses in 21 days: 3 loading doses during the first week on alternate days (Days 1, 3, and 5), and then once a week for the next 3 weeks (Days 8, 15, and 22).

There were no serious adverse events (SAEs), or clinically-relevant changes in laboratory assessments and all subjects completed the treatment and post-treatment follow-up periods.

Constitutional symptoms such as fever, chills, increase in body temperature and arthralgias have been observed following parenteral administration of ASOs, primarily during the initial dosing period. Following SC administration of ISIS 681257 constitutional symptoms were observed in 4 of the 6 subjects who received a single-dose of 120 mg. The symptoms were mild in severity and resolved spontaneously with or without treatment with acetaminophen.

Fluctuations in platelet counts to below the lower limit of normal were observed in 5 study subjects on active drug and across doses. These changes were not considered adverse or clinically-significant by the Investigator and did not appear to be dose related.

Two (2) mild AEs of redness at the site of injection occurred 48 to 72 hours after administration in 1 subject who received ISIS 681257 in the 20 mg multiple-dose cohort. Both AEs resolved by the time of the subject's next visit.

Following SC administration, ISIS 681257 was absorbed rapidly into the systemic circulation, with median time to maximum plasma concentrations (T_{max}) ranging from 1 to 4 hours. Similar T_{max} values were observed at all dose levels. Maximum observed plasma concentrations (C_{max}) and $AUC_{0\text{-}24hr}$ were dose-dependent over the studied SC dose range. The mean peak (C_{max}) and total exposure ($AUC_{0\text{-}24hr}$) increased proportionally with dose at dose levels ranging from 10 to 40 mg, and greater than dose proportionally at dose levels ranging from 40 to 120 mg.

After reaching C_{max}, mean plasma concentrations of ISIS 681257 declined in a biphasic fashion over time, with an initial, relatively fast distribution phase that dominated the plasma clearance followed by a slower elimination phase. Characterization of the terminal elimination phase yielded an apparent terminal elimination half-life of approximately 3 to 4 weeks over a dose range of 10 to 120 mg (either single- or multiple-dose), and appeared to be independent of dose. This result is consistent with the slow elimination of ISIS 681257 observed from monkey tissues, and the comparatively long elimination half-lives observed for this chemical class.

Plasma trough concentrations (168 hours or 7 days from previous dose) monitored during the treatment period in the multiple-dose cohorts increased with increasing dose, consistent with expectations (based on preclinical assessments and experience with other compounds of this chemical class) that trough plasma concentrations reflect exposure in tissues. Plasma trough concentrations did not increase greatly after the loading period (Day 15), suggesting that accumulation in major tissues of distribution had approached steady-state after the loading period.

Overall, the human PK of ISIS 681257 are consistent with the expected PK for compounds within this chemical class.

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a).

The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) $\leq$ 30 mg/dL).

The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally

driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio (225 ISIS 681257 and 45 placebo) to receive ISIS 681257 or placebo. Study Drug (ISIS 681257 or placebo) will be administered SC every week, every 2 weeks (biweekly), 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.

The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy analysis (to evaluate whether the treatment effect is maintained) and safety analysis (for the purpose of dose(s) selection) will be repeated at the completion of Study Drug treatment.

The treatment portion of the study will be complete when the last enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period.

Patients ≥ 18 and ≤ 80 years old with elevated plasma Lp(a) levels (≥ 60 mg/dL) and a clinical diagnosis of CVD are eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for other than elevated Lp(a) 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 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). 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 5 parallel dosing cohorts, with each cohort having a 5:1 ratio to receive ISIS 681257 or matching volume of placebo, respectively, by SC injection for up to 52 weeks.

Following the End-of-Treatment, patients will enter the 16-week post-treatment follow-up period.

3.2 Number of Study Centers

This is a multicenter, multinational study.

3.3 Number of Patients

Approximately 270 patients will be randomized in this study, with approximately 54 patients assigned to each of the 5 treatment cohorts.

3.4 Overall Study Duration and Follow-up

The length of patients' participation in the study may be up to 18 months (72 weeks), which includes a 4-week screening period, an up to 52-week treatment period with Study Drug (ISIS 681257 or placebo), and a 16-week post-treatment follow-up period. The treatment portion of the study will be complete when the last enrolled 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 maximum of 52 weeks.

All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may continue treatment within the same randomized cohort until the last enrolled patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. When this milestone is met, all patients will then enter a 16-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 681257 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 16-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits 4, 10, and 16 weeks after their last injection of Study Drug as per Appendix A (Follow-up).

The final study visit for each patient will be 16 weeks after the last dose of Study Drug.

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 681257 during this study. The DSMB will be constituted to include expertise in medical specialties relevant to the safety of antisense drugs (nephrology, hepatology, hematology and cardiology). Specialist members of the DSMB will be informed and consulted on all treatment-related SAEs relevant to their expertise and all changes of relevant laboratory parameters that trigger stopping rules (Section 8.6), within 24 hours of receipt of such results. In addition, all accrued safety data relevant to each of medical area specialist will be forwarded monthly for review.

The full DSMB review of all accumulated data will be performed quarterly. Based on its ongoing assessment of the safety and tolerability of ISIS 681257, 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 1:1:1:1:1 ratio to 1 of the 5 parallel-dose cohorts (Cohorts A, B, C, D, or E). Within each dose cohort, patients will be randomized in a 5:1 ratio to receive ISIS 681257 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 a 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 at within 4 weeks of Study Day 1or 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. Clinical diagnosis of CVD defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease
4. Lp(a) plasma level ≥ 60 mg/dL
5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors
6. 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, proprotein convertase subtilisin/kexin type 9 [PCSK9s] 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
7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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

8. 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 16 weeks after the last dose of ISIS 681257

5.2 Exclusion Criteria

1. Within 6 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 New York Heart Association (NYHA) class 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 with a history of major bleed or high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Known history or presence of systemic allergic or pseudoallergic (drug) reactions
13. Hypersensitivity to the active substance or to any of the excipients

14. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
    a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr
    b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr
    c. Estimated GFR < 60 mL/min (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance
    d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN
    e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
    f. Alkaline phosphatase (ALP) > ULN
    g. Platelet count < LLN
15. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors
16. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
17. Treatment with any 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
18. BMI > 40 kg/m^2
19. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
21. 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. A 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.

On confirmation of eligibility and prior to randomization, patients will also undergo a 24 hr urine collection for creatinine, albumin, and protein as a baseline assessment.

6.1.2 Treatment Period

During the treatment period, patients will report to the study center for clinic visits. Patients will receive 20 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort A, 40 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort B, 60 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort C, 20 mg doses of Study Drug administered by SC injection once every 2 weeks for up to 52 weeks in Cohort D, or 20 mg doses of Study Drug administered by SC injection once per week (weekly) for up to 52 weeks in Cohort E (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 681257 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 12 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 681257. 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 16 weeks after the last dose of Study Drug. During the post-treatment follow-up period, patients will return to the Study Center for 3 outpatient visits at Weeks 4, 10, and 16 after the last dose of Study Drug 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 (excluding 24-hour urine collection) should be taken after fasting for at least 10 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status. 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. Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample 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 and sent to the central laboratory for analysis, per Section 8.5.2. If there are no test results available within 14 days of the last set of results for parameters considered critical to patient safety, the Investigator will contact the patient to hold dosing until a new test set is obtained and reviewed.

While on treatment liver function testing will also be collected every 14 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 sent to the central laboratory are received on the next day 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 on the day of sample collection, 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 24 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 (Grade 3 or Grade 4) 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 24 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 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, B, and C at Weeks 5, 13, 21, 25, 33, 41, 49, and 53
- Cohorts D and E at Weeks 5, 13, 21, 27, 33, 41, 49, and 53

In all cohorts, ECGs will be conducted during the post-treatment follow-up period at 4, 10, and 16 weeks after the last dose of Study Drug.

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 681257 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 16 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 16 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 before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 681257 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 681257 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 681257

ISIS 681257 vials contains 100 mg/mL ISIS 681257 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 681257 vials.

Table 1 Study Drug Characteristics

Study Drug	ISIS 681257	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 681257 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 681257 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 681257 will be administered to patients by Study Center staff as follows:

Cohort A: a single SC dose of 20 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort B: a single SC dose of 40 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort C: a single SC dose of 60 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort D: a single SC dose of 20 mg every 2 weeks for up to 52 weeks and a maximum of 26 doses

Cohort E: a single SC dose of 20 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, B, and C should receive 1 dose every 4 weeks, patients in Cohort D should receive 1 dose every 2 weeks and Cohort E 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 681257 or placebo) preparation and administration.

Table 2 Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 681257
A	20 mg ISIS 681257 or placebo (Every 4 weeks)	0.2 mL	≤ 13	≤ 260 mg
B	40 mg ISIS 681257 or placebo (Every 4 weeks)	0.4 mL	≤ 13	≤ 520 mg
C	60 mg ISIS 681257 or placebo (Every 4 weeks)	0.6 mL	≤ 13	≤ 780 mg
D	20 mg ISIS 681257 or placebo (Every 2 weeks)	0.2 mL	≤ 26	≤ 520 mg
E	20 mg ISIS 681257 or placebo (Every week)	0.2 mL	≤ 52	≤ 1040 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

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 681257 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, patients must not be re-dosed 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 681257 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 2 weeks for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period.

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 24 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 (within 24 hours of receipt) reviewed by the Investigator and Medical Monitors.

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 2 weeks throughout the study. Upon completion of the study treatment period, urine renal biomarkers should be monitored every 2 weeks for the first 6 weeks and then at 10 and 16 weeks post last dose (as per visit schedule).

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 to estimate glomerular filtration rate (eGFR), which will be monitored every 2 weeks. In addition, biomarkers of acute renal injury will also be measured every 2 weeks (Appendix B).

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than every 2 weeks 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 at the weekly safety review by the Medical Monitor.

All results of renal function tests must be reviewed promptly (within 24 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: Creatinine clearance (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 an 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.

In the event of a confirmed (as described in Section 8.5) laboratory result meeting one or more of the above criteria, dosing with the Study Drug should be interrupted and the Study Medical Monitor informed. In addition, the following supplemental renal tests should be immediately obtained:

> Serum creatinine, urine culture, 24-hour urine sample for creatinine clearance, urine albumin and urine protein, urine microscopy sample with inspection of sediment.

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.

8.5.3 Safety Monitoring for Platelet Count Results

All patients will have platelet counts monitored every 2 weeks for the duration of the study treatment period and must not receive Study Drug without an interpretable platelet count result in the prior 2 weeks. Upon completion of the study treatment period, platelets should be monitored every 2 weeks for the first 6 weeks and then at 10 and 16 weeks post last dose (as per visit schedule). In addition, platelet function will be evaluated by aggregometry, using an approved point-of-care diagnostic device, in all patients at each study site visit; additional functional testing may be performed at selected study centers.

As described in Section 6.2.1, all platelet count results must be reviewed promptly (within 24 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.

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm^3; 2) when platelet count is ≥ 30% decreased from baseline, or 3) when 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 D, 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 Minor Bleeding Events

Patients will be instructed to promptly report any signs or symptoms of bleeding. Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, or gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, hepatic enzymes, bilirubin and platelet count should be performed.

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 symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.6 Stopping Rules

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 of an estimated creatinine clearance (by CKD-EPI formula) meeting any of the following criteria, or any change in renal biomarkers deemed by the nephrologist on the DSMB to require further evaluation, a serum creatinine, urine culture, 24-hour urine sample for creatinine clearance and protein, and urine microscopy sample with inspection of sediment should be immediately obtained:

1. CKD-EPI decrease of > 40% from Baseline
2. CKD-EPI value < 45 mL/min/1.73 m^2

Dosing of a patient with Study Drug (ISIS 681257 or placebo) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

1. Urine protein is > 1.0 g
2. Creatinine clearance decrease of > 40% from baseline
3. Creatinine clearance < 45 mL/min/1.73 m^2

Irrespective of whether the stopping rule is confirmed or not, 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

Stopping Rules 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 steroids 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

steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids 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; Schulman et al. 2005), 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 irrespective of whether the platelet count rises into the normal range.

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

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every week*
75K-100K/mm^3	Permanently reduce as follows: For Cohort A: reduce to 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 weeks For Cohort E: reduce to 10 mg every week	Closer observation Monitor every week*
50K-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 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 week For Cohort E: reduce to 10 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)/ anticoagulant medication
25K-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/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 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 and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* Once a patient commences weekly monitoring this frequency of monitoring should continue irrespective of whether the platelet count rises into the normal range.

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: 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 Section 8.6.3 and 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 8.6.3
- 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 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 after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), platelets should be tested 10 and 16 weeks post last dose (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 16-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 16 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, PCSK9 inhibitors, niacin, fibrates, fish oil, other products containing omega-3 fatty acids (including OTC preparations)
- Anti-platelet therapies
- Testosterone, estrogens, progesterone, growth hormone, or progestins.

Disallowed Concomitant Therapy

Use of the following is disallowed:

- Warfarin, 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 of platelet count, and liver and renal function as described in Section 6.2.1, Sections 8.5.1-8.5.3, and Sections 8.6.1-8.6.3.

While on treatment patients will be required to have platelet counts every 2 weeks 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 2 weeks, and must not receive Study Drug if there are no test results for parameters considered critical to patient safety available within the prior 2 weeks. 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 (Grade 3 or Grade 4), 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. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. 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 681257 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 681257 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 681257 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 681257 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 24 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 as per Sections 9.3.3.1 and 9.4.1).

All results of liver function tests must be reviewed promptly (within 24 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 24 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 681257 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 681257 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-C) and at Week 27 for patients who received weekly or biweekly dosing (Cohorts D and E). 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 endpoint is the percent change in Lp(a) from baseline at the primary analysis time point achieved by ISIS 681257 compared to pooled placebo.

Lp(a) levels will be analyzed from patient blood samples taken at specified time points throughout the study.

10.1.2 Secondary Endpoints

The secondary endpoints include the following parameters from baseline at the primary analysis time point for ISIS 681257 compared to placebo:

- Percent change from baseline in LDL-C
- Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL (≤ 125 nmol/L)
- Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL (≤ 75 nmol/L)
- Percent change from baseline in apoB
- Percent change from baseline in OxPL-apo(a)
- Percent change from baseline in OxPL-apoB

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
- 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 clinically-meaningful reduction in plasma Lp(a) 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, and renal or hepatic injury.

10.2 Sample Size Considerations

Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients.

Based upon prior clinical trial experience with Ionis ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event.

Therefore, approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.

10.3 Analysis Populations

Full Analysis Set (FAS): All patients who are randomized, received at least 1 dose of Study Drug (ISIS 681257 or placebo), and have a Baseline Lp(a) 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, B, and C or at least 20 weekly doses for patients randomized in Cohorts D and E, 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 Study Drug, and have sufficient data for the analysis of PK parameters. This population will be used for analysis of PK data.

10.4 Definition of Baseline

Baseline for Lp(a), LDL-C, apoB, OxPL-apo(a), OxPL-apoB, and other lipid measurements will be defined the pre-dose measurement on Day 1 or 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 681257 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 681257 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 681257 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 analysis of the primary endpoint will be the pairwise comparison of percent change from baseline to primary analysis time point in fasting Lp(a) between ISIS 681257 treatment groups and pooled placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the Baseline Lp(a) 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 LDL-C will be compared between each ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate
- Proportion of patients who achieve ≤ 50 mg/dL (≤ 125 nmol/L) in fasting Lp(a) at the primary analysis time point will be compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with Baseline Lp(a) as a covariate. Proportion of patients who achieve ≤ 30 mg/dL (≤ 75 nmol/L) in fasting Lp(a) at the primary analysis time point will be analyzed similarly
- Percent change from baseline at the primary analysis time point in fasting apoB, OxPL-apo(a) and OxPL-apoB will be compared between ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate

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 681257 in plasma (as total full length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 681257) will be determined and summarized by treatment with stratification by subject immunogenicity status using descriptive statistics.

In addition, non-compartmental PK analysis of ISIS 681257 concentrations will be carried out on each individual patient data set in patients who received ISIS 681257 treatment, and the plasma

disposition half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate, using available data at the End-of-Treatment and the post-treatment follow-up period from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, where λz is the rate constant associated with the apparent terminal elimination phase.

For patients in the PK subgroup only, non-compartmental PK analysis of ISIS 681257 will be carried out on each individual patient data set in patients who received ISIS 681257 treatment. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Following single dosing (Day 1), area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours after the dose ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Following multiple dosing, $AUC_{0\text{-}24hr}$ and area under the plasma concentration-time curve during the time of each sampled dosing interval (tau,τ) at steady-state (AUC_{τ}) will be calculated using the linear trapezoidal rule.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Plasma PK parameters will be summarized using descriptive statistics with stratification by subject immunogenicity status. Exposure-response relationships between selected PD [e.g., Lp(a)] and PK measures (including but may not be limited to plasma trough concentrations) may be explored (including with and without stratification by IM status) in this study, or in a separate population PK analysis with all clinical studies combined.

The immunogenicity (IM) of ISIS 681257 will be assessed before, during, and after treatment with Study Drug (ISIS 681257 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 681257 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 681257 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.

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
12- lead ECG (triplicate)	X	X		X		X		X		X				X		X		X	X	X	X	X
24-Hour Urine for Creatinine Clearance and Protein	X																					
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																		X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																		X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																		X	X	X
Genetic Testing		X																				
Chemistry Panel [j,k]	X	EVERY 14 DAYS [f]				X	X	X	X				X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																		X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Coagulation	X	X								X												
Hepatitis B, C, HIV	X																					
Thyroid Panel	X																					
hsCRP		X								X									X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X	X[3]	X[1]	X[2]	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X				X									X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
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
Archived Serum & Plasma Samples [j, n]		X			X		X			X					X		X		X	X	X	X
PD Panel [j]	X	X		X	X	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
Lp(a) Characterization		X																				
Study Drug: SC Injection		WEEKLY AND EVERY 2-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 53/Day 365)[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
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then at Week 10 and Week 16 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.

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

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 24 hours of receipt) by the Investigator as per Section 6.2.1. 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 enrolled reaches 6 months of exposure. When this milestone is met, all patients still on treatment will then enter a 16-week post-treatment follow-up period.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8 hours post SC injection

Appendix A Schedule of Procedures – Every 4-Week Dosing

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
Physical Examination	X	X		X		X		X	X						X		X		X	X	X	X	X
Body Weight and Height [d]	X								X								X						X
12- lead ECG (triplicate)	X	X		X		X		X	X						X		X		X	X	X	X	X
24-hour Urine for Creatinine Clearance and Protein	X																						
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																			X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																			X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																			X	X	X
Genetic Testing		X																					
Chemistry Panel [j, k]	X	EVERY 14 DAYS [f]				X	X	X						X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																			X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X														
Hepatitis B, C, HIV	X																						
Thyroid Panel	X																						
hsCRP		X							X											X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X[3]	X[1]	X[2]	X	X	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X			X											X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit and Testing Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
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
Archived Serum & Plasma Samples [j, n]		X			X		X		X					X		X		X		X	X	X	X
PD Panel [j]	X	X		X	X	X	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	X
Lp(a) Characterization		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
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

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then at Week 10 and Week 16 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.

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

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 24 hours of receipt) by the Investigator as per Section 6.2.1. 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 enrolled reaches 6 months of exposure. When this milestone is met, all patients still on treatment will then enter a 16-week post-treatment follow-up period.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8, hrs post SC injection

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 681257 or other similar oligonucleotides.

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

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)
- TSH
- Free T4
- Free T3

Coagulation
- aPTT
- PT
- INR
- Fibrinogen
- Plasminogen

PD Panel
- Lp(a)
- OxPL-apoB
- OxPL-apo(a)

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL

Lp(a) Characterization
- Apo(a) isoforms

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 681257 (total full length ASO) levels in plasma

Immunogenicity
- Anti-ISIS 681257 antibodies

Genetic Testing
- LPA SNPs associated with elevated Lp(a)

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

24 Hour Urine Test[3]
- Creatinine clearance
- Protein
- Albumin

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 681257 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.

3 To be performed during Screening upon confirmation of eligibility

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 681257 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 681257 with plasma constituents. Extensive PK samples will be collected in PK subgroup only (10 subjects 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**	**27**			**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184**	**185**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime
PK Sub-group Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	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	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

1 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

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**	**25**			**26**	**27**	**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**170**	**171**	**176**	**183**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose,	NA	NA	NA	NA	NA	Pre-dose	Pre-dose	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	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

1 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

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/mm^3

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
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
Platelet Antibody Bead Array (PABA)

Sponsor:
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2855 Gazelle Court
Carlsbad, CA 92010

Collaborator:
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IONIS PHARMACEUTICALS, INC.

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 4 – 5 January 2017

EudraCT No: 2016-003373-18

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 4 – 5 January 2017

Protocol History:

Original Protocol:	15 August 2016
Protocol Amendment 1:	12 October 2016
Protocol Amendment 2:	29 November 2016
Protocol Amendment 3:	30 December 2016

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ISIS 681257-CS6

Ionis Protocol Number ISIS 681257-CS6

Protocol Amendment 4

EudraCT No: 2016-003373-18

Clinical Phase: 2

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

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Date: 5 January 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment: Amendment 4

Date: 5 January 2017

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 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)," dated 5 January 2017, 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.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENTS

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 4

Amendment Date: 5 January 2017

The following table summarizes the history and nature of amendments to the protocol of Study ISIS 681257-CS6.

None of the antecedent versions of the study protocol has been enacted clinically and therefore no patients have been enrolled prior to issuance of Amendment 4.

Protocol Version	Date	Rationale for Amendments
Original Protocol	15 August 2016	
Amendment 1	6 October 2016	Regulatory advice on inclusion of more detailed description of processes for platelet monitoring, and more frequent monitoring of liver function.
Amendment 2	29 November 2016	Regulatory advice on inclusion of biomarkers of renal damage and increased frequency of renal monitoring. Addition of a DSMB.
Amendment 3	30 December 2016	Adjustment of the frequency, and alert and intervention limits, for renal safety and adjustment of the frequency of liver safety testing.
Amendment 4	5 January 2017	The study population was increased to 270 patients (54 per cohort) to support a statistical assessment of risk of platelet reduction in this population. In addition, the 10 mg weekly treatment cohort has been modified to 20 mg every 2 weeks (biweekly).

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)
Study Phase	2
Indication	Patients with hyperlipoproteinemia(a) and established CVD.
Investigational Drug	ISIS 681257 is a second generation 2'-MOE modified, $GalNAc_3$–conjugated antisense oligonucleotide inhibitor of apolipoprotein (a) [apo(a)].
Primary Objective	To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.
Secondary Objective(s)	To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B100 (apoB), oxidized phospholipids (OxPL) on apo(a) [OxPL-apo(a)], and OxPL on apoB (OxPL-apoB). To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in patients with hyperlipoproteinemia(a) and established CVD.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio to receive ISIS 681257 or placebo. This number was chosen to provide statistical power for both efficacy and safety assessments. Study Drug (ISIS 681257 or placebo) will be administered SC 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 enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period. The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, 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 (as needed) data collected on ISIS 681257 during this study, both individual events and aggregate data.
Number of Subjects	Approximately 270
Study Population	<u>Inclusion Criteria</u> 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. Clinical diagnosis of CVD defined as documented coronary artery disease, stroke, or peripheral artery disease 4. Lp(a) plasma level ≥ 60 mg/dL 5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Inclusion Criteria 6. 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 7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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 8. 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 16 weeks after the last dose of ISIS 681257 Exclusion Criteria 1. Within 6 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 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

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria 10. Patients with a history of major bleed or high-risk of bleeding diathesis 11. Recent history of, or current drug or alcohol abuse 12. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following: a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr c. Estimated GFR < 60 mL/min as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL f. Alkaline phosphatase (ALP) > ULN g. Platelet count < LLN 13. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors 14. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 15. Treatment with any 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 16. BMI > 40 kg/m^2 17. Blood donation of 50-499 mL within 30 days of screening or of > 499 mL within 8 weeks of Screening 18. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 19. 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

PROTOCOL SYNOPSIS *Continued*

Treatment Groups

Patients will be randomized to 5 parallel cohorts:

Cohort A (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort B (n = 54): Patients will be randomized 5:1 to receive 40 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort C (n = 54): Patients will be randomized 5:1 to receive 60 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort D (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every 2 weeks for up to 26 doses.

Cohort E (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every week for up to 52 doses.

Cohort	Treatment	# Doses	Total ISIS 681257
A	20 mg ISIS 681257 or placebo (Every 4 weeks)	≤ 13	≤ 260 mg
B	40 mg ISIS 681257 or placebo (Every 4 weeks)	≤ 13	≤ 520 mg
C	60 mg ISIS 681257 or placebo (Every 4 weeks)	≤ 13	≤ 780 mg
D	20 mg ISIS 681257 or placebo (Every 2 weeks)	≤ 26	≤ 520 mg
E	20 mg ISIS 681257 or placebo (Every week)	≤ 52	≤ 1040 mg

Study Drug Dosage and Administration

The Sponsor will provide ISIS 681257 in a concentration of 100 mg/mL and matching volume placebo:

Cohort A: 20 mg every 4 weeks ISIS 681257 or placebo (0.2 mL)

Cohort B: 40 mg every 4 weeks ISIS 681257 or placebo (0.4 mL)

Cohort C: 60 mg every 4 weeks ISIS 681257 or placebo (0.6 mL)

Cohort D: 20 mg every 2 weeks ISIS 681257 or placebo (0.2 mL)

Cohort E: 20 mg every week ISIS 681257 or placebo (0.2 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 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a). The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) ≤ 30 mg/dL).

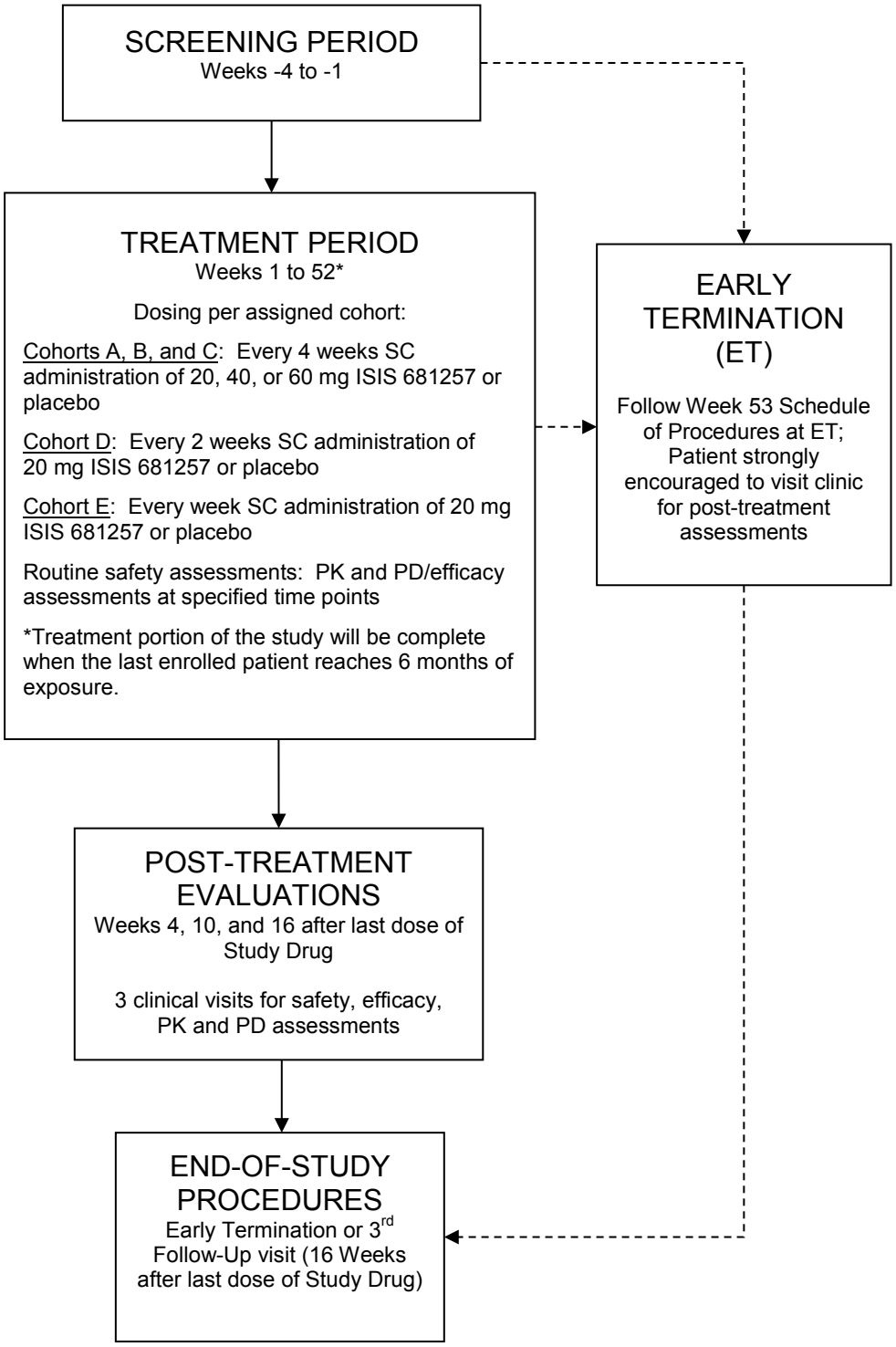
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection ***Continued***	The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.
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 are outlined in Section 6, Appendices A and C. All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may continue treatment within the same randomized cohort until the last enrolled patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. The study for an individual patient will generally consist of the following periods: • An up to 4-week screening period • An up to 52-week treatment period during which Study Drug will be administered per assigned cohort by SC injection • A 16-week post-treatment follow-up period Patients in Cohorts A through C will receive up to 13 SC doses of ISIS 681257 or placebo every 4 weeks. Patients in Cohort D will receive up to 26 SC doses of ISIS 681257 or placebo every 2 weeks and patients in Cohort E will receive up to 52 SC doses of ISIS 681257 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). 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 and use of concomitant medications. Safety and tolerability results in patients dosed with ISIS 681257 will be compared with those dosed with placebo.
Efficacy Evaluations	The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). The primary endpoint is the percent change in plasma Lp(a) from baseline at the primary analysis time point for ISIS 681257 treatment groups compared to placebo. The secondary endpoints comprise the effect of ISIS 681257 as compared to placebo at the primary analysis time point on the following: • Percent change from baseline in LDL-C • Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL • Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL • Percent change from baseline in apoB • Percent change from baseline in OxPL-apo(a) • Percent change from baseline in OxPL-apoB

PROTOCOL SYNOPSIS *Continued*

Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 681257 plasma trough levels throughout treatment and during the post-treatment follow-up period. In addition, in a subset of patients (approximately 12 patients per cohort), more frequent plasma samples will be taken following the first and Day 169 (for Cohorts A, B, and C) or Day 183 (for Cohorts D and E) dose to determine PK parameters. Plasma sample collection time points are detailed in Appendices A and C. The plasma ISIS 681257 levels over time will be descriptively summarized by treatment with stratification by subject immunogenicity status. Apparent terminal elimination half-life will be calculated in patients who received ISIS 681257 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 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 Lp(a) between ISIS 681257 treated groups and placebo group in the Full Analysis Set. The data will be analyzed using an ANCOVA model with the baseline Lp(a) 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 plasma Lp(a) 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. Sample Size Considerations: <u>Efficacy:</u> Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients. <u>Safety:</u> Based upon prior clinical trial experience with ISIS ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event. A total of approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.
Sponsor/Collaborator	Ionis Pharmaceuticals/Akcea Therapeutics

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
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
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
CVD	cardiovascular disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
Cys C	Cystatin C
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
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL-1β	interleukin-1 beta
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 681257	antisense inhibitor of apolipoprotein (a)
IV	intravenous(ly)
IXRS	interactive voice/internet response system
KIM-1	kidney injury molecule 1
kg	kilogram

STUDY GLOSSARY *Continued*

Abbreviation	Definition
L	liter
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MI	myocardial infarction
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
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OxPL	oxidized phospholipids
PAD	peripheral arterial disease
PBS	phosphate buffered saline
PCSK9	proprotein convertase subtilisin/kexin type 9
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLA_2	Lp(a)-associated Lp-phospholipase A_2
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

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
SC	subcutaneous(ly)
Study Drug	ISIS 681257 or placebo
SUSAR	suspected unexpected serious adverse reaction
Tg	transgenic
T_{max}	time to maximal concentration
UACR	urine albumin -creatinine ratio
ULN	upper limit of normal
UPCR	urine protein- creatinine ratio
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established cardiovascular disease (CVD).

1.2 Secondary Objective(s)

To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), oxidized phospholipids (OxPL) on apolipoprotein (a) [apo(a)] [OxPL-apo(a)] and OxPL on apoB (OxPL-apoB).

To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in in patients with hyperlipoproteinemia(a) and established CVD.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Lipoprotein (a)

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein (Figure 1, Koschinsky and Marcovina 2004) in which the apoB component of LDL is linked by a disulfide bond to apolipoprotein(a) [apo(a)], the distinct protein component of Lp(a) that is mainly responsible for its signature structural and functional properties (Dubé et al. 2012; Kronenberg and Utermann 2013). Lp(a) is now recognized as an independent, genetic, causal risk factor for coronary artery disease (CAD), stroke, peripheral arterial disease (PAD), and calcific aortic stenosis (Erquo et al. 2009; Nordestgaard et al. 2010; Thanassoulis et al. 2013).

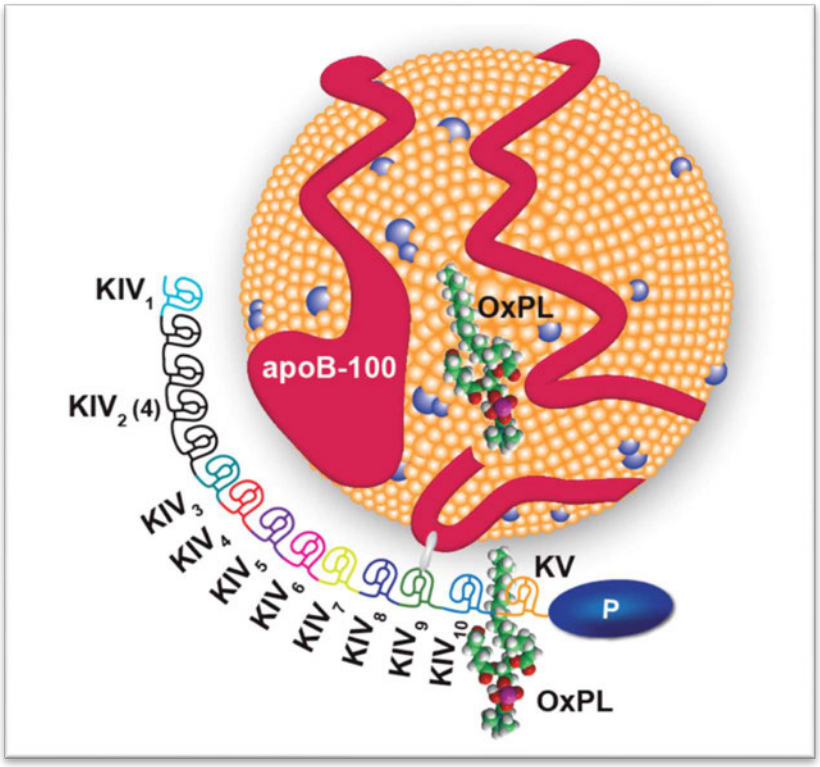


Figure 1 Schematic Representation of the Lp(a) Particle. Lp(a) is Composed of apo(a) Covalently Bound to apoB

Apo(a) contains 10 unique units of kringle IV repeats, of which KIV2 are present in variable copies (1 to > 40) conferring structural heterogeneity to Lp(a). Apo(a) also contains kringle V and an inactive protease-like (P) domain. In this model, 4 KIV2 repeats are shown. Lp(a) also contains OxPL in the lipid phase of apoB as well as covalently bound to apo(a).

Plasma levels of Lp(a) vary substantially among individuals, and most of this variation reflects the effects of genetic variation in the *LPA* gene which encodes the apo(a) protein.

A second contributor to plasma-level variability are LPA single nucleotide polymorphisms (SNPs) that can be associated with either higher or lower Lp(a) levels (Clarke et al. 2009; Li et al. 2011). Significant associations exist between 2 particular LPA variants, rs10455872 and rs3798220, increased Lp(a) levels, CVD, and aortic stenosis, with the CVD risk primarily mediated by Lp(a) plasma levels rather than an independent effect of the SNPs (Clarke et al. 2009; Li et al. 2011).

Lp(a) plasma levels are generally inversely associated with apo(a) size, and can vary by > 1,000-fold (0.1 to > 250 mg/dL or < 0.25 to > 625 nmol/L) between individuals (Merki et al. 2011). Despite this inter-individual variation, intra-individual Lp(a) levels are thought to be generally stable over time along a pre-set genetically determined levels without significant impact from dietary or environmental factors, mediating CVD risk throughout the patient's lifetime.

2.1.2 Pathophysiology

Lp(a) adheres to plaque sites and is retained in the artery wall and has proatherogenic and pro-inflammatory properties due to its LDL and apo(a) components (Spence and Koschinsky 2012). In addition, Lp(a) may be prothrombotic by inhibiting fibrinolysis because of its structural similarity to plasminogen and its enhancement of platelet aggregation (Rand et al. 1998). *In vitro* studies have provided evidence for both of these pathogenic mechanisms, but *in vivo* data are not definitive (Dubé et al. 2012). In humans, Lp(a) is the main lipoprotein carrier of OxPL, which may drive the risk associated with Lp(a) (Bergmark et al. 2008; Leibundgut et al. 2013; Tsimikas et al. 2014). In fact, OxPL measured on apoB (OxPL-apoB), which largely reflect the OxPL on Lp(a), have been shown to be a prognostic indicator for future CV events (Tsimikas et al. 2010; Tsimikas et al. 2012; Tsimikas et al. 2014). OxPL associated with Lp(a) can be subjected to degradation by the Lp(a)-associated Lp-phospholipase A_2 (PLA_2), implicating Lp(a) in novel proinflammatory and atherogenic pathways (Kiechl et al. 2007).

Hyperlipoproteinemia(a) in humans is associated with increased risk of cardiac death, myocardial infarction (MI), stroke, aortic stenosis, and peripheral arterial disease (PAD), particularly in subjects with small apo(a) isoforms (Bennett 2008; Erqou et al. 2009; Erqou et al. 2010; Bertoia et al. 2013; Thanassoulis et al. 2013). Although prospective, randomized, controlled outcomes studies have not been conducted, epidemiological, genome-wide association and Mendelian randomized controlled study data to date provide supporting evidence for a role of Lp(a) as a risk factor for CVD (Kamstrup et al. 2009). For example, in the Copenhagen City Heart Studies of 42,000 subjects with a 15-year follow-up (Kamstrup et al. 2009) using a Mendelian randomization approach, higher Lp(a) levels were related to risk of MI.

2.1.3 Current Treatment Options

In 2010, the European Atherosclerosis Society (EAS) Consensus Panel recommended screening for elevated Lp(a) in people at moderate to high risk of CVD to reach a treatment goal of < 50 mg/dL (125 nmol/L), after therapeutic management of LDL-C (Nordestgaard et al. 2010). Approximately 20% of people are estimated to have plasma Lp(a) levels over 50 mg/dL (125 nmol/L) and approximately 0.3% to have levels over 175 mg/dL (438 nmol/L). There are no gender differences in Lp(a) concentrations but racial differences have been observed, with whites and Asians having lower levels while blacks and Hispanics generally have somewhat higher levels (Nordestgaard et al. 2010).

Lifestyle and diet are thought to have little impact on an individual's Lp(a) level. Current treatment recommendations from the EAS Consensus Panel are limited to the use of 1 to 3 g of niacin (nicotinic acid) daily which could result in an up to 30% reduction in Lp(a). However, niacin is associated with side effects (e.g., flushing) that reduce patient tolerability and compliance (Parker et al. 2006; Guyton 2007).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are neither indicated nor formally recommended for treatment of hyperlipoproteinemia(a) but have been reported to reduce Lp(a) levels by ~20%-35% in patients with hypercholesterolemia (Desai et al. 2013; Raal et al. 2015).

The other current option for patients with significantly elevated Lp(a) levels (≥ 60 mg/dL) is lipoprotein apheresis, either general lipoprotein apheresis (Jaeger et al. 2009;

Leebmann et al. 2013; Rosada et al. 2014) or Lp(a)-specific apheresis (Safarova 2012). While very effective at acutely lowering Lp(a) (acute and interval Lp(a) reductions of > 60% and > 30% respectively), this treatment option is expensive, burdensome for patients, and unavailable/not reimbursed in many countries and regions.

2.2 Therapeutic Rationale

Therapeutic modalities to reduce Lp(a) levels in humans are few, and there are no drugs currently available that specifically target Lp(a) alone. Antisense oligonucleotides (ASOs) are emerging as viable therapeutic agents to treat disorders where overexpression of proteins is associated with a disease process. Apo(a) is synthesized primarily in the liver, a target organ for ASOs, where it is subsequently covalently linked to the apoB-100 component of LDL to form the Lp(a) lipoprotein. The goal of treatment with ISIS 681257 is to reduce the production of apo(a) in the liver and thus, the level of Lp(a) lipoprotein by using an ASO directed against the messenger ribonucleic acid (mRNA) of apo(a). It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse CVD by reducing thrombotic, atherogenic, or inflammatory events in patients with elevated Lp(a) levels (Nordestgaard et al. 2010).

Importantly, there is no evidence that lowering Lp(a) will result in adverse consequences in individuals, and there are no reports linking very low Lp(a) to any deleterious effects.

2.3 ISIS 681257

Please refer to the ISIS 681257 Investigator's Brochure for more details on ISIS 681257 mechanism of action, chemistry, pre-clinical and clinical experience. The summary is provided below.

2.3.1 Mechanism of Action

ISIS 681257 is a second-generation ASO drug targeted to apo(a) that has been covalently bonded to triantennary *N*-acetyl galactosamine ($GalNAc_3$), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-$GalNAc_3$ conjugate. This $GalNAc_3$-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold compared to unconjugated ASOs in mice (Prakash et al. 2014).

The ASO portion of ISIS 681257 is complementary to a region spanning the Exon 24-25 splice site at position 3901 of apo(a) transcript sequence (NM_005577.2) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 681257 to the cognate mRNA results in the Ribonuclease H1 (a non-specific endonuclease that catalyzes the cleavage of RNA via hydrolytic mechanism RNase H1-mediated degradation of the apo(a) mRNA, thus preventing production of the apo(a) protein). Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

ISIS 681257 does not have any complementary homology to plasminogen mRNA (Graham et al. 2016).

2.3.2 Chemistry

Chemically, ISIS 681257 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and further enhances potency of $GalNAc_3$ conjugated ASOs.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities, thereby resulting in an improved safety profile compared to first-generation antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 681257 employs this chimeric structure to enable use of the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). The fourth region is composed of a triantennary cluster of $GalNAc_3$ sugars that is linked to the 5′ end of ISIS 681257 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 681257 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the $GalNAc_3$ cluster is metabolized to release “free ASO” inside the cell (Prakash et al. 2014).

2.3.3 Preclinical Experience

The pharmacology of ISIS 681257 has been examined in apo(a) transgenic (Tg) mice which express the entire human apo(a) genomic sequence (Frazer et al. 1995) and nonhuman primates.

Administration of ISIS 681257, a human apo(a) antisense inhibitor, to mice containing the human apo(a) transgene produced dose-dependent reductions in human apo(a) liver mRNA and apo(a) plasma protein after 6 weeks of ASO administration at 0.3, 1, 3, and 10 mg/kg/wk.

When ISIS 681257 was administered to normal chow fed cynomolgus monkeys for 4 weeks at the dose of 12 mg/kg/wk, it significantly reduced hepatic apo(a) mRNA by 90% relative to the cohort administered phosphate buffered saline (PBS). As there is an 80% sequence conservation between apo(a) and plasminogen nucleotide sequences, plasminogen mRNA levels were also measured, and no change compared to the PBS cohort was observed.

Findings from the chronic studies with ISIS 681257 (the 26-week mice and 39-week monkey studies) were similar to those observed in the 4- and 6-week studies and were not considered adverse. The plasma and tissue concentrations observed for ISIS 681257 in mice and monkeys were generally similar to those observed for other unconjugated 20-mer 2′-MOE ASOs in this chemical class with and without $GalNAc_3$-conjugation. However, the proportion of drug in

hepatocytes compare to nonparenchymal liver cells was greater for ISIS 681257, compared to the parent drug ISIS 494372 (without $GalNAc_3$-conjugation), which is the basis for increased potency of ISIS 681257 (unpublished results; Geary et al. 2003; Yu et al. 2007; Prakash et al. 2016).

The most noteworthy safety finding in the chronic monkey study was a marked platelet reduction that, occurred in 2 male monkeys in the high-dose group (20 mg/kg/wk) and 1 animal (1 female) in the mid-dose (10 mg/kg/wk) group beginning on Days 44-135, which led to the subsequent early termination (ET) of these 3 animals. An additional male monkey in the 10 mg/kg/wk dose group had a moderate decrease in platelets that was successfully treated with steroid, and was terminated at the scheduled 6-month interim sacrifice. There were no platelet reductions or other toxicologically significant findings in monkeys treated with 2 mg/kg/wk for up to 39 weeks. There were no marked platelet reductions in mice at doses up to 70 mg/kg/wk for 26 weeks. However, mice exposed to ISIS 681257 at doses of ≥ 10 mg/kg/wk for up to 26 weeks showed evidence of hepatobiliary effects in both sexes as indicated by increases in ALT (up to + 10.3x), AST (up to + 10.4x), and/or ALP (+ 2.5x).

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 681257 can be found in the Investigator's Brochure. A summary of the study that has been conducted with ISIS 681257 is included below.

ISIS 681257-CS1 was a Phase 1 double-blind, placebo-controlled, dose-escalation study designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple doses of ISIS 681257 administered subcutaneously (SC) to 45 healthy subjects with Lp(a) ≥ the upper limit of normal (ULN) (30 mg/dL). Twenty one (21) subjects received 10 to 120 mg SC (10, 20, 40, 80, and 120 mg) as a single-dose, and 24 subjects received 10, 20, and 40 mg as multiple doses (6 doses in 21 days: 3 loading doses during the first week on alternate days (Days 1, 3, and 5), and then once a week for the next 3 weeks (Days 8, 15, and 22).

There were no serious adverse events (SAEs), or clinically-relevant changes in laboratory assessments and all subjects completed the treatment and post-treatment follow-up periods.

Constitutional symptoms such as fever, chills, increase in body temperature and arthralgias have been observed following parenteral administration of ASOs, primarily during the initial dosing period. Following SC administration of ISIS 681257 constitutional symptoms were observed in 4 of the 6 subjects who received a single-dose of 120 mg. The symptoms were mild in severity and resolved spontaneously with or without treatment with acetaminophen.

Fluctuations in platelet counts to below the lower limit of normal were observed in 5 study subjects on active drug and across doses. These changes were not considered adverse or clinically-significant by the Investigator and did not appear to be dose related.

Two (2) mild AEs of redness at the site of injection occurred 48 to 72 hours after administration in 1 subject who received ISIS 681257 in the 20 mg multiple-dose cohort. Both AEs resolved by the time of the subject's next visit.

Following SC administration, ISIS 681257 was absorbed rapidly into the systemic circulation, with median time to maximum plasma concentrations (T_{max}) ranging from 1 to 4 hours. Similar T_{max} values were observed at all dose levels. Maximum observed plasma concentrations (C_{max}) and $AUC_{0\text{-}24hr}$ were dose-dependent over the studied SC dose range. The mean peak (C_{max}) and total exposure ($AUC_{0\text{-}24hr}$) increased proportionally with dose at dose levels ranging from 10 to 40 mg, and greater than dose proportionally at dose levels ranging from 40 to 120 mg.

After reaching C_{max}, mean plasma concentrations of ISIS 681257 declined in a biphasic fashion over time, with an initial, relatively fast distribution phase that dominated the plasma clearance followed by a slower elimination phase. Characterization of the terminal elimination phase yielded an apparent terminal elimination half-life of approximately 3 to 4 weeks over a dose range of 10 to 120 mg (either single- or multiple-dose), and appeared to be independent of dose. This result is consistent with the slow elimination of ISIS 681257 observed from monkey tissues, and the comparatively long elimination half-lives observed for this chemical class.

Plasma trough concentrations (168 hours or 7 days from previous dose) monitored during the treatment period in the multiple-dose cohorts increased with increasing dose, consistent with expectations (based on preclinical assessments and experience with other compounds of this chemical class) that trough plasma concentrations reflect exposure in tissues. Plasma trough concentrations did not increase greatly after the loading period (Day 15), suggesting that accumulation in major tissues of distribution had approached steady-state after the loading period.

Overall, the human PK of ISIS 681257 are consistent with the expected PK for compounds within this chemical class.

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 681257 doses of 10 mg, 20 mg, and 40 mg given weekly that were found to be generally well-tolerated and to induce clinically-relevant reductions in Lp(a).

The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) $\leq$ 30 mg/dL).

The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally

driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio (225 ISIS 681257 and 45 placebo) to receive ISIS 681257 or placebo. Study Drug (ISIS 681257 or placebo) will be administered SC every week, every 2 weeks (biweekly), 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.

The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received 2-week or weekly dosing (Cohorts D and E). For patients continuing treatment beyond the primary analysis time point additional supportive efficacy analysis (to evaluate whether the treatment effect is maintained) and safety analysis (for the purpose of dose(s) selection) will be repeated at the completion of Study Drug treatment.

The treatment portion of the study will be complete when the last enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period.

Patients ≥ 18 and ≤ 80 years old with elevated plasma Lp(a) levels (≥ 60 mg/dL) and a clinical diagnosis of CVD are eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for other than elevated Lp(a) 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 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). 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 5 parallel dosing cohorts, with each cohort having a 5:1 ratio to receive ISIS 681257 or matching volume of placebo, respectively, by SC injection for up to 52 weeks.

Following the End-of-Treatment, patients will enter the 16-week post-treatment follow-up period.

3.2 Number of Study Centers

This is a multicenter, multinational study.

3.3 Number of Patients

Approximately 270 patients will be randomized in this study, with approximately 54 patients assigned to each of the 5 treatment cohorts.

3.4 Overall Study Duration and Follow-up

The length of patients' participation in the study may be up to 18 months (72 weeks), which includes a 4-week screening period, an up to 52-week treatment period with Study Drug (ISIS 681257 or placebo), and a 16-week post-treatment follow-up period. The treatment portion of the study will be complete when the last enrolled 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 maximum of 52 weeks.

All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may continue treatment within the same randomized cohort until the last enrolled patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. When this milestone is met, all patients will then enter a 16-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 681257 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 16-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits 4, 10, and 16 weeks after their last injection of Study Drug as per Appendix A (Follow-up).

The final study visit for each patient will be 16 weeks after the last dose of Study Drug.

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 681257 during this study. The DSMB will be constituted to include expertise in medical specialties relevant to the safety of antisense drugs (nephrology, hepatology, hematology and cardiology). Specialist members of the DSMB will be informed and consulted on all treatment-related SAEs relevant to their expertise and all changes of relevant laboratory parameters that trigger stopping rules (Section 8.6), within 48 hours of receipt of such results. In addition, all accrued safety data relevant to each of medical area specialist will be forwarded monthly for review.

The full DSMB review of all accumulated data will be performed quarterly. Based on its ongoing assessment of the safety and tolerability of ISIS 681257, 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 1:1:1:1:1 ratio to 1 of the 5 parallel-dose cohorts (Cohorts A, B, C, D, or E). Within each dose cohort, patients will be randomized in a 5:1 ratio to receive ISIS 681257 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 a 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 at within 4 weeks of Study Day 1or 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. Clinical diagnosis of CVD defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease
4. Lp(a) plasma level ≥ 60 mg/dL
5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors
6. 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, proprotein convertase subtilisin/kexin type 9 [PCSK9s] 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

7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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

8. 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 16 weeks after the last dose of ISIS 681257

5.2 Exclusion Criteria

1. Within 6 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke/transient ischemic attach

2. Within 3 months of Screening: coronary or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis

3. Heart failure New York Heart Association (NYHA) class 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 with a history of major bleed or high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
    a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr
    b. Urine albumin/creatinine ratio (UACR) ≥ 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of < 150 mg/24-hr
    c. Estimated GFR < 60 mL/min (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance
    d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN
    e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
    f. Alkaline phosphatase (ALP) > ULN
    g. Platelet count < LLN
13. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors
14. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
15. Treatment with any 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
16. BMI > 40 kg/m^2
17. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
18. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
19. 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. A 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.

On confirmation of eligibility and prior to randomization, patients will also undergo a 24 hr urine collection for creatinine, albumin, and protein as a baseline assessment.

6.1.2 Treatment Period

During the treatment period, patients will report to the study center for clinic visits. Patients will receive 20 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort A, 40 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort B, 60 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort C, 20 mg doses of Study Drug administered by SC injection once every 2 weeks for up to 52 weeks in Cohort D, or 20 mg doses of Study Drug administered by SC injection once per week (weekly) for up to 52 weeks in Cohort E (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 681257 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 12 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 681257. 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 16 weeks after the last dose of Study Drug. During the post-treatment follow-up period, patients will return to the Study Center

for 3 outpatient visits at Weeks 4, 10, and 16 after the last dose of Study Drug 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. A list of these analytes is contained in Appendix B.

Routine blood chemistry and urine samples (excluding 24-hour urine collection) should be taken after fasting for at least 10 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status. 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).

Hematology samples will be collected every 14 days. Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample must 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.

Blood and urine samples for renal function testing will also be collected every 14 days and sent to the central laboratory for analysis, per Section 8.5.2. If there are no test results available within 14 days of the last set of results for parameters considered critical to patient safety, the Investigator will contact the patient to hold dosing until a new test set is obtained and reviewed.

Liver function testing will also be collected every 14 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 sent to the central laboratory are received on the next day 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 on the day of sample collection, 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 (Grade 3 or Grade 4) 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.

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

In all cohorts, ECGs will be conducted during the post-treatment follow-up period at 4, 10, and 16 weeks after the last dose of Study Drug.

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 681257 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 16 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 16 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 1 or more 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 before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 681257 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 681257 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 681257

ISIS 681257 vials contains 100 mg/mL ISIS 681257 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 681257 vials.

Table 1 Study Drug Characteristics

Study Drug	ISIS 681257	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 681257 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 681257 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 681257 will be administered to patients by Study Center staff as follows:

Cohort A: a single SC dose of 20 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort B: a single SC dose of 40 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort C: a single SC dose of 60 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort D: a single SC dose of 20 mg every 2 weeks for up to 52 weeks and a maximum of 26 doses

Cohort E: a single SC dose of 20 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, B, and C should receive 1 dose every 4 weeks, patients in Cohort D should receive 1 dose every 2 weeks and Cohort E 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 681257 or placebo) preparation and administration.

Table 2 Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 681257
A	20 mg ISIS 681257 or placebo (Every 4 weeks)	0.2 mL	≤ 13	≤ 260 mg
B	40 mg ISIS 681257 or placebo (Every 4 weeks)	0.4 mL	≤ 13	≤ 520 mg
C	60 mg ISIS 681257 or placebo (Every 4 weeks)	0.6 mL	≤ 13	≤ 780 mg
D	20 mg ISIS 681257 or placebo (Every 2 weeks)	0.2 mL	≤ 26	≤ 520 mg
E	20 mg ISIS 681257 or placebo (Every week)	0.2 mL	≤ 52	≤ 1040 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

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 681257 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, patients must not be re-dosed 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 681257 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 2 weeks for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period.

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 (within 48 hours of receipt) reviewed by the Investigator and Medical Monitors.

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

All patients will have renal function tests monitored every 2 weeks throughout the study.

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.

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 to estimate glomerular filtration rate

(eGFR), which will be monitored every 2 weeks. In addition, biomarkers of acute renal injury will also be measured every 2 weeks (Appendix B).

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than every 2 weeks 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 at the weekly safety review 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: Creatinine clearance (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 an 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.

In the event of a confirmed (as described in Section 8.5) laboratory result meeting one or more of the above criteria, dosing with the Study Drug should be interrupted and the Study Medical Monitor informed. In addition, the following supplemental renal tests should be immediately obtained:

> Serum creatinine, urine culture, 24-hour urine sample for creatinine clearance, urine albumin and urine protein, urine microscopy sample with inspection of sediment.

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.

8.5.3 Safety Monitoring for Platelet Count Results

All patients will have platelet counts monitored every 2 weeks for the duration of the study and must not receive Study Drug without an interpretable platelet count result in the prior 2 weeks. In addition, platelet function will be evaluated by aggregometry, using an approved point-of-care diagnostic device, in all patients at each study site visit, with additional functional testing being performed at selected study centers.

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.

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm^3; 2) when platelet count is ≥ 30% decreased from baseline, or 3) when 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 D, 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 Minor Bleeding Events

Patients will be instructed to promptly report any signs or symptoms of bleeding. Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, or gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, hepatic enzymes, bilirubin and platelet count should be performed.

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 symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.6 Stopping Rules

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 of an estimated creatinine clearance (by CKD-EPI formula) meeting any of the following criteria, or any change in renal biomarkers deemed by the nephrologist on the DSMB to require further evaluation, a serum creatinine and 24-hour urine sample for creatinine clearance and protein should be obtained:

1. CKD-EPI decrease of > 40% from Baseline

2. CKD-EPI value < 45 mL/min/1.73 m^2

Dosing of a patient with Study Drug (ISIS 681257 or placebo) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

1. Urine protein is > 1.0 g

2. Creatinine clearance decrease of > 40% from baseline

3. Creatinine clearance < 45 mL/min/1.73 m^2

Irrespective of whether the stopping rule is confirmed or not, 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

Stopping Rules 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 steroids 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

steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids 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; Schulman et al. 2005), 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 irrespective of whether the platelet count rises into the normal range.

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

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every week*
75K-100K/mm^3	Permanently reduce as follows: For Cohort A: reduce to 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 weeks For Cohort E: reduce to 10 mg every week	Closer observation Monitor every week*
50K-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 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 week For Cohort E: reduce to 10 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)/ anticoagulant medication
25K-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/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 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 and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* Once a patient commences weekly monitoring this frequency of monitoring should continue irrespective of whether the platelet count rises into the normal range.

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: 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 Section 8.6.3 and 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 8.6.3
- 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 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 after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Following 6 weeks of Study Drug discontinuation, patients should be strongly encouraged to attend planned Study Center visits (including End-of-Treatment Week 53 visit and final Post-Treatment Follow-up visit 16 weeks after their last dose of Study Drug) to collect the study assessments in accordance with the Schedule of Procedures in Appendix A.

If the patient declines or is unable to participate in the above, an ET visit (Week 53 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

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 permanently discontinues Study Drug (see Section 8.8)
- 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 study procedures 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 study procedures and observations at the time of withdrawal (see Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. 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, PCSK9 inhibitors, niacin, fibrates, fish oil, other products containing omega-3 fatty acids (including OTC preparations)
- Anti-platelet therapies
- Testosterone, estrogens, progesterone, growth hormone, or progestins.

Disallowed Concomitant Therapy

Use of the following is disallowed:

- Warfarin, 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 of platelet count, and liver and renal function as described in Section 6.2.1, Sections 8.5.1-8.5.3, and Sections 8.6.1-8.6.3.

Patients will be required to have platelet counts every 2 weeks 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.

Patients will also be required to have renal function testing and assessment of biomarkers of renal damage every 2 weeks, and must not receive Study Drug if there are no test results for parameters considered critical to patient safety available within the prior 2 weeks. 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 (Grade 3 or Grade 4) is considered an adverse event 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 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 Suspected Adverse Reaction

An adverse reaction is any AE caused by the Study Drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

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

- Results in death
- Is life threatening, that is, poses an immediate risk of death at the time of the event
- An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 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. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. 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 681257 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 681257 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 681257 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 681257 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 (Grade 3 or Grade 4) 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.

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 681257 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 681257 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 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-C) and at Week 27 for patients who received weekly or biweekly dosing (Cohorts D and E). 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 endpoint is the percent change in Lp(a) from baseline at the primary analysis time point achieved by ISIS 681257 compared to pooled placebo.

Lp(a) levels will be analyzed from patient blood samples taken at specified time points throughout the study.

10.1.2 Secondary Endpoints

The secondary endpoints include the following parameters from baseline at the primary analysis time point for ISIS 681257 compared to placebo:

- Percent change from baseline in LDL-C
- Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL
- Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL
- Percent change from baseline in apoB
- Percent change from baseline in OxPL-apo(a)
- Percent change from baseline in OxPL-apoB

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 events by severity, number of patients meeting renal stopping rules, and change in renal function tests by severity.
- ECGs
- 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 clinically-meaningful reduction in plasma Lp(a) 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, and renal or hepatic injury.

10.2 Sample Size Considerations

Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients.

Based upon prior clinical trial experience with Ionis ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event.

Therefore, approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.

10.3 Analysis Populations

Full Analysis Set (FAS): All patients who are randomized, received at least 1 dose of Study Drug (ISIS 681257 or placebo), and have a Baseline Lp(a) 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, B, and C or at least 20 weekly doses for patients randomized in Cohorts D and E, 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 Study Drug, and have sufficient data for the analysis of PK parameters. This population will be used for analysis of PK data.

10.4 Definition of Baseline

Baseline for Lp(a), LDL-C, apoB, OxPL-apo(a), OxPL-apoB, and other lipid measurements will be defined the pre-dose measurement on Day 1 or 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 681257 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 681257 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 681257 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 analysis of the primary endpoint will be the pairwise comparison of percent change from baseline to primary analysis time point in fasting Lp(a) between ISIS 681257 treatment groups and pooled placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the Baseline Lp(a) 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 at least 50% of randomized patients have completed Week 52 visits, 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 LDL-C will be compared between each ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate
- Proportion of patients who achieve $\leq$ 50 mg/dL in fasting Lp(a) at the primary analysis time point will be compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with Baseline Lp(a) as a covariate. Proportion of patients who achieve $\leq$ 30 mg/dL in fasting Lp(a) at the primary analysis time point will be analyzed similarly
- Percent change from baseline at the primary analysis time point in fasting apoB, OxPL-apo(a) and OxPL-apoB will be compared between ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate

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 681257 in plasma (as total full length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 681257) will be determined and summarized by treatment with stratification by subject immunogenicity status using descriptive statistics.

In addition, non-compartmental PK analysis of ISIS 681257 concentrations will be carried out on each individual patient data set in patients who received ISIS 681257 treatment, and the plasma disposition half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate, using available data at the End-of-Treatment and the post-treatment follow-up period from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, where λz is the rate constant associated with the apparent terminal elimination phase.

For patients in the PK subgroup only, non-compartmental PK analysis of ISIS 681257 will be carried out on each individual patient data set in patients who received ISIS 681257 treatment. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Following single dosing (Day 1), area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours after the dose ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Following multiple dosing, $AUC_{0\text{-}24hr}$ and area under the plasma concentration-time curve during the time of each sampled dosing interval (tau,τ) at steady-state (AUC_{τ}) will be calculated using the linear trapezoidal rule.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Plasma PK parameters will be summarized using descriptive statistics with stratification by subject immunogenicity status. Exposure-response relationships between selected PD [e.g., Lp(a)] and PK measures (including but may not be limited to plasma trough concentrations) may be explored (including with and without stratification by IM status) in this study, or in a separate population PK analysis with all clinical studies combined.

The immunogenicity (IM) of ISIS 681257 will be assessed before, during, and after treatment with Study Drug (ISIS 681257 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 681257 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 681257 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.

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
12- lead ECG (triplicate)	X	X		X		X		X		X				X		X		X	X	X	X	X
24-Hour Urine for Creatinine Clearance and Protein	X																					
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																		X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																		X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																		X	X	X
Genetic Testing		X																				
Chemistry Panel [j,k]	X	EVERY 14 DAYS [f]				X	X	X	X				X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																		X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Coagulation	X	X								X												
Hepatitis B, C, HIV	X																					
Thyroid Panel	X																					
hsCRP		X								X									X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X	X[3]	X[1]	X[2]	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X				X									X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[a]**	**185[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
FSH (women only, if applicable) [j, m]	X																					
Serum Pregnancy Test [m]	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
PD Panel [j]	X	X		X	X	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
Lp(a) Characterization		X																				
Study Drug: SC Injection		WEEKLY AND EVERY 2-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 53/Day 365)[o]																				
Adverse Events	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

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then every 6 weeks.

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.

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

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 as per Section 6.2.1. 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.) in this or subsequent clinical studies of ISIS 681257.

o Patients will continue treatment in the study until the last patient enrolled reaches 6 months of exposure, and 50% of the enrolled patients have received Study Drug for 52 weeks. When both of these milestones are met, all patients will then enter a 16-week post-treatment follow-up period.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8 hours post SC injection

Appendix A Schedule of Procedures – Every 4-Week Dosing

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
Physical Examination	X	X		X		X		X	X						X		X		X	X	X	X	X
Body Weight and Height [d]	X								X								X						X
12- lead ECG (triplicate)	X	X		X		X		X	X						X		X		X	X	X	X	X
24-hour Urine for Creatinine Clearance and Protein	X																						
Extended Urinalysis [e]	X	EXTENDED URINALYSIS PERFORMED EVERY 14 DAYS [e, f]																			X	X	X
Renal Biomarkers [g]	X	RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [f, g]																			X[h]	X[h]	X[h]
Serum Creatinine and Cys-C [i, j]		SERUM CREATININE and Cys-C PERFORMED EVERY 14 DAYS [f, i]																					
Genetic Testing		X																					
Chemistry Panel [j, k]	X	EVERY 14 DAYS [f]				X	X	X						X	X	X	X	X	X	X	X	X	X
Hematology [j, k]	X	HEMATOLOGY PERFORMED EVERY 14 DAYS [f, k]																			X[h]	X[h]	X[h]
Platelet Function		X		X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X														
Hepatitis B, C, HIV	X																						
Thyroid Panel	X																						
hsCRP		X							X											X			X
Plasma PK - ISIS 681257 [l]		X[3]	X[1]	X	X	X	X	X	X[3]	X[1]	X[2]	X	X	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X			X											X			X

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[a]**	**171[a]**	**176[a]**	**183[a]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[b]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
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
Archived Serum & Plasma Samples [j, n]		X			X		X		X					X		X		X		X	X	X	X
PD Panel [j]	X	X		X	X	X	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	X
Lp(a) Characterization		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
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X

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 (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then every 6 weeks.

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.

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

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 as per Section 6.2.1. 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.) in this or subsequent clinical studies of ISIS 681257.

o Patients will continue treatment in the study until the last patient enrolled reaches 6 months of exposure, and 50% of the enrolled patients have received Study Drug for 52 weeks. When both of these milestones are met, all patients will then enter a 16-week post-treatment follow-up period.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8, hrs post SC injection

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 681257 or other similar oligonucleotides.

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

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)
- TSH
- Free T4
- Free T3

Coagulation
- Fibrinogen
- Plasminogen

PD Panel
- Lp(a)
- OxPL-apoB
- OxPL-apo(a)

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL

Lp(a) Characterization
- Apo(a) isoforms

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 681257 (total full length ASO) levels in plasma

Immunogenicity
- Anti-ISIS 681257 antibodies

Genetic Testing
- LPA SNPs associated with elevated Lp(a)

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

24 Hour Urine Test[3]
- Creatinine clearance
- Protein
- Albumin

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 681257 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.

3 To be performed during Screening upon confirmation of eligibility

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 681257 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 681257 with plasma constituents. Extensive PK samples will be collected in PK subgroup only (10 subjects 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**	**27**			**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184**	**185**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime
PK Sub-group Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	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	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

1 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

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**	**25**			**26**	**27**	**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**170**	**171**	**176**	**183**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose,	NA	NA	NA	NA	NA	Pre-dose	Pre-dose	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	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

1 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

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/mm^3

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

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

Collaborator:
Akcea Therapeutics
55 Cambridge Parkway, Suite 100
Cambridge, MA 02142

IONIS PHARMACEUTICALS, INC.

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 3 – 9 December 2016

EudraCT No: 2016-003373-18

ISIS 681257-CS6

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Protocol Amendment 3 – 9 December 2016

Protocol History:

Original Protocol:	15 August 2016
Protocol Amendment 1:	12 October 2016
Protocol Amendment 2:	29 November 2016

Sponsor:

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2855 Gazelle Court
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[redacted]
[redacted], MD, MBA
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55 Cambridge Parkway, Suite 100
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ISIS 681257-CS6

Ionis Protocol Number ISIS 681257-CS6

Protocol Amendment 3

EudraCT No: 2016-003373-18

Clinical Phase: 2

A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

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Mobile: [redacted]
E-mail: [redacted]

Date: 9 December 2016

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment: Amendment 3

Date: 9 December 2016

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 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)," dated 9 December 2016, 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.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 681257-CS6

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

Amendment Number: 3

Amendment Date: 9 December 2016

The following table summarizes the history of amendments to the protocol of Study ISIS 681257-CS6. None of the antecedent versions of the study protocol has been enacted clinically and therefore no patients have been enrolled prior to issuance of Amendment 3.

Protocol Version	Date	Rationale for Amendments
Original Protocol	15 August 2016	
Amendment 1	6 October 2016	Regulatory advice on inclusion of more detailed description of processes for platelet monitoring, and more frequent monitoring of liver function.
Amendment 2	29 November 2016	Regulatory advice on inclusion of biomarkers of renal damage and increased frequency of renal monitoring.
Amendment 3	9 December 2016	The study population was increased to 270 patients (54 per cohort) to support a statistical assessment of risk of platelet reduction in this population. In addition, the treatment cohorts have been modified to reflect both potential doses and dose regimens.

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)
Study Phase	2
Indication	Patients with hyperlipoproteinemia(a) and established CVD.
Investigational Drug	ISIS 681257 is a second generation 2'-MOE modified, $GalNAc_3$–conjugated antisense oligonucleotide inhibitor of apolipoprotein (a) [apo(a)].
Primary Objective	To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy and safety of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.
Secondary Objective(s)	To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B100 (apoB), oxidized phospholipids (OxPL) on apo(a) [OxPL-apo(a)], and OxPL on apoB (OxPL-apoB). To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in patients with hyperlipoproteinemia(a) and established CVD.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio to receive ISIS 681257 or placebo. This number was chosen to provide statistical power for both efficacy and safety assessments. Study Drug (ISIS 681257 or placebo) will be administered SC 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 enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period. The primary efficacy and safety analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, 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 (as needed) data collected on ISIS 681257 during this study, both individual events and aggregate data.
Number of Subjects	Approximately 270
Study Population	<u>Inclusion Criteria</u> 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. Clinical diagnosis of CVD defined as documented coronary artery disease, stroke, or peripheral artery disease 4. Lp(a) plasma level ≥ 60 mg/dL 5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Inclusion Criteria 6. 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 7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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 8. 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 16 weeks after the last dose of ISIS 681257 Exclusion Criteria 1. Within 6 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 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

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria 10. Patients with a history of major bleed or high-risk of bleeding diathesis 11. Recent history of, or current drug or alcohol abuse 12. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following: a. Urine protein/creatinine (P/C) ratio ≥ 0.25 mg/mg. In the event of a P/C ratio above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24-hr b. Positive test (including trace) for blood upon urinalysis. In the event of a positive test, eligibility may be confirmed with a urine microscopy showing ≤ 5 red blood cells (RBCs) per high power field c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN d. Estimated GFR < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance) e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL f. Alkaline phosphatase (ALP) > ULN g. Platelet count < LLN 13. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors 14. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 15. Treatment with any 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 16. BMI > 40 kg/m^2 17. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening 18. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 19. 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

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Treatment Groups</td><td>Patients will be randomized to 5 parallel cohorts:

Cohort A (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort B (n = 54): Patients will be randomized 5:1 to receive 40 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort C (n = 54): Patients will be randomized 5:1 to receive 60 mg ISIS 681257 or placebo SC once every 4 weeks for up to 13 doses.

Cohort D (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every 2 weeks for up to 26 doses.

Cohort E (n = 54): Patients will be randomized 5:1 to receive 20 mg ISIS 681257 or placebo SC every week for up to 52 doses.

<table>
<tr><th>Cohort</th><th>Treatment</th><th># Doses</th><th>Total ISIS 681257</th></tr>
<tr><td>A</td><td>20 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 260 mg</td></tr>
<tr><td>B</td><td>40 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 520 mg</td></tr>
<tr><td>C</td><td>60 mg ISIS 681257 or placebo (Every 4 weeks)</td><td>≤ 13</td><td>≤ 780 mg</td></tr>
<tr><td>D</td><td>20 mg ISIS 681257 or placebo (Every 2 weeks)</td><td>≤ 26</td><td>≤ 520 mg</td></tr>
<tr><td>E</td><td>20 mg ISIS 681257 or placebo (Every week)</td><td>≤ 52</td><td>≤ 1040 mg</td></tr>
</table>
</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>The Sponsor will provide ISIS 681257 in a concentration of 100 mg/mL and matching volume placebo:

Cohort A: 20 mg every 4 weeks ISIS 681257 or placebo (0.2 mL)

Cohort B: 40 mg every 4 weeks ISIS 681257 or placebo (0.4 mL)

Cohort C: 60 mg every 4 weeks ISIS 681257 or placebo (0.6 mL)

Cohort D: 20 mg every 2 weeks ISIS 681257 or placebo (0.20 mL)

Cohort E: 20 mg every week ISIS 681257 or placebo (0.20 mL)

All doses will be given by SC injection. Self-administration will be allowed after appropriate training of patient and/or caregiver.</td></tr>
<tr><td>Rationale for Dose and Schedule Selection</td><td>The Phase 1 study, ISIS 681257-CS1, evaluated 3 multiple-dose cohorts of ISIS 681257, 10 mg, 20 mg, and 40 mg. Subjects were randomized (8:2 active:placebo) to receive ISIS 681257 for a total of 6 doses administered by SC injection: 3 doses during the first week and then once a week for the next 3 weeks. These doses at this frequency of administration were found to be generally well-tolerated and to induce clinically-relevant reductions in LP(a).

The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) ≤ 30 mg/dL).</td></tr>
</table>

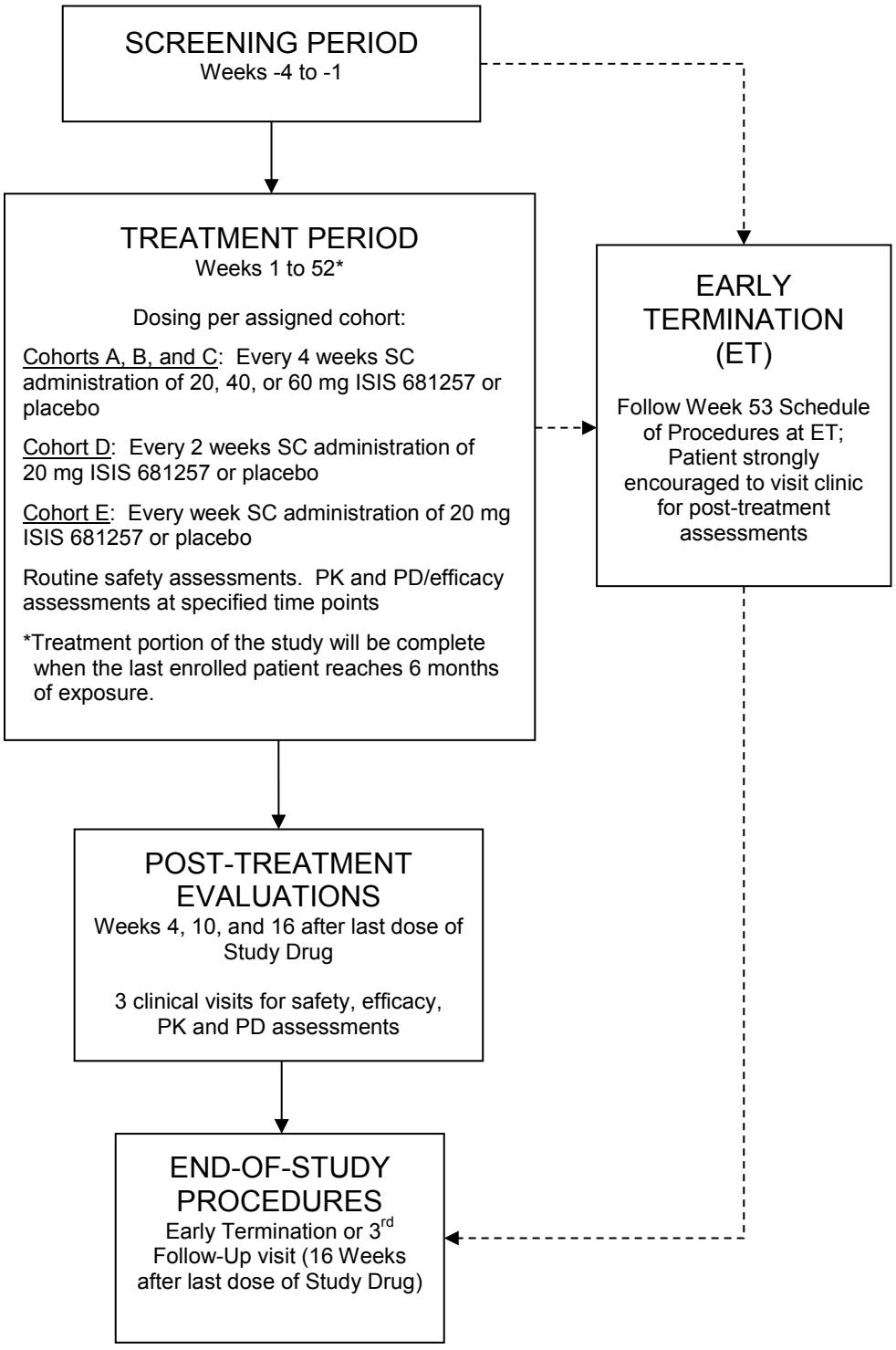
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection *Continued*	The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.
Adjustment of Dose and/or Treatment Schedule	Dose adjustments, including dose interruptions, and/or decreasing the dose 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 are outlined in Section 6, Appendices A and C. All patients enrolled will be randomized to a minimum of 6 months of treatment in 1 of 5 treatment cohorts. On completion of the 6 months, patients may continue treatment within the same randomized cohort until the last enrolled patient reaches 6 months of exposure (for continuing safety assessments), with a maximal exposure period of 12 months. The study for an individual patient will generally consist of the following periods: An up to 4-week screening period An up to 52-week treatment period during which Study Drug will be administered per assigned cohort by SC injection A 16-week post-treatment follow-up period Patients in Cohorts A through C will receive up to 13 SC doses of ISIS 681257 or placebo every 4 weeks. Patients in Cohort D will receive up to 26 SC doses of ISIS 681257 or placebo every 2 weeks and patients in Cohort E will receive up to 52 weekly SC doses of ISIS 681257 or placebo. Patients will return regularly for outpatient visits throughout the treatment and post-treatment follow-up periods according to the Schedule of Procedures (Appendix A). 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 and use of concomitant medications. Safety and tolerability results, including results of laboratory tests related to the monitoring rules for platelets, liver and renal functions, in patients dosed with ISIS 681257 will be compared with those dosed with placebo.
Efficacy Evaluations	The primary analysis time point is at Week 25 for patients who received every 4-week dosing (Cohorts A-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, respectively). The primary endpoint is the percent change in plasma Lp(a) from baseline at the primary analysis time point for ISIS 681257 treatment groups compared to placebo. The secondary endpoints comprise the effect of ISIS 681257 as compared to placebo at the primary analysis time point on the following: • Percent change from baseline in LDL-C • Proportion of patients who achieve plasma Lp(a) ≤ 50 mg/dL • Proportion of patients who achieve plasma Lp(a) ≤ 30 mg/dL, • Percent change from baseline in apoB • Percent change from baseline in OxPL-apo(a) • Percent change from baseline in OxPL-apoB

PROTOCOL SYNOPSIS *Continued*

Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 681257 plasma trough levels throughout treatment and during the post-treatment follow-up period. In addition, in a subset of patients (approximately 12 patients per cohort), more frequent plasma samples will be taken following the Day 1 and Day 169 doses (for Cohorts A, B, and C) or following the Day 1 and Day 183 doses (for Cohorts D and E) to determine PK parameters. Plasma sample collection time points are detailed in Appendices A and C. The plasma ISIS 681257 levels over time will be descriptively summarized by treatment with stratification by subject immunogenicity status. Apparent terminal elimination half-life will be calculated in patients who received ISIS 681257 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 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 Lp(a) between ISIS 681257 treated groups and placebo group in the Full Analysis Set. The data will be analyzed using an ANCOVA model with the baseline Lp(a) 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 plasma Lp(a) 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. Sample Size Considerations: <u>Efficacy:</u> Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients. <u>Safety:</u> Based upon prior clinical trial experience with ISIS ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event. A total of approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.
Sponsor/Collaborator	Ionis Pharmaceuticals/Akcea Therapeutics

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
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
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
CMV	cytomegalovirus
CRF	case report form
CRP	C-reactive protein
CVD	cardiovascular disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
DNA	phosphorothioate-modified oligodeoxynucleotides
DSMB	Data and Safety Monitoring Board
CKD-EPI	Chronic Kidney Disease –Epidemiological Collaboration
Cys C	Cystatin C
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
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL-1β	interleukin-1 beta
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 681257	antisense inhibitor of apolipoprotein (a)
IV	intravenous(ly)
IXRS	interactive voice/internet response system
KIM-1	kidney injury molecule 1
kg	kilogram

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
L	Liter
LLN	lower limit of normal
m^2	square meter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MI	myocardial infarction
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
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OxPL	oxidized phospholipids
PAD	peripheral arterial disease
PBS	phosphate buffered saline
PCSK9	proprotein convertase subtilisin/kexin type 9
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLA_2	Lp(a)-associated Lp-phospholipase A_2
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

STUDY GLOSSARY *Continued*

Abbreviation	**Definition**
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Drug	ISIS 681257 or placebo
SUSAR	suspected unexpected serious adverse reaction
Tg	transgenic
T_{max}	time to maximal concentration
UACR	urine albumin -creatinine ratio
ULN	upper limit of normal
UPCR	urine protein- creatinine ratio
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy and safety of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established cardiovascular disease (CVD).

1.2 Secondary Objective(s)

To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), oxidized phospholipids (OxPL) on apolipoprotein (a) [apo(a)] [OxPL-apo(a)] and OxPL on apoB (OxPL-apoB).

To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in in patients with hyperlipoproteinemia(a) and established CVD.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Lipoprotein (a)

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein (Figure 1, Koschinsky and Marcovina 2004) in which the apoB component of LDL is linked by a disulfide bond to apolipoprotein(a) [apo(a)], the distinct protein component of Lp(a) that is mainly responsible for its signature structural and functional properties (Dubé et al. 2012; Kronenberg and Utermann 2013). Lp(a) is now recognized as an independent, genetic, causal risk factor for coronary artery disease (CAD), stroke, peripheral arterial disease (PAD), and calcific aortic stenosis (Erquo et al. 2009; Nordestgaard et al. 2010; Thanassoulis et al. 2013).

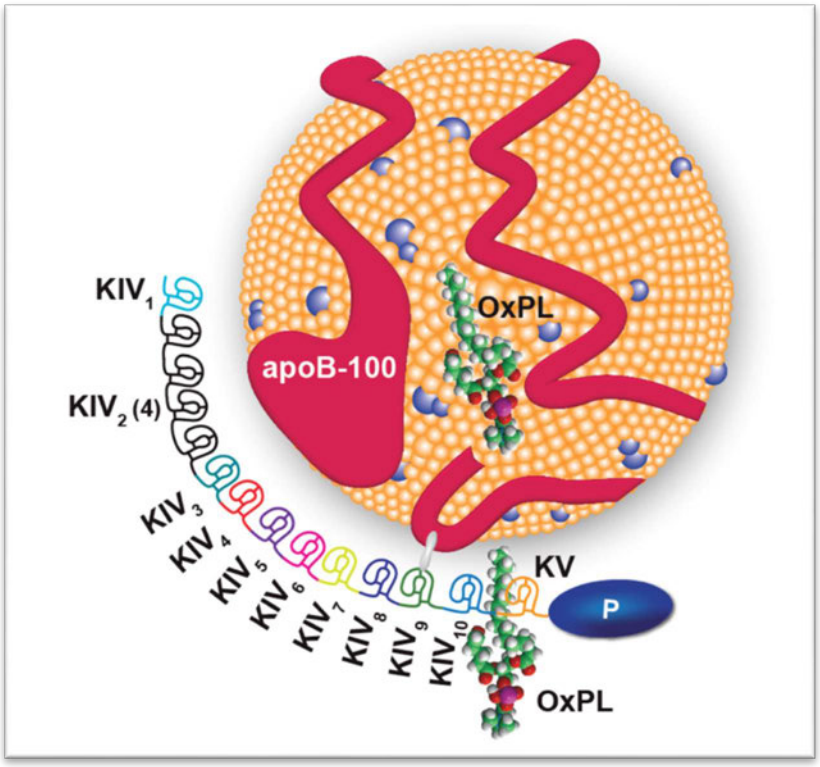


Figure 1 Schematic Representation of the Lp(a) Particle. Lp(a) is Composed of apo(a) Covalently Bound to apoB

Apo(a) contains 10 unique units of kringle IV repeats, of which KIV2 are present in variable copies (1 to > 40) conferring structural heterogeneity to Lp(a). Apo(a) also contains kringle V and an inactive protease-like (P) domain. In this model, 4 KIV2 repeats are shown. Lp(a) also contains OxPL in the lipid phase of apoB as well as covalently bound to apo(a).

Plasma levels of Lp(a) vary substantially among individuals, and most of this variation reflects the effects of genetic variation in the *LPA* gene which encodes the apo(a) protein.

A second contributor to plasma-level variability are LPA single nucleotide polymorphisms (SNPs) that can be associated with either higher or lower Lp(a) levels (Clarke et al. 2009; Li et al. 2011). Significant associations exist between 2 particular LPA variants, rs10455872 and rs3798220, increased Lp(a) levels, CVD, and aortic stenosis, with the CVD risk primarily mediated by Lp(a) plasma levels rather than an independent effect of the SNPs (Clarke et al. 2009; Li et al. 2011).

Lp(a) plasma levels are generally inversely associated with apo(a) size, and can vary by > 1,000-fold (0.1 to > 250 mg/dL or < 0.25 to > 625 nmol/L) between individuals (Merki et al. 2011). Despite this inter-individual variation, intra-individual Lp(a) levels are thought to be generally stable over time along a pre-set genetically determined levels without significant impact from dietary or environmental factors, mediating CVD risk throughout the patient's lifetime.

2.1.2 Pathophysiology

Lp(a) adheres to plaque sites and is retained in the artery wall and has proatherogenic and pro-inflammatory properties due to its LDL and apo(a) components (Spence and Koschinsky 2012). In addition, Lp(a) may be prothrombotic by inhibiting fibrinolysis because of its structural similarity to plasminogen and its enhancement of platelet aggregation (Rand et al. 1998). *In vitro* studies have provided evidence for both of these pathogenic mechanisms, but *in vivo* data are not definitive (Dubé et al. 2012). In humans, Lp(a) is the main lipoprotein carrier of OxPL, which may drive the risk associated with Lp(a) (Bergmark et al. 2008; Leibundgut et al. 2013; Tsimikas et al. 2014). In fact, OxPL measured on apoB (OxPL-apoB), which largely reflect the OxPL on Lp(a), have been shown to be a prognostic indicator for future CV events (Tsimikas et al. 2010; Tsimikas et al. 2012; Tsimikas et al. 2014). OxPL associated with Lp(a) can be subjected to degradation by the Lp(a)-associated Lp-phospholipase A_2 (PLA_2), implicating Lp(a) in novel proinflammatory and atherogenic pathways (Kiechl et al. 2007).

Hyperlipoproteinemia(a) in humans is associated with increased risk of cardiac death, myocardial infarction (MI), stroke, aortic stenosis, and peripheral arterial disease (PAD), particularly in subjects with small apo(a) isoforms (Bennett 2008; Erqou et al. 2009; Erqou et al. 2010; Bertoia et al. 2013; Thanassoulis et al. 2013). Although prospective, randomized, controlled outcomes studies have not been conducted, epidemiological, genome-wide association and Mendelian randomized controlled study data to date provide supporting evidence for a role of Lp(a) as a risk factor for CVD (Kamstrup et al. 2009). For example, in the Copenhagen City Heart Studies of 42,000 subjects with a 15-year follow-up (Kamstrup et al. 2009) using a Mendelian randomization approach, higher Lp(a) levels were related to risk of MI.

2.1.3 Current Treatment Options

In 2010, the European Atherosclerosis Society (EAS) Consensus Panel recommended screening for elevated Lp(a) in people at moderate to high risk of CVD to reach a treatment goal of < 50 mg/dL (125 nmol/L), after therapeutic management of LDL-C (Nordestgaard et al. 2010). Approximately 20% of people are estimated to have plasma Lp(a) levels over 50 mg/dL (125 nmol/L) and approximately 0.3% to have levels over 175 mg/dL (438 nmol/L). There are no gender differences in Lp(a) concentrations but racial differences have been observed, with whites and Asians having lower levels while blacks and Hispanics generally have somewhat higher levels (Nordestgaard et al. 2010).

Lifestyle and diet are thought to have little impact on an individual's Lp(a) level. Current treatment recommendations from the EAS Consensus Panel are limited to the use of 1 to 3 g of niacin (nicotinic acid) daily which could result in an up to 30% reduction in Lp(a). However, niacin is associated with side effects (e.g., flushing) that reduce patient tolerability and compliance (Parker et al. 2006; Guyton 2007).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are neither indicated nor formally recommended for treatment of hyperlipoproteinemia(a) but have been reported to reduce Lp(a) levels by ~20%-35% in patients with hypercholesterolemia (Desai et al. 2013; Raal et al. 2015).

The other current option for patients with significantly elevated Lp(a) levels (≥ 60 mg/dL) is lipoprotein apheresis, either general lipoprotein apheresis (Jaeger et al. 2009;

Leebmann et al. 2013; Rosada et al. 2014) or Lp(a)-specific apheresis (Safarova 2012). While very effective at acutely lowering Lp(a) (acute and interval Lp(a) reductions of > 60% and > 30% respectively), this treatment option is expensive, burdensome for patients, and unavailable/not reimbursed in many countries and regions.

2.2 Therapeutic Rationale

Therapeutic modalities to reduce Lp(a) levels in humans are few, and there are no drugs currently available that specifically target Lp(a) alone. Antisense oligonucleotides (ASOs) are emerging as viable therapeutic agents to treat disorders where overexpression of proteins is associated with a disease process. Apo(a) is synthesized primarily in the liver, a target organ for ASOs, where it is subsequently covalently linked to the apoB-100 component of LDL to form the Lp(a) lipoprotein. The goal of treatment with ISIS 681257 is to reduce the production of apo(a) in the liver and thus, the level of Lp(a) lipoprotein by using an ASO directed against the messenger ribonucleic acid (mRNA) of apo(a). It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse CVD by reducing thrombotic, atherogenic, or inflammatory events in patients with elevated Lp(a) levels (Nordestgaard et al. 2010).

Importantly, there is no evidence that lowering Lp(a) will result in adverse consequences in individuals, and there are no reports linking very low Lp(a) to any deleterious effects.

2.3 ISIS 681257

Please refer to the ISIS 681257 Investigator's Brochure for more details on ISIS 681257 mechanism of action, chemistry, pre-clinical and clinical experience. The summary is provided below.

2.3.1 Mechanism of Action

ISIS 681257 is a second-generation ASO drug targeted to apo(a), that has been covalently bonded to triantennary *N*-acetyl galactosamine ($GalNAc_3$), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-$GalNAc_3$ conjugate. This $GalNAc_3$-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold compared to unconjugated ASOs in mice (Prakash et al. 2014).

The ASO portion of ISIS 681257 is complementary to a region spanning the Exon 24-25 splice site at position 3901 of apo(a) transcript sequence (NM_005577.2) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 681257 to the cognate mRNA results in the Ribonuclease H1 (a non-specific endonuclease that catalyzes the cleavage of RNA via hydrolytic mechanism RNase H1-mediated degradation of the apo(a) mRNA, thus preventing production of the apo(a) protein). Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

ISIS 681257 does not have any complementary homology to plasminogen mRNA (Graham et al. 2016).

2.3.2 Chemistry

Chemically, ISIS 681257 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and further enhances potency of $GalNAc_3$ conjugated ASOs.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities, thereby resulting in an improved safety profile compared to first-generation antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 681257 employs this chimeric structure to enable use of the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). The fourth region is composed of a triantennary cluster of $GalNAc_3$ sugars that is linked to the 5′ end of ISIS 681257 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high affinity ligand for the ASGPR, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 681257 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc3 cluster is metabolized to release “free ASO” inside the cell (Prakash et al. 2014).

2.3.3 Preclinical Experience

The pharmacology of ISIS 681257 has been examined in apo(a) transgenic (Tg) mice which express the entire human apo(a) genomic sequence (Frazer et al. 1995) and nonhuman primates.

Administration of ISIS 681257, a human apo(a) antisense inhibitor, to mice containing the human apo(a) transgene produced dose-dependent reductions in human apo(a) liver mRNA and apo(a) plasma protein after 6 weeks of ASO administration at 0.3, 1, 3, and 10 mg/kg/wk.

When ISIS 681257 was administered to normal chow fed cynomolgus monkeys for 4 weeks at the dose of 12 mg/kg/wk, it significantly reduced hepatic apo(a) mRNA by 90% relative to the cohort administered phosphate buffered saline (PBS). As there is an 80% sequence conservation between apo(a) and plasminogen nucleotide sequences, plasminogen mRNA levels were also measured, and no change compared to the PBS cohort was observed.

Findings from the chronic toxicology studies with ISIS 681257 (the 26-week mice and 39-week monkey studies) were similar to those observed in the 4- and 6-week studies and were not considered adverse. The plasma and tissue concentrations observed for ISIS 681257 in mice and monkeys were generally similar to those observed for other unconjugated 20-mer 2′-MOE ASOs in this chemical class with and without $GalNAc_3$-conjugation. However, the proportion of drug

in hepatocytes compare to nonparenchymal liver cells was greater for ISIS 681257, compared to the parent drug ISIS 494372 (without $GalNAc_3$-conjugation), which is the basis for increased potency of ISIS 681257 (unpublished results; Geary et al. 2003; Yu et al. 2007; Prakash et al. 2016).

The most noteworthy safety finding in the chronic monkey study was a marked platelet reduction that occurred in 2 male monkeys in the high-dose group (20 mg/kg/wk) and 1 female animal in the mid-dose (10 mg/kg/wk) group beginning on Days 44-135, which led to the subsequent early termination (ET) of these 3 animals. An additional male monkey in the 10 mg/kg/wk dose group had a moderate decrease in platelets that was successfully treated with steroids, and was terminated at the scheduled 6-month interim sacrifice. There were no platelet reductions or other toxicologically significant findings in monkeys treated with 2 mg/kg/wk for up to 39 weeks. There were no marked platelet reductions in mice at doses up to 70 mg/kg/wk for 26 weeks. However, mice exposed to ISIS 681257 at doses of ≥ 10 mg/kg/wk for up to 26 weeks showed evidence of adverse hepatobiliary effects in both sexes as indicated by increases in ALT (up to + 10.3x), AST (up to + 10.4x), and/or ALP (+ 2.5x).

Detailed information concerning the preclinical pharmacology and toxicology studies conducted with ISIS 681257 can be found in the Investigator's Brochure.

2.3.4 Clinical Experience

To date, ISIS 681257 has been studied in a single Phase 1 clinical trial of 45 healthy subjects. ISIS 681257-CS1 was a Phase 1 double-blind, placebo-controlled, dose-escalation study designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple doses of ISIS 681257 administered subcutaneously (SC) to 45 healthy subjects with Lp(a) ≥ the upper limit of normal (ULN) (30 mg/dL). Twenty one (21) subjects received 10 to 120 mg SC (10, 20, 40, 80, and 120 mg) as a single-dose, and 24 subjects received 10, 20, and 40 mg as multiple doses (6 doses in 22 days: 3 loading doses during the first week on alternate days [Days 1, 3, and 5], and then once a week for the next 3 weeks [Days 8, 15, and 22]).

There were no serious adverse events (SAEs), or clinically-relevant changes in laboratory assessments and all subjects completed the treatment and post-treatment follow-up periods.

Constitutional symptoms such as fever, chills, increase in body temperature and arthralgias have been observed following parenteral administration of ASOs, primarily during the initial dosing period. Following SC administration of ISIS 681257 constitutional symptoms were observed in 4 of the 6 subjects who received a single-dose of 120 mg. The symptoms were mild in severity and resolved spontaneously with or without treatment with acetaminophen.

Fluctuations in platelet counts to below the lower limit of normal were observed in 5 study subjects on active drug and across doses. These changes were not considered adverse or clinically-significant by the Investigator and did not appear to be dose related.

Two (2) mild AEs of redness at the site of injection occurred 48 to 72 hours after administration in 1 subject who received ISIS 681257 in the 20 mg multiple-dose cohort. Both AEs resolved by the time of the subject's next visit.

Following SC administration, ISIS 681257 was absorbed rapidly into the systemic circulation, with median time to maximum plasma concentrations (T_{max}) ranging from 1 to 4 hours. Similar T_{max} values were observed at all dose levels. Maximum observed plasma concentrations (C_{max}) and $AUC_{0\text{-}24hr}$ were dose-dependent over the studied SC dose range. The mean peak (C_{max}) and total exposure ($AUC_{0\text{-}24hr}$) increased proportionally with dose at dose levels ranging from 10 to 40 mg, and greater than dose proportionally at dose levels ranging from 40 to 120 mg.

After reaching C_{max}, mean plasma concentrations of ISIS 681257 declined in a biphasic fashion over time, with an initial, relatively fast distribution phase that dominated the plasma clearance followed by a slower elimination phase. Characterization of the terminal elimination phase yielded an apparent terminal elimination half-life of approximately 3 to 4 weeks over a dose range of 10 to 120 mg (either single- or multiple-dose), and appeared to be independent of dose. This result is consistent with the slow elimination of ISIS 681257 observed from monkey tissues, and the comparatively long elimination half-lives observed for this chemical class.

Plasma trough concentrations (168 hours or 7 days from previous dose) monitored during the treatment period in the multiple-dose cohorts increased with increasing dose, consistent with expectations (based on preclinical assessments and experience with other compounds of this chemical class) that trough plasma concentrations reflect exposure in tissues. Plasma trough concentrations did not increase greatly after the loading period (Day 15), suggesting that accumulation in major tissues of distribution had approached steady-state after the loading period.

Overall, the human PK of ISIS 681257 are consistent with the expected PK for compounds within this chemical class.

Detailed information concerning the Phase 1 clinical study conducted with ISIS 681257 can be found in the Investigator's Brochure and recent publication (Viney et al. 2016).

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 study, ISIS 681257-CS1, evaluated 3 multiple-dose cohorts of ISIS 681257, 10 mg, 20 mg, and 40 mg. Subjects were randomized (8:2 active:placebo) to receive ISIS 681257 for a total of 6 doses administered by SC injection: 3 doses during the first week and then once a week for the next 3 weeks. These doses at this frequency of administration were found to be generally well-tolerated and to induce clinically-relevant reductions in LP(a).

The range of dosing proposed for the present study will provide the equivalent drug exposure of 5 mg, 10 mg, 15 mg, and 20 mg administered weekly, and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from baseline in plasma Lp(a) ranging from approximately 60% to 85% at steady-state.

The highest dose selected for this study, 20 mg per week, is predicted to provide an approximately 85% reduction in Lp(a) at steady-state that is expected to be sufficient to bring almost all patients with hyperlipoproteinemia(a) into the normal range (Lp(a) $\leq$ 30 mg/dL).

The present study will also evaluate safety and efficacy at different dosing frequencies: every 4 weeks, every 2 weeks, and weekly. Patients with hyperlipoproteinemia(a) 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. Dosing regimens of 20 mg every 2 weeks and 40 mg every 4 weeks will test if similar monthly exposure, at different frequencies of administration, will achieve similar safety and similar level of Lp(a) reduction since the reduction achieved by a given dose level is principally driven by total exposure, while individual dose levels and the related peak concentration (C_{max}) may influence tolerance and safety.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 270 patients will be randomized in a 5:1 ratio (225 ISIS 681257 and 45 placebo) to receive ISIS 681257 or placebo. Study Drug (ISIS 681257 or placebo) will be administered SC 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.

The treatment portion of the study will be terminated when the last enrolled patient reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period irrespective of antecedent duration of treatment.

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

Patients ≥ 18 and ≤ 80 years old with elevated plasma Lp(a) levels (≥ 60 mg/dL) and a clinical diagnosis of CVD are eligible for enrollment upon meeting the study specific eligibility criteria. Patients will be on standard-of-care preventative therapy for other than elevated Lp(a) 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 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). 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 5 parallel dosing cohorts, with each cohort having a 5:1 ratio to receive ISIS 681257 or matching volume of placebo, respectively, by SC injection for a minimum of 6 months and up to 52 weeks.

Following the End-of-Treatment, patients will enter the 16-week post-treatment follow-up period.

3.2 Number of Study Centers

This is a multicenter, multinational study.

3.3 Number of Patients

Approximately 270 patients will be randomized in this study, with approximately 54 patients assigned to each of the 5 treatment cohorts.

3.4 Overall Study Duration and Follow-up

The length of patients' participation in the study may be up to 18 months (72 weeks), which includes a 4-week screening period, an up to 52-week treatment period with Study Drug (ISIS 681257 or placebo), and a 16-week post-treatment follow-up period. The treatment portion of the study will be complete when the last enrolled 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 maximum of 52 weeks. Patients will continue treatment in the study until the last patient enrolled reaches 6 months of exposure. All patients will then enter a 16-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 681257 or placebo) will be administered by SC injection once weekly, once every 2 weeks, or once every 4 weeks, depending on cohort assignment.

3.4.3 Post-Treatment

Patients when completed dosing will enter the 16-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits 4, 10, and 16 weeks after their last injection of Study Drug as per Appendix A (Follow-up).

The final study visit for each patient will be 16 weeks after the last dose of Study Drug.

3.5 End-of-Study

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

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be established to review safety, tolerability and efficacy (as needed) data collected on ISIS 681257 during this study. The DSMB will be constituted to include expertise in medical specialties relevant to the safety of antisense drugs (nephrology, hepatology, hematology), and the underlying disease state of the patients (cardiology). Specialist members of the DSMB will be informed and consulted on all relevant treatment-related SAEs, and changes of relevant laboratory parameters that trigger stopping rules (Section 8.6) within 48 hours of receipt of such results. In addition, all accrued safety data relevant to each of medical area specialist will be forwarded at regular intervals for review.

Based on its ongoing assessment of the safety and tolerability of ISIS 681257, 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 1:1:1:1:1 ratio to 1 of the 5 parallel-dose cohorts (Cohorts A, B, C, D, or E). Within each dose cohort, patients will be randomized in a 5:1 ratio to receive ISIS 681257 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 a 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 at within 4 weeks of Study Day 1or 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. Clinical diagnosis of CVD defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease
4. Lp(a) plasma level ≥ 60 mg/dL
5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors
6. 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, proprotein convertase subtilisin/kexin type 9 [PCSK9s] 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
7. 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 16 weeks after the last dose of Study Drug (ISIS 681257 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

8. 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 16 weeks after the last dose of ISIS 681257

5.2 Exclusion Criteria

1. Within 6 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke
2. Within 3 months of Screening: coronary or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis
3. Heart failure New York Heart Association (NYHA) class IV
4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
5. History of acute kidney injury within the past 12 months
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 with a history of major bleed or high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:

a. Urine protein/creatinine (P/C) ratio ≥ 0.25 mg/mg. In the event of a P/C ratio above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24-hr

b. Positive test (including trace) for blood upon urinalysis. In the event of a positive test, eligibility may be confirmed with a urine microscopy showing ≤ 5 red blood cells (RBCs) per high power field

c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x ULN

d. Estimated GFR < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance)

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

f. Alkaline phosphatase (ALP) > ULN

g. Platelet count < LLN

13. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors
14. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
15. Treatment with any 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
16. BMI > 40 kg/m^2
17. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
18. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
19. 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. A 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.

6.1.2 Treatment Period

During the treatment period, patients will report to the study center for clinic visits. Patients will receive 20 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort A, 40 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort B, 60 mg doses of Study Drug administered by SC injection once every 4 weeks for up to 52 weeks in Cohort C, 20 mg doses of Study Drug administered by SC injection once every 2 weeks for up to 52 weeks in Cohort D, or 20 mg doses of Study Drug administered by SC injection once per week for up to 52 weeks in Cohort E (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 681257 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 12 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 681257. 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 16 weeks after their last dose of Study Drug. During the post-treatment follow-up period, patients will return to the Study Center for 3 outpatient visits at Weeks 4, 10, and 16 after the last dose of Study Drug 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. A list of these analytes is contained in Appendix B.

Blood chemistry and urine samples (excluding 24-hour urine collection) should be taken be taken after fasting for at least 10 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

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

Hematology samples will be collected every 14 days. Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample must 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.

Blood and urine samples for renal function testing and assessment of biomarkers of renal damage will also be collected every 14 days and sent to the central laboratory for analysis, per Section 8.5.2. If there are no test results available within 14 days of the last set of results for parameters considered critical to patient safety, the Investigator will contact the patient to hold dosing until a new test set is obtained and reviewed.

All lab samples sent to the central laboratory are received on the next day 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 on the day of sample collection, 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 (Grade 3 or Grade 4) 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.

All lab alerts received, including those related to platelet, liver, or renal function monitoring/stopping rules, are reviewed promptly by the Sponsor and the CRO Medical Monitors who discuss them and 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 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, 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, B, and C at Weeks 5, 13, 21, 25, 33, 41, 49, and 53
- Cohorts D and E at Weeks 5, 13, 21, 27, 33, 41, 49, and 53

In all cohorts, ECGs will be conducted during the post-treatment follow-up period at 4, 10, and 16 weeks after the last dose of Study Drug.

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 681257 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 16 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 16 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 1 or more 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 before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 681257 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 681257 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 681257

ISIS 681257 vials contains 100 mg/mL ISIS 681257 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 681257 vials.

Table 1 Study Drug Characteristics

Study Drug	ISIS 681257	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 681257 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 681257 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 681257 will be administered to patients by Study Center staff as follows:

Cohort A: a single SC dose of 20 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort B: a single SC dose of 40 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort C: a single SC dose of 60 mg once every 4 weeks for up to 52 weeks and a maximum of 13 doses

Cohort D: a single SC dose of 20 mg every 2 weeks for up to 52 weeks and a maximum of 26 doses

Cohort E: a single SC dose of 20 mg every week (weekly) for up to 52 weeks and a maximum of 52 doses

Self-administration for patients in Cohorts D and E will be allowed after appropriate training of patient and/or caregiver.

Patients in Cohorts A, B, and C should receive 1 dose every 4 weeks, patients in Cohort D should receive 1 dose every 2 weeks and patients in Cohort E 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 at least 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 681257 or placebo) preparation and administration

Table 2 Study Drug Dosing Information

Cohort	Treatment	Volume to Administer/Dose	# Doses	Total ISIS 681257
A	20 mg ISIS 681257 or placebo (Every 4 weeks)	0.2 mL	≤ 13	≤ 260 mg
B	40 mg ISIS 681257 or placebo (Every 4 weeks)	0.4 mL	≤ 13	≤ 520 mg
C	60 mg ISIS 681257 or placebo (Every 4 weeks)	0.6 mL	≤ 13	≤ 780 mg
D	20 mg ISIS 681257 or placebo (Every 2 weeks)	0.2 mL	≤ 26	≤ 520 mg
E	20 mg ISIS 681257 or placebo (Every week)	0.2 mL	≤ 52	≤ 1040 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

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 Day 1.

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

In case of discrepancy between the test results from 2 sources, such as between the central and local lab, safety-mandated action must be initiated based on the lower 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 681257 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: In the event of an initial clinical laboratory result that meets a stopping criterion, patients must not be re-dosed 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 681257 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 pharmacokinetic 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 pharmacokinetic 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 2 weeks for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period.

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 and Medical Monitors.

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

All patients will have renal function tests monitored every 2 weeks throughout the study.

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.

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 to estimate glomerular filtration rate (eGFR), which will be monitored every 2 weeks. In addition, biomarkers of acute renal injury will also be measured every 2 weeks (Appendix B). Results that exceed predetermined alert values will be reviewed, together with related safety data, by the nephrologist on the DSMB as specified in the DSMB charter. eGFR may also be evaluated based upon serum cys-C to further characterize the significance of changes in renal function or renal biomarkers.

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: Creatinine clearance (by CKD-EPI formula) decrease from baseline > 15%, urine Alb/C ratio (UACR) > 2.5 x ULN, or an increase in serum creatinine from baseline > 0.25 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.

In the event of a confirmed (as described in Section 8.5) laboratory result meeting one or more of the following criteria, dosing with the Study Drug should be interrupted and the Study Medical Monitor informed.

If any of the following changes from baseline in renal laboratory parameters should occur following from Day 1 of Study Drug administration:

> Creatinine clearance (by CKD-EPI formula) decrease from baseline > 25%, urine Alb/C ratio (UACR) > 5 x ULN, or an increase in serum creatinine from baseline > 0.5 mg/dL,

the following additional renal tests should be immediately obtained:

> Fasting serum creatinine, urine culture, 24-hour urine sample for creatinine clearance and urine protein, urine microscopy sample with inspection of sediment.

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.

8.5.3 Safety Monitoring for Platelet Count Results

All patients will have platelet counts monitored every 2 weeks for the duration of the study and must not receive Study Drug without an interpretable platelet count result in the prior 2 weeks. In addition, platelet function will be evaluated by aggregometry in all patients at each study site visit, with additional functional testing being performed at selected study centers.

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.

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm^3; 2) when platelet count is ≥ 30% decreased from baseline, or 3) when 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 D 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 Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, hepatic enzymes, bilirubin and platelet count should be performed.

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 symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.6 Stopping Rules

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 of an estimated creatinine clearance (by CKD-EPI formula) meeting any of the following criteria, or any change in renal biomarkers deemed by the nephrologist on the DSMB to require further evaluation, a serum creatinine and 24-hour urine sample for creatinine clearance and protein should be obtained:

1. CKD-EPI decrease of > 50% from Baseline
2. CKD-EPI value < 45 mL/min/1.73 m^2

Dosing of a patient with Study Drug (ISIS 681257 or placebo) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

1. Urine protein is > 2.0 g
2. Creatinine clearance decrease of > 50% from baseline
3. Creatinine clearance < 45 mL/min/1.73 m^2

Irrespective of whether the stopping rule is confirmed or not, 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.

8.6.3 Stopping Rule for Platelet Count Results

Stopping Rules 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 steroids 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 steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids 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; Schulman and Kearon 2005), 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 irrespective of whether the platelet count rises into the normal range.

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

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

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman and Kearon 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every week*
75K-100K/mm^3	Permanently reduce as follows: For Cohort A: reduce to 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 weeks For Cohort E: reduce to 10 mg every week	Closer observation Monitor every week*
50K-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 10 mg every 4 weeks For Cohort B: reduce to 20 mg every 4 weeks For Cohort C: reduce to 30 mg every 4 weeks For Cohort D: reduce to 10 mg every 2 weeks For Cohort E: reduce to 10 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)/ anticoagulant medication
25K-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/anticoagulant medication while platelet count < 50K/mm^3 if possible

Table 3 Actions in Patients with Low Platelet Count *Continued*

Platelet Count on Rx	Drug Dose	Monitoring
< 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 and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* Once a patient commences weekly monitoring this frequency of monitoring should continue irrespective of whether the platelet count rises into the normal range.

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: 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 Section 8.6.3 and 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 8.6.3
- 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 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 after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Following 6 weeks of Study Drug discontinuation, patients should be strongly encouraged to attend planned Study Center visits (including End-of-Treatment Week 53 visit and final Post-Treatment Follow-up visit 16 weeks after their last dose of Study Drug) to collect the study assessments in accordance with the Schedule of Procedures in Appendix A.

If the patient declines or is unable to participate in the above, an ET visit (Week 53 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

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 permanently discontinues Study Drug (see Section 8.8)
- 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 study procedures 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 study procedures and observations at the time of withdrawal (see Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. 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, PCSK9 inhibitors, niacin, fibrates, fish oil, other products containing omega-3 fatty acids (including OTC preparations)
- Anti-platelet therapies
- Testosterone, estrogens, progesterone, growth hormone, or progestins.

Disallowed Concomitant Therapy

Use of the following is disallowed:

- Warfarin, 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 of platelet count, liver and renal function as described in Sections 6.2.1, 8.5.1-8.5.3, and 8.6.1-8.6.3.

Patients will be required to have platelet counts every 2 weeks 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.

Patients will also be required to have renal function testing and assessment of biomarkers of renal damage every 2 weeks, and must not receive Study Drug if there are no test results for parameters considered critical to patient safety available within the prior 2 weeks. In such a case the Investigator must contact the patient to hold dosing until these 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 potential hepatic and renal risks, the importance of adherence to the monitoring program. 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.

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 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 Suspected Adverse Reaction

An adverse reaction is any AE caused by the Study Drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

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

- Results in death
- Is life threatening, that is, poses an immediate risk of death at the time of the event
- An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 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. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. 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]

Phone: [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 681257 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 681257 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 681257 or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 681257 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 (Grade 3 or Grade 4) 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.

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 681257 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 681257 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 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-C) and at Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E, 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.

10.1.1 Primary Endpoint(s)

The primary efficacy endpoint is the percent change in Lp(a) from baseline at the primary analysis time point achieved by ISIS 681257 compared to pooled placebo.

Lp(a) levels will be analyzed from patient blood samples taken at specified time points throughout the study.

10.1.2 Secondary Endpoints

The secondary endpoints include the following parameters from baseline at the primary analysis time point for ISIS 681257 compared to placebo:

- Percent change from baseline in LDL-C
- Proportion of patients who achieve plasma Lp(a) $\leq$ 50 mg/dL
- Proportion of patients who achieve plasma Lp(a) $\leq$ 30 mg/dL
- Percent change from baseline in apoB
- Percent change from baseline in OxPL-apo(a)
- Percent change from baseline in OxPL-apoB

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
- ECGs
- Use of concomitant medications

10.1.4 Dose Selection

Dose selection for 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 clinically-meaningful reduction in plasma Lp(a) 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.

10.2 Sample Size Considerations

Based upon prior clinical trial experience with ISIS 681257 (Viney et al. 2016), it is estimated that the standard deviation of the percent change in Lp(a) is approximately 20%. With 23 patients in each ISIS 681257 treatment group and 23 in placebo group there would be approximately 90% power to detect a 20% difference in percent change in Lp(a) levels between the ISIS 681257 treatment groups and placebo group at an alpha level of 0.05, assuming 30% reduction in the ISIS 681257 patients and 10% reduction in the placebo patients.

Based upon prior clinical trial experience with Ionis ASOs, assuming the incidence rate of platelet count below lower limit of normal (LLN) in placebo treated patients is 1.9%, in the ISIS 681257 treated patients is 3.8%, twice the incidence rate observed in placebo, with 45 patients in each ISIS 681257 treatment group, there would be approximately 80% power to detect at least 1 event.

Therefore, approximately 270 patients (54 patients per cohort, including 45 patients per cohort treated with ISIS 681257) will be randomized to ensure that both the safety and efficacy of ISIS 681257 will be adequately characterized in the study.

10.3 Analysis Populations

Full Analysis Set (FAS): All patients who are randomized, received at least 1 dose of Study Drug (ISIS 681257 or placebo), and have a Baseline Lp(a) 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 every 4-week doses of Study Drug for patients randomized in Cohorts A, B, and C or at least 10 every 2-week doses for patients randomized in Cohort D or 20 weekly doses for patients randomized in Cohort E, 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 Study Drug, and have sufficient data for the analysis of PK parameters. This population will be used for analysis of PK data.

10.4 Definition of Baseline

Baseline for Lp(a), LDL-C, apoB, OxPL-apo(a), OxPL-apoB, and other lipid measurements will be defined, the pre-dose measurement on Day 1 or 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 681257 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 681257 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 681257 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 analysis of the primary endpoint will be the pairwise comparison of percent change from baseline to primary analysis time point in fasting Lp(a) between ISIS 681257 treatment groups and pooled placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the Baseline Lp(a) 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 LDL-C will be compared between each ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate
- Proportion of patients who achieve $\leq$ 50 mg/dL in fasting Lp(a) at the primary analysis time point will be compared between each ISIS 681257 treatment group and pooled placebo group using a logistic regression model with Baseline Lp(a) as a covariate. Proportion of patients who achieve $\leq$ 30 mg/dL in fasting Lp(a) at the primary analysis time point will be analyzed similarly

- Percent change from baseline at the primary analysis time point in fasting apoB, OxPL-apo(a) and OxPL-apoB will be compared between ISIS 681257 treatment groups and pooled placebo group using an ANCOVA model with baseline as covariate

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 681257 in plasma (as total full length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 681257) will be determined and summarized by treatment with stratification by subject immunogenicity status using descriptive statistics.

In addition, non-compartmental PK analysis of ISIS 681257 concentrations will be carried out on each individual patient data set in patients who received ISIS 681257 treatment, and the plasma disposition half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate, using available data at the End-of-Treatment and the post-treatment follow-up period from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, where λz is the rate constant associated with the apparent terminal elimination phase.

For patients in the PK subgroup only, non-compartmental PK analysis of ISIS 681257 will be carried out on each individual patient data set in patients who received ISIS 681257 treatment. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Following single dosing (Day 1), area under the plasma concentration-time curve from time zero (pre-dose) to 24 hours after the dose ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Following multiple dosing, $AUC_{0\text{-}24hr}$ and area under the plasma concentration-time curve during the time of each sampled dosing interval (tau,τ) at steady-state (AUC_{τ}) will be calculated using the linear trapezoidal rule.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Plasma PK parameters will be summarized using descriptive statistics with stratification by subject immunogenicity status. Exposure-response relationships between selected PD [e.g., Lp(a)] and PK measures (including but may not be limited to plasma trough concentrations) may be explored (including with and without stratification by IM status) in this study, or in a separate population PK analysis with all clinical studies combined.

The immunogenicity (IM) of ISIS 681257 will be assessed before, during, and after treatment with Study Drug (ISIS 681257 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 681257 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 681257 or placebo) are administered.

Importantly, patients should be informed of the possibility and risks of a reduction in platelet count, and other potential risks (hepatic and renal), 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.

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 Every Week and Every 2-Week Dosing Cohort

Schedule of Procedures for Every 4-Week Dosing Cohorts

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

	Screen	Treatment Period																		Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**28**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[j]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[j]**	**185[j]**	**190[o]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[a]**	**0**	**2**	**2**	**2**	**3**	**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
Inclusion/Exclusion Criteria	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
12- lead ECG (triplicate)	X	X		X		X		X		X					X		X		X	X	X	X	X
Urinalysis	X	**URINALYSIS PERFORMED EVERY 14 DAYS**																			X	X	X
Renal Biomarkers [m]	X	**RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [m]**																			X[l]	X[l]	X[l]
Serum Creatinine [f]		**SERUM CREATININE PERFORMED EVERY 14 DAYS [n]**																			X	X	X
Genetic Testing		X																					
Chemistry Panel [e, f]	X	EVERY 14 DAYS					X	X	X	X				X	X	X	X	X	X	X	X	X	X
Hematology [e, f]	X	**HEMATOLOGY PERFORMED EVERY 14 DAYS [b]**																			X[l]	X[l]	X[l]
Platelet Function		X		X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X
Coagulation	X	X								X													
Hepatitis B, C, HIV	X																						
Thyroid Panel	X																						
hsCRP		X								X										X			X
Plasma PK - ISIS 681257 [i]		X[3]	X[1]	X	X	X	X	X	X	X[3]	X[1]	X[2]	X	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X				X										X			X

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

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**28**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[j]**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184[j]**	**185[j]**	**190[o]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[a]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
FSH (women only, if applicable)[e, g]	X																						
Serum Pregnancy Test [g]	X	X			X		X		X							X		X		X	X	X	X
Archived Serum & Plasma Samples [e, h]		X			X		X			X						X		X		X	X	X	X
PD Panel [e]	X	X		X	X	X	X	X		X				X		X		X		X	X	X	X
Lipid Panel [e]	X	X		X	X	X	X	X		X				X		X		X		X	X	X	X
Lp(a) Characterization		X																					
Study Drug: SC Injection		**WEEKLY SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 53/Day 365)[k]**																					
Adverse Events	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

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

a 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.

b 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.

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 Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours.

f 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 as per Section 6.2.1. Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

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

h 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.) in this or subsequent clinical studies of ISIS 681257.

i Refer to Appendix C for PK Sampling schedule.

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

j Visit only required for patients in PK subgroup.

k Patients will continue treatment in the study until the last patient enrolled reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period.

l During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then every 6 weeks.

m Samples for renal biomarkers will be collected. Urine samples will be collected as part of urinalysis collection. Blood samples for CysC will be collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone sample at other time points. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function (Section 8.5.2).

n Collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone sample at other time points.

o Week 28 visit is only required for patients on Every 2-Week dosing schedule and who are assigned to the PK sub-group.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8 hours post SC injection

Appendix A Schedule of Procedures – Every 4-Week Dosing

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[j]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[j]**	**171[j]**	**176[j]**	**183[j]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[a]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**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
Inclusion/Exclusion Criteria	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
Physical Examination	X	X		X		X		X	X						X		X		X	X	X	X	X
Body Weight and Height [d]	X								X								X						X
12- lead ECG (triplicate)	X	X		X		X		X	X						X		X		X	X	X	X	X
Urinalysis	X	**URINALYSIS PERFORMED EVERY 14 DAYS**																			X	X	X
Renal Biomarkers	X	**RENAL BIOMARKERS PERFORMED EVERY 14 DAYS [m]**																			X[l]	X[l]	X[l]
Serum Creatinine [f]		**SERUM CREATININE PERFORMED EVERY 14 DAYS [n]**																					
Genetic Testing		X																					
Chemistry Panel [e]	X	EVERY 14 DAYS					X	X	X					X	X	X	X	X	X	X	X	X	X
Hematology [e, f]	X	**HEMATOLOGY PERFORMED EVERY 14 DAYS [b]**																			X	X	X
Platelet Function		X		X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X														
Hepatitis B, C, HIV	X																						
Thyroid Panel	X																						
hsCRP		X							X											X			X
Plasma PK - ISIS 681257 [i]		X[3]	X[1]	X	X	X	X	X	X[3]	X[1]	X[2]	X	X	X		X				X	X	X	X
ISIS 681257 Antibodies		X		X	X	X			X											X			X
FSH (women only, if applicable) [e, g]	X																						

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

	Screen	Treatment Period																			Follow-up Period		
Study Week	**-4 to -1**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**			**26**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53/ET**	**4***	**10***	**16***
Study Day	**-28 to -1**	**1**	**2[j]**	**29**	**57**	**85**	**113**	**141**	**169**	**170[j]**	**171[j]**	**176[j]**	**183[j]**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	***Post Last Dose**		
Visit Window +/- Days	**0**	**-3[a]**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Serum Pregnancy Test [g]	X	X		X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X
Archived Serum & Plasma Samples [e, h]		X			X		X		X					X		X		X		X	X	X	X
PD Panel [e]	X	X		X	X	X	X	X	X				X	X		X		X		X	X	X	X
Lipid Panel [e]	X	X		X	X	X	X	X	X			X	X	X		X		X		X	X	X	X
Lp(a) Characterization		X																					
Study Drug: SC Injection		**EVERY 4-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 49/Day 337)[k]**																					
Adverse Events	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

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

a 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.

b 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.

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 Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours.

f If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen for should be re-drawn as soon as possible (ideally within 7 days). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator as per Section 6.2.1. Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

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

h 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.) in this or subsequent clinical studies of ISIS 681257.

i Refer to Appendix C for PK Sampling schedule.

j Visit only required for patients in PK subgroup.

k Patients will continue treatment in the study until the last patient enrolled reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period.

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

l During follow-up period, hematology sampling for platelet values and urine renal biomarker samples are taken every 14 days for 6 weeks after last dose of Study Drug, then every 6 weeks.

m Samples for renal biomarkers will be collected. Urine samples will be collected as part of urinalysis collection. Blood samples for CysC will be collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone sample at other time points. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function (Section 8.5.2).

n Collected as a part of chemistry panel at visits when chemistry panel is performed, or as stand-alone sample at other time points.

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

1 24-hr from previous dose of Study Drug

2 48-hr from previous dose of Study Drug

3 Pre-dose, 1, 2, 4, 8, hrs post SC injection

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 681257 or other similar oligonucleotides.

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

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)
- Drug/Alcohol screen
- TSH
- Free T4
- Free T3

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

PD Panel
- Lp(a)
- OxPL-apoB
- OxPL-apo(a)
- OxPL-plasminogen

Lipid Panel
- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- ApoB
- Triglycerides
- VLDL

Lp(a) Characterization
- Apo(a) isoforms

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 681257 (total full length ASO) levels in plasma

Immunogenicity
- Anti-ISIS 681257 antibodies

Genetic Testing
- LPA SNPs associated with elevated Lp(a)

Inflammatory
- hs-CRP

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

Renal Urine Biomarkers
- 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 681257 with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Blood samples for the determination of plasma ISIS 681257 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 681257 with plasma constituents. Extensive PK samples will be collected in PK subgroup only (10 subjects per cohort) (see tables below):

Sampling Schedule for Every Week Dosing Cohort

	Treatment Period														Follow-up Period		
Study Week	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184**	**185**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime
PK Sub-group Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	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	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

1 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

Appendix C PK Sampling Schedule *Continued*

Sampling Schedule for Every 2-Week Dosing Cohort

	Treatment Period														Follow-up Period		
Study Week	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**			**28**	**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**184**	**185**	**190**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	NA	NA	NA	NA	Pre-dose	Pre-dose	Anytime	Anytime	Anytime
PK Sub-group Only	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 1, 2, 4, & 8-hr[1]	24-hr[2]	48-hr[3]	Anytime	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

1 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

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**	**25**			**26**	**27**	**29**	**37**	**53**	**4***	**10***	**16***
Study Day	**1**	**2**	**29**	**57**	**85**	**113**	**141**	**169**	**170**	**171**	**176**	**183**	**197**	**253**	**365**	***Post Last Dose**		
All Patients	Pre-dose	NA	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose,	NA	NA	NA	NA	NA	Pre-dose	Pre-dose	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	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

1 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

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

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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
Fibrinogen
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
von Willebrand factor (vWF) Antigen
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody
Platelet Antibody Bead Array (PABA)