**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):** Statistical Analysis Plan Version 1: 16-April-2018

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# STATISTICAL ANALYSIS PLAN

# PROTOCOL 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 Number: | ISIS 681257-CS6 |
| Protocol Version and Date: | Original Protocol: 15 August 2016<br>Protocol Amendment 6: 25 January 2018 |
| Name of Test Drug: | ISIS 681257 |
| Phase: | Phase 2 |
| Methodology: | Multicenter, Randomized, Double-blind, Placebo-Controlled, Dose-Ranging |
| Sponsor: | Akcea Therapeutics, Inc.<br>55 Cambridge Parkway, Suite 100<br>Cambridge, MA 02142<br>Tel: (617) 207-0202 |
| Sponsor Representative: | [redacted] MD, PhD<br>[redacted]<br>Akcea Therapeutics |
| Analysis Plan Date: | 12 April 2018 |
| Analysis Plan Version: | Final Version 1.0 |

# APPROVAL SIGNATURE PAGE

| | |
|---|---|
| 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) |
| Protocol Number: | ISIS 681257-CS6 |
| Sponsor: | Akcea Therapeutics, Inc.<br>55 Cambridge Parkway, Suite 100<br>Cambridge, MA 02142 |
| Author: | [redacted] |

Author Signatory:

[redacted], MS

Signature: [redacted]

Date: 16 April 2018

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted] MD, PhD

Signature: [redacted]

Date: 12 April, 2018

Akcea Therapeutics

# REVISION HISTORY

| Version Number | Version Date | Summary and Rational of Revision(s) |
|---|---|---|
| Final 1.0 | 12 April 2018 | There are no revisions as this is the first final version. |
| | | |
| | | |

# TABLE OF CONTENTS

# TABLES INCLUDED IN THE TEXT

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ALT | Alanine transaminase |
| ANCOVA | Analysis of covariance |
| apo(a) | Apolipoprotein(a) |
| apoB | Apolipoprotein B |
| ASO | Antisense oligonucleotide |
| ASGPR | Asialoglycoprotein receptor |
| AST | Aspartate transaminase |
| ATC | Anatomical therapeutic chemical |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| CAD | Coronary artery disease |
| CI | Confidence interval |
| CKD-EPI | Chronic Kidney Disease –Epidemiological Collaboration |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVD | Cardiovascular disease |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ET | Early Termination |
| FAS | Full analysis set |
| FLR | Flu-like Reaction |
| GalNAc3 | *N*-acetyl galactosamine |
| GFR | Glomerular Filtration Rate |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IM | Immunogenicity |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISIS 681257 | Antisense inhibitor of apolipoprotein (a) |
| ITT | Intent-to-treat |
| IXRS | Interactive Web-Response System |
| LCRIS | Local Cutaneous Reaction at the Injection Site |
| LDL | Low density lipoprotein |
| LDL-C | Low density lipoprotein cholesterol |
| LLN | Lower limit of normal |
| Lp(a) | Lipoprotein(a) |

| Abbreviation | Definition |
|---|---|
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRNA | Messenger ribonucleic acid |
| n | Number of patients |
| OxPL | Oxidized phospholipids |
| OxPL-apo(a) | oxidized phospholipids on apolipoprotein(a) |
| OxPL-apoB | oxidized phospholipids on apolipoprotein B |
| PAD | Peripheral arterial disease |
| PK | Pharmacokinetic |
| PKS | Pharmacokinetic set |
| PPS | Per-protocol set |
| PT | Preferred term |
| Rel Day | Relative study day |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SI | Système International (International System of Units) |
| SNP | Single nucleotide polymorphism |
| SOC | System organ class |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| UACR | Urine albumin/creatinine ratio |
| ULN | Upper limit of normal |
| UPCR | Urine protein/creatinine ratio |
| WBC | White blood cell (count) |
| WHO | World Health Organization |

# 1. INFORMATION FROM THE STUDY PROTOCOL

## 1.1. Introduction and Objectives

### 1.1.1. Introduction

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein in which the apolipoprotein B (apoB) component of low density lipoprotein (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 (Erqou et al. 2009; Nordestgaard et al. 2010; Thanassoulis et al. 2013).

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 [antisense inhibitor of apolipoprotein (a)] 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).

### 1.1.2. Study Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

#### 1.1.2.1. Primary Objective

To evaluate the safety and 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).

#### 1.1.2.2. Secondary Objectives

To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), 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.

## 1.2. Study Design

### 1.2.1. Synopsis of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. ISIS 681257 (or placebo) will be administered subcutaneously (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 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. A description of each cohort is presented in Table 1.

**Table 1: Study Drug Dosing Information**

| Cohort | Treatment | Volume to Administer/Dose | # Doses | Total ISIS 681257 |
|---|---|---|---|---|
| A | 20 mg ISIS 651257or placebo (every 4 weeks) | 0.2 mL | ≤ 13 | ≤ 260 mg |
| B | 40 mg ISIS 651257or placebo (every 4 weeks) | 0.4 mL | ≤ 13 | ≤ 520 mg |
| C | 60 mg ISIS 651257or placebo (every 4 weeks) | 0.6 mL | ≤ 13 | ≤ 780 mg |
| D | 20 mg ISIS 651257or placebo (every 2 weeks) | 0.2 mL | ≤ 26 | ≤ 520 mg |
| E | 20 mg ISIS 651257or placebo (every week) | 0.2 mL | ≤ 52 | ≤ 1040 mg |

The treatment portion of the study will be complete when the last enrolled patient reaches 6 months of exposure. All patients still on treatment will have their last dose taken as scheduled, and they will enter a 16-week post-treatment follow-up period at one dosing interval post last dose. Accordingly, for each treatment cohort treatment period is defined as the time from the first dose through one dosing interval post last dose.

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 CAD, stroke, or 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 electrocardiogram (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.

The length of patients' participation in the study may be up to 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 adverse events (AEs) or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

The independent Data Safety Monitoring Board (DSMB) will oversee the safety, tolerability, efficacy (when needed) and the overall conduct of the study.

### 1.2.2. Randomization Methodology

Patients will be randomized after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Protocol Sections 5.1 and 5.2. No 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 the Unblinded Biostatistician at [redacted].

### 1.2.3. Stopping Rules and Unblinding

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 serious AE (as defined in Protocol 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 suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's or designee's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Protocol Section 9.2).

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 are met and are confirmed, the patient will be permanently discontinued from further treatment with ISIS 681257 or placebo:

1) Liver chemistry elevations.
2) Renal function test results.
3) Platelet count results.

For more details on the criteria of stopping rules, refer to Protocol Section 8.6.

#### 1.2.4. Study Procedures

The schedule of procedures for all cohorts can be found in Appendix A of the study protocol.

#### 1.2.5. Efficacy and Safety Parameters

##### 1.2.5.1. Primary Efficacy Parameters

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 placebo.

##### 1.2.5.2. Secondary Efficacy Parameters

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

##### 1.2.5.3. Safety Parameters

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 AEs 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.

# 2. PATIENT POPULATION

## 2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- 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.
- Full Analysis Set (FAS): All patients who are randomized and received at least 1 dose of Study Drug (ISIS 681257 or placebo). The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in International Conference on Harmonisation (ICH) Guideline E9. This population will be used for the primary analysis of efficacy.
- Per-Protocol Set (PPS): Subset of the FAS who have a baseline assessment for lipids, received within 6 months at least 5 out of 6 monthly doses of Study Drug for patients randomized in Cohorts A, B, and C, at least 11out of 13 planned every-2-week doses for patients randomized in Cohort D, or at least 22 out of 26 planned weekly doses for patients randomized in Cohort E, and who have no major protocol deviations that would be expected to affect efficacy assessments. This population will be used for supportive inferences concerning efficacy.
- Pharmacokinetic Set (PKS): All patients who are randomized and received at least 1 dose of active Study Drug (ISIS 681257), and have at least 1 evaluable PK data. This population will be used for analysis of PK data.

## 2.2. Protocol Deviations

The list of prespecified major deviations is provided in the Appendix 2 of the SAP. All protocol deviations that could compromise the interpretation of efficacy or safety of the study drug will be considered as major deviations. The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with [redacted] and the data monitoring group as applicable; this file will include a description of the protocol deviation and clearly identify whether or not this deviation warrants exclusion from the PPS. This file will be finalized prior to database lock for the primary analysis.

All protocol deviations will be presented in a data listing.

# 3. GENERAL STATISTICAL METHODS

## 3.1. Sample Size Justification

Based upon prior clinical trial experience with ISIS 681257, it is estimated that the standard deviation (SD) 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 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% probability of observing 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.

## 3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (eg, Day 14L).

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

All electronic case report form (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 number of patients (n), mean, median, SD, standard error, interquartile range ($25^{th}$ percentile, $75^{th}$ percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. A 'Missing' category may be presented, if warranted. Where appropriate, p-values will be reported.

Assuming raw or derived variables are to 'x' decimal places, the data will be presented as follows:

- Range to x decimal places
- Mean and median to (x+1) decimal places
- SD to (x+2) decimal places
- (x+2) should not be greater than 4 decimal places
- percentages may be calculated without a decimal place or with (x+1) decimal place

Presentation of pharmacokinetic data will be separately defined in the TFL shells.

Formal statistical hypothesis testing will be performed on the primary and select secondary efficacy endpoints, with all tests conducted at the 2-sided and 5% Type I error rate unless otherwise stated. Summary statistics will be presented, as well as confidence intervals (CIs) on selected parameters, as described in the sections below.

## 3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software v9.3, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v20.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version March 2017.

## 3.4. Baseline Definitions

Baseline for Lp(a), LDL-C, apoB, OxPL-apo(a), OxPL-apoB, and other lipid measurements will be defined as the pre-dose measurement on Day 1 or closest to Day 1, prior to administration of Study Drug. The baseline for platelet count is defined as the average of all platelet count data points prior to the first dose of the study drug. The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of study drug.

## 3.5. Methods of Pooling Data

Data from patients who receive placebo will be pooled for analysis. For the primary and secondary efficacy endpoints, the primary analysis timepoint will combine Week 25 for patients who received every 4-week dosing (Cohorts A-C) and Week 27 for patients who received every 2-week or weekly dosing (Cohorts D and E). For all other parameters, pooling will be based on the data available at each visit per the schedule of procedures in the Study Protocol.

In addition to being pooled for analysis, patients who receive placebo will also be compared with patients receiving ISIS 681257 on a within-cohort basis. Details can be found in Section 4.

Data from patients who receive ISIS 681257 will be pooled in summary tabulations, where appropriate.

## 3.6. Adjustments for Covariates

Baseline Lp(a), LDL-C, apoB, OxPL-apo(a), and OxPL-apoB will act as covariates in their respective analyses using an analysis of covariance (ANCOVA) model.

## 3.7. Multiple Comparisons/Multiplicity

A multiple testing procedure will not be used for this study with a single primary efficacy endpoint.

## 3.8. Subpopulations

Subgroup analyses using pooled data for the primary and secondary efficacy enpoints as well as TEAE incidences are planned as follow:

- By age (age categories <65 and ≥ 65 years old)
- By gender

## 3.9. Withdrawals, Dropouts, Loss to Follow-up

Patients must be withdrawn from the study for any of the following, but not limited to:

- Withdrawal of consent.
- The patient is unwilling or unable to comply with the protocol.
- The patient meets any of the Exclusion Criteria after enrolling in the study that in the opinion of the Investigator representes a safety risk to the patient.

All efforts will be made to complete and report the observations as throroughly 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 Early Termination (ET) study procedures and observations at the time of withdrawal.

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.

Patients who are withdrawn or discontinue from the study will not be replaced.

## 3.10. Missing, Unused, and Spurious Data

### 3.10.1. Efficacy Data

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

The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing primary endpoint by treatment group (ISIS 681257 treatment group or pooled placebo treatment group as defined in Section 4). In order to be compliant with the normality assumption, baseline and post-baseline Lp(a) data will be log-transformed prior to the imputation process, and will be reverted back when creating the imputed dataset. Jeffreys' prior will be used to derive the posterior distribution of the parameters. The MCMC method will impute 100 datasets in order to estimate the treatment effect, where the median value across the imputed datasets will be used for patients with missing endpoint.

Missing data for the secondary endpoints will be handled similarly.

### 3.10.2. Adverse Event Data

When tabulating AE data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the onset day to the date of the first dose.

- If the month and day are missing, and the year is:
    - the same as the year of first dose, then set the onset day as the first day of the month of the first dose;
    - earlier than the year of first dose, then set the onset day as December 31;
    - after the year of the first dose, then set the onset day as January 1.
- If only the day is missing, then
    - if the month/year is the same as the first dose, then set the onset day as the date of first dose;
    - if the month/year is earlier than the month/year of the first dose, then set the onset day as the last day of the month;
    - if the month/year is later than the month/year of the first dose, then set the onset day as the first day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing, and the year is the same as the year of the last dose then set the end day as the last day of the month of the first dose. Otherwise, set the end date as December 31.
- If only the day is missing, then set the end day as the last day of the month.

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

### 3.10.3. Prior and Concomitant Medication Data

When tabulating prior/concomitant medication data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the start date to the date of first dose.
- If the month and day are missing and the year is earlier than the year of the first dose, then set the start date to December 31. Otherwise, set the start date to January 1.
- If only the day is missing, if the month/year is earlier than the month/year of the first dose then set the start date to the first day of the month. Otherwise, set the start date to the last day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing then set the end date to December 31.
- If only the day is missing, then set the end day as the last day of the month.

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

## 3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule within the allowed protocol-specified window. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

## 3.12. Interim Analyses

No interim analyses are planned for this study.

# 4. STUDY ANALYSES

Treatment groups are ISIS 681257 treatment groups and pooled placebo group. ISIS 681257 treatment groups include:

ISIS 681257 20 mg (Every 4 weeks)

ISIS 681257 40 mg (Every 4 weeks)

ISIS 681257 60 mg (Every 4 weeks)

ISIS 681257 20 mg (Every 2 weeks)

ISIS 681257 20 mg (Every week)

Within cohort comparions between patients receiving ISIS 681257 and patients receiving placebo will be performed for selected safety endpoints, as appropriate.

## 4.1. Patient Disposition

Patient disposition will be tabulated by ISIS 681257 treatment group and pooled placebo group. Tabulations will include the number screened, the number randomized, the number treated in total, the number in each patient population for analysis, the number who completed treatment, the number who withdrew prior to completing treatment and reason(s) for withdrawal, the number of patients who discontinued prior to completing post-treatment follow-up, along with reasons for ET post-treatment.

A by-patient data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

## 4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by ISIS 681257 treatment group and pooled placebo group. Age (years), height (cm), weight (kg), race, gender, ethnicity and body mass index (BMI, $kg/m^2$), as well as fasting lipids results including Lp(a), apoB, LDL-C, OxPL-apo(a), and OxPL-apoB will be summarized using descriptive statistics. Demographic and baseline data for each patient will be provided in data listings.

Medical history will be coded using MedDRA v20.0 and presented by system organ class and preferred term by ISIS 681257 treatment groups and pooled placebo group. If a patient had more than one medical history event within a system organ class, the patient is counted once for each preferred term and once for the system organ class. Medical history data will also be provided in by-patient listings.

Cardiovascular disease history data will be tabulated by ISIS 681257 treatment group and pooled placebo group. A by-patient data listing will also be provided.

Ancillary procedures and genetic testing data will be provided in by-patient listings.

Demographics and baseline characteristics summary tabulations will be produced for the Safety Set, the FAS, and the PPS.

## 4.3. Efficacy Evaluation

All efficacy analyses related to Lp(a) will be primarily performed, and the actual changes in Lp(a) will be presented in nanomoles per liter (nmol/L) because the direct output of the Lp(a) assay used in this study is provided in molar units. Due to high degree of size heterogeneity of apo(a) protein, use of molar concentrations is considered highly preferable over use of mass concentrations (mg/dL) (Markovina SM and Albers JJ, 2016). For completeness, the actual Lp(a) results will also be presented in mg/dL using conversion factor of 2.5. Although the conversion factor for transforming Lp(a) values from nmol/L to mg/dL highly varies due to variability of mass of nonprotein components of Lp(a), it is accepted in the literature that Lp(a) in nmol/L is approximately 2.4-2.5 fold higher than Lp(a) in mg/dL (Tsimikas S et al 2015, Viney et al, 2016).

### 4.3.1. Analysis of the Primary Efficacy Endpoint

As described in Section 1.2.5, the primary efficacy endpoint is the percent change in fasting Lp(a) from baseline at the primary analysis time point (Week 25 for patients in Cohorts A-C; Week 27 for patients in Cohorts D-E) achieved by ISIS 681257 compared to placebo.

The percent change from baseline in Lp(a) will be analyzed using an ANCOVA model with treatment group as factors and log-transformed baseline Lp(a) as covariate. The ANCOVA model will use log(Y/X) as dependent variable, where Y is the post-baseline value of Lp(a) and X is the baseline value of Lp(a). The model will provide an estimate of the log ratio, which will then be converted back to the original ratio scale. The percent change from baseline will then be estimated based on the estimated ratio. Patients with missing primary endpoint will have their fasting Lp(a) value imputed using the multiple imputation method described in Section 3.10.1.

The primary endpoint will be compared between ISIS 681257 treatment groups and the pooled placebo group for each of the 100 imputed datasets. The estimates from the 100 fitted models will be combined to provide an overall estimate, with corresponding CIs and p-value (Little and Rubin, 2002). Results from the ANCOVA model will be tabulated by ISIS 681257 treatment groups compared to the pooled placebo group.

Mean (SD) percent change over time in fasting Lp(a) will be plotted by ISIS 681257 treatment group and pooled placebo group, until there are fewer than 10% of the FAS/PPS population at a given visit. Waterfall plots of by-patient percent changes from baseline to the primary analysis time point will also be provided.

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

All primary efficacy data will be provided in data listings.

The primary efficacy analysis will be done using the FAS population.

#### 4.3.1.1. Sensitivity Analyses of the Primary Efficacy Endpoint

The following sensitivity analyses are planned to show the robustness of the primary analysis:

1) The primary analysis will be repeated using the PPS population (using an ANCOVA model and the same MCMC multiple imputation method).

2) The primary efficacy endpoint will be analyzed using a non-parametric Wilcoxon Rank Sum test using both the FAS and the PPS. Missing data will be handled using the same MCMC multiple imputation method as the primary analysis. The treatment effect will be estimated using the Hodges-Lehmann estimator of the location shift between ISIS 681257 treatment groups and the pooled placebo group. Asymptotic 95% CI and corresponding p-value will be provided.
3) The primary analysis will be repeated on the set of patients with non-missing Lp(a) values at the primary analysis time point using the FAS and the PPS.
4) Using controlled imputations (pattern mixture models [PMM] with ANCOVA) will be conducted to assess the robustness of the missing at random assumption. With this approach, missing not at random (MNAR) is assumed, and the mean function for the missing data from patients treated with ISIS 651257 who discontinue the study is pre-specified. Missing Lp(a) for placebo patients will be imputed using the same MCMC multiple imputation method as the primary analysis. Patients treated with ISIS 681257 who discontinue the study due to AE or lack of efficacy will have their post-discontinuation Lp(a) values imputed using estimates from the placebo patients using the copy increment from reference (CIR) approach, detailed in (Carpenter et al. 2013). The assumption is based on the fact that when a patient discontinues treatment due to informative missing data, at the time of discontinuation they would progress in a similar manner as placebo-treated patients. Otherwise, non-informative missing data will be imputed using the same MCMC method as the primary analysis, since it is assumed that those patients would have continued in a similar manner to similar patients in their own treatment group who remained on the study. Therefore, the missing data for these patients is expected to be missing at random.

#### 4.3.2. Analysis of the Secondary Efficacy Endpoints

##### 4.3.2.1. Percent Change from Baseline in fasting LDL-C

The percent change from baseline at the primary analysis time point in fasting LDL-C will be compared between each ISIS 681257 treatment groups and the pooled placebo group using an ANCOVA model with treatment groups as factors and log-transformed baseline LDL-C values as covariate. Similar to the primary endpoint, the ANCOVA model will use log(Y/X) as dependent variable, where Y is the post-baseline value of LDL-C and X is the baseline value of LDL-C. Corresponding 95% CIs and p-value will be provided.

Mean (SD) percent change over time in fasting LDL-C will be plotted by ISIS 681257 treatment group and pooled placebo group, until there are fewer than 10% of the FAS/PPS population at a given visit. Waterfall plots of by-patient percent changes from baseline to the primary analysis time point will also be provided.

##### 4.3.2.2. Responder-Type Analysis

The proportion of patients who achieve:

- ≤125 nmol/L (≤ 50 mg/dL) in fasting Lp(a), or
- ≤75 nmol/L (≤ 30 mg/dL) in fasting Lp(a)

at the primary analysis time point will be compared between each ISIS 681257 treatment group and the pooled placebo group using a logistic regression model with log-transformed baseline Lp(a) as a covariate.

#### 4.3.2.3. Percent Change from Baseline in Other Lipid Parameters

The percent change from baseline at the primary analysis time point in fasting apoB, OxPL-apo(a), and OxPL-apoB will be compared between each ISIS 681257 treatment groups and the pooled placebo group using an ANCOVA model with treatment groups as factors and the respective log-transformed baseline lipid parameter values as covariate. Similar to the primary endpoint, the ANCOVA model will use log(Y/X) as dependent variable, where Y and X are the post-baseline values and the baseline value of the lipid parameter being analyzed, respectively. Corresponding 95% CIs and p-value will be provided.

Mean (SD) percent change over time, until there are fewer than 10% of the FAS/PPS population at a given visit, in these fasting lipid parameters will be plotted by ISIS 681257 treatment group and pooled placebo group. Waterfall plots of by-patient percent changes from baseline to the primary analysis time point will also be provided.

All analyses of secondary endpoints will be performed using the FAS as primary and the PPS as supportive. Patients with missing data for any secondary endpoints will have their respective parameter values (LDL-C, Lp(a), apoB, OxPL-apo(a), and OxPL-apoB) imputed using the imputation method described in Section 3.10.1.

All secondary endpoint data will be provided in data listings.

### 4.3.3. Supportive Efficacy Analysis

Supportive efficacy analyses will be conducted on data collected beyond the primary analysis time point. Log-transformed ratio of post-baseline to baseline will be analyzed for the primary endpoint using a Mixed Model of Repeated Measurements (MMRM). Treatment group and visit will be fitted as factors and log transformed baseline will be fitted as a continuous covariate. Treatment group by visit and visit by baseline will be included as interaction terms in the model. A term for visit will be included in the repeated statement (in SAS PROC MIXED) and an unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within subjects. The Kenward-Roger adjustment for degrees of freedom will be used.

Since not all patients will have the same duration on-treatment, the number of patients at each visit after the primary analysis time point will be different. The supportive efficacy analyses will include the changes (summary statistics only) and percent changes from baseline of Lp(a), LDL-C, apoB, OxPL-apo(a), and OxPL-apoB at each subsequent visit after the primary analysis time point. The supportive analysis of percent changes will be modeled in a similar way as the supportive primary efficacy analysis. Visits will be presented until there are fewer than 10% of the FAS/PPS.

Mean (SD) percent changes over time in all parameters above will be plotted by ISIS 681257 treatment group and pooled placebo group.

Supportive efficacy analyses will be performed using the FAS and the PPS.

## 4.4. Pharmacokinetic and Immunogenicity Analyses

Pharmacokinetic Analysis

All PK data analysis will be conducted using the PKS.

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 and without stratification by patient immunogenicity (IM) status using descriptive statistics. In addition, plasma terminal elimination half-life of ISIS 681257 will be calculated using the post-treatment follow-up data if data permits.

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

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

Immunogenicity Analysis

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

The 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. Subject IM status (positive/negative or unknown) for all evaluable patients, along with the study day associated with the first positive IM status emerged (i.e., onset of ADA development), the last positive IM status observed (Tlast), and max and/or end of treatment titer will be listed by treatment group. Study patients with positive anti-ISIS 681257 antibody status may be qualitatively discussed as being either ‘persistent’, ‘transient’, or ‘not determinable’. Potential relationships of immunogenicity with selected efficacy, safety, and PK measures may be evaluated.

PK and IM sampling times will be provided in data listings.

## 4.5. Safety Analyses

Safety analyses will be conducted primarily using the Safety Set population. The analyses may be reproduced on other populations if warranted.

### 4.5.1. Study Drug Exposure

Study drug exposure will be calculated as the number of days patients were administered study drug, as determined below, and will be summarized by ISIS 681257 treatment group and pooled placebo group using descriptive statistics.

$$Duration\ of\ Study\ Drug\ Exposure\ (days) = (Date\ of\ last\ dose - Date\ of\ first\ dose) + 1$$

Duration of study drug exposure will also be presented in the following categories: ≤13 weeks, >13 to ≤26 weeks, >26 to ≤30 weeks, >30 to ≤34 weeks, >34 to ≤38 weeks, >38 to ≤42 weeks, >42 to ≤46 weeks, >46 to ≤50 weeks, and >50 weeks.

Percent compliance will be summarized for each patient from date of first dose through the treatment period per the following definition:

$$Percent\ Compliance\ (\%) = \frac{Total\ Number\ of\ Infusions\ Received}{Total\ Number\ of\ Infusions\ Planned\ Per\ Protocol} \times 100\%$$

Patient compliance with study drug will be summarized by treatment groups and pooled placebo group and presented in a by-patient data listing. For patients who withdrew/discontinued treatment early, the volume of study drug planned will be calculated based on the period on-treatment up to their withdrawal/termination.

The proportion of patients with compliance ≥ 80% and <80% will be calculated.

Total drug received will be summarized by treatment group and pooled placebo group. Actual dose intensity, defined as the ratio of total drug received and the actual duration of treatment (in weeks), and relative dose intensity, defined as the ratio of actual dose intensity and planned dose intensity, will be summarized by ISIS 681257 treatment group and pooled placebo group.

Duration of study drug exposure (in days and in weeks), percent compliance, total drug received, actual dose intensity and relative dose intensity for each patient will also be provided in data listings.

In addition to the Safety Set, all exposure analyses will be perfomed using the FAS as well.

### 4.5.2. Adverse Events

All AEs will be coded using the MedDRA v20.0 coding system and displayed in tables and data listings using system organ class (SOC) and preferred term. Missing and partial dates will be handled as described in Section 3.10.2.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the first administration of study medication through the end of the study, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study.

All analyses of TEAEs will be performed on the following periods:

- TEAEs On Study, defined as any TEAE reported after onset of the administration of study medication through the end of the study
- TEAEs On Treatment, defined as any TEAE reported during treatment period defined as period from first dose through one dosing interval post last dose

Adverse events are summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given AE in both SOC and preferred term.

The number and percentage of patients with any treatment-emergent adverse event (TEAE), with any TEAE assessed by the Investigator as related to treatment (related, possible, unlikely/remove, and not related relationships), with any serious TEAE, and with any treatment-emergent serious AE potentially related to treatment will be summarized by ISIS 681257 treatment group and pooled placebo group. All incidences will also be summarized within each cohort, by ISIS 681257 and placebo.

In addition, AEs will be summarized by relationship to study drug and by severity. In these tabulations, each patient will contribute only once (ie, the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

Three additional TEAE analyses will be performed:

1. Local cutaneous reaction at injection site (LCRIS) defined as either:
    a. Moderate or severe Injection Site Erythema, Swelling, Pruritus, Pain or Tenderness that started on the day of injection, persisted for at least two days; or
    b. Any AE at the injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the injection site is the principal reason for discontinuation.
2. LCRIS defined as any AE with preferred term (PT) or verbatim term that contained "injection site" and persisted for at least two days
3. Flu-like reactions (FLR) are defined as either:
    a. Flu-like illness; or
    b. Pyrexia or feeling hot or body temperature increased, plus at least two of the following: Chills, Myalgia, and Arthralgia, starting on day of injection or the next day.

The incidences of both LCRIS and FLR will be tabulated by ISIS 681257 treatment group and pooled placebo group, and may be plotted over time if warranted. They will additionally be tabulated within each cohort, by ISIS 681257 and placebo.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in patient data listings.

By-patient listings also will be provided for the following: patient deaths, serious AEs, severe AEs, and AEs leading to withdrawal.

#### 4.5.2.1. Adverse Events of Special Interest

Adverse events of special interest will be tabulated by severity and listed separately as well. These primarily include, but are not limited to, severe reductions in platelet count (< 50,000 $mm^3$), regardless of their relationship to the Study Drug. Liver- and renal-related AEs may be considered of special interest; these may be tabulated by severerity and listed separately as well.

The incidence of AEs of special interest may be plotted over time.

In addition, all bleeding AEs will be tabulated by ISIS 681257 treatment group and pooled placebo group and by the use of antiplatelet drugs. Tabulations will also be provided within cohort, by ISIS 681257 and placebo.

The results of platelet function tests (measured by the [redacted] instrument) will be tabulated by ISIS 681257 treatment group and pooled placebo group and by the use of antiplatelet drugs. The results of platelet function tests will be plotted by ISIS 681257 treatment group and pooled placebo group, and by use of antiplatelet drugs.

### 4.5.3. Laboratory Data

Clinical laboratory values will be expressed in international system of units (SI).

The actual value and change (both actual and percent) from baseline to each on-study evaluation will be summarized by ISIS 681257 treatment group and pooled placebo group for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation, and quantitative urinalysis. In the event of repeat values, the average of all values per study day/time will be used. For platelet counts separate summary tabulations will be provided for the results from central and local laboratories. Measurements that are unscheduled (ie, that are not on a protocol-specified visit) will not count towards the summary tabulations. Tabulations will also be provided within cohort, by ISIS 681257 and placebo.

Mean (SD) by ISIS 681257 treatment group and pooled placebo group over time will be plotted for the selected key parameters: alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), bilirubin (total, direct, indirect), creatinine, hemoglobin, absolute lymphocytes and neutrophils, platelet count, and white blood cell (WBC) count.

Patients with diagnosis of Gilbert's syndrome will be excluded from the summary tabulations and plots for bilirubin (total, direct, indirect), and separate summary tabulations and plots for bilirubin values will be provided for these patients.

Shift tables for selected hematology parameters (hemoglobin, WBC and platelet count), and for selected clinical chemistry parameters (all liver and renal function tests) from baseline to last and baseline to worst value based on the on-treatment and on-study periods defined in Section 4.5.2 will be provided, as appropriate. All unscheduled visits, if any, will contribute to the last or worst value. By-patient spaghetti plots of values over time will also be provided.

All laboratory data will be provided in data listings.

A subset listing will be presented for all clinically significant laboratory values.

#### 4.5.3.1. Abnormalities in Clinical Laboratory Evaluations

In addition, the number of patients who experience abonormalities in clinical laboratory evaluations will be summarized by ISIS 681257 treatment group and pooled placebo group, as well as summarized within cohort by ISIS 681257 and placebo.

#### 4.5.3.2. Liver Funtion Tests

The number and percent of patients falling into each of the categories below representing stopping rules will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- ALT or AST > 8×Upper Limit of Normal (ULN).
- ALT or AST > 5×ULN and persists for ≥2 weeks.
- ALT or AST > 3×ULN (or the greater of 2×[Baseline Value] or 3×ULN if the baseline value was > ULN), **and** total bilirubin > 2×ULN **or** international normalized ratio (INR) > 1.5.
- ALT or AST > 3×ULN (or the greater of 2×[Baseline Value] or 3×ULN if the baseline value was >ULN), and the new appearance (ie, 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

All events described above are required to be confirmed per the confirmation guidance described in Protocol Section 8.5.

Furthermore, the number and percent of patients who have the following reported events will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- Increase in ALT or AST > ULN-3xULN
- Increase in ALT or AST > 3-5xULN
- Increase in ALT or AST > 5xULN

Box plots of ALT and AST values in terms of ULN will be plotted by ISIS 681257 treatment group and pooled placebo group at each visit.

All analyses will also be conducted within each cohort, by ISIS 681257 and placebo, as applicable.

#### 4.5.3.3. Renal Function Tests

Actual values and changes in Glomerular Filtration Rate (GFR) (estimated by the Chronic Kidney Disease –Epidemiological Collaboration [CKD-EPI] formula) will be summarized by ISIS 681257 treatment group and pooled placebo group.

The number of patients falling into each of the categories below representing monitoring rules will be tabulated by treatment group:

- eGFR decrease of > 25% from baseline.
- Urine albumin/creatinine ratio (UACR) > 250 mg/g.

- Urine protein/creatinine ratio (UPCR) > 500 mg/g.
- An increase in serum creatinine of > 0.3 mg/dL from baseline.
- An increase in serum creatinine of > 50% from baseline.
- eGFR decrease of > 40% from baseline.
- eGFR value < 45 mL/min/1.73 $m^2$.

All events described above are required to be confirmed per the confirmation guidance described in Protocol Section 8.5.

The number and percent of patients who have the following reported events representing stopping rules will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- 24 hr creatinine clearance decrease of > 40% from baseline
- 24 hr creatinine clearance value < 45 mL/min/1.73 $m^2$
- 24 hr urine protein > 1g

Furthermore, the number and percent of patients who have the following reported events will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- 5-fold increase from baseline in any of renal biomarkers (KIM-1, NAG, or NGAL)
- Serum creatinine increased >1-1.5 x baseline
- Serum creatinine increased >1.5-3.0 x baseline
- Serum creatinine increased >3.0 x baseline

Spaghetti plots of by-patient estimated GFR, UACR, and UPCR over time will be produced. Spaghetti plots of by-patient 24 hr creatinine clearance and any renal biomarker will be produced, if warranted.

All analyses will also be conducted within each cohort, by ISIS 681257 and placebo, as applicable.

#### 4.5.3.4. Platelet Count

The number and percent of patients falling into each of the categories below will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- Platelet count decrease below LLN.
- Platelet count decrease of ≥ 30% from baseline.

All events described above are required to be confirmed per the confirmation guidance described in Protocol Section 8.5.

Furthermore, the number and percent of patients who have the following reported events will be tabulated by ISIS 681257 treatment group and pooled placebo group, and separately for the subset of patients with normal baseline (≥ 140,000/mm3):

- Any 2 occurrences of platelet count < 140,000/$mm^3$

- Any single occurrence of platelet count < 100,000/$mm^3$
- Any 2 occurrences of platelet count < 140,000/$mm^3$ or any single occurrence of platelet count < 100,000/$mm^3$
- Platelet count < 140,000 but ≥ 100,000/$mm^3$
- Platelet count < 100,000 but ≥ 75,000/$mm^3$
- Platelet count < 75,000 but ≥ 50,000/$mm^3$
- Platelet count < 50,000/$mm^3$
- Platelet count decrease of ≥ 30% from baseline
- Platelet count decrease of ≥ 50% from baseline

Additionally, the analysis above will be performed for patients with baseline platelet count of ≥160,000/$mm^3$ , and those with baseline platelet count <160,000/$mm^3$.

Plots of platelet count, change from baseline in platelet count, and percent change from baseline in platelet count over time will be generated for each treatment group and pooled placebo group.

Time to platelet count < 100,000/$mm^3$ will be performed if warranted.

All analyses will also be conducted within each cohort, by ISIS 681257 and placebo, as applicable.

#### 4.5.4. Vital Signs and Physical Examinations

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs by ISIS 681257 treatment group and pooled placebo group.

Mean (SD) values by treatment group and by-patient spaghetti plots over time of weight and BMI will be produced.

Vital sign measurements and changes from baseline will be presented for each patient in data listings.

Any abnormalities in physical examination deemed clinically significant by the Investigator will be reported as adverse events. All physical examination dates will be presented in a data listing.

#### 4.5.5. Electrocardiogram

Average of triplicate ECG results will be summarized using descriptive statistics of actual values and changes from baseline at each on-study visit by ISIS 681257 treatment group and pooled placebo group. Responses to overall interpretation will be tabulated by counts and percentages at each on-study visit.

Furthermore, the number and percent of patients who have the following reported events will be tabulated by ISIS 681257 treatment group and pooled placebo group:

- Absolute QT/QTc >450 msec
- Absolute QT/QTc >480 msec

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

ECG data for each patient will be provided in a data listing.

#### 4.5.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (Version March 2017). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term. Patients will be counted only once by ATC and preferred term. Missing and partial dates will be handled as described in Section 3.10.3.

Concomitant medications will be tabulated by ISIS 681257 treatment group and pooled placebo group, where any medications that did not end prior to first dose will be included. Prior medications consist of all medication that ended prior to the first dose. If an end date is missing or the medication is ongoing, the medication will be included.

The use of prior and concomitant medications will be included in a by-patient data listing.

# 5. CHANGES TO PLANNED ANALYSES

All changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the study report. Decisions to deviate from planned analyses will be documented at the time they are made.

If any modifications in the experimental design, dosages, parameters, patient selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

# 6. REFERENCES

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# 7. APPENDIX 1: GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

The following grading recommendations for AEs relating to laboratory test abnormalities are based upon the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, June 2010.

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| **Hematology** | | | |
| aPTT prolonged | >ULN – 1.5 × ULN | >1.5 – 2.5 × ULN | >2.5 × 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 × LLN or <25% decrease from baseline | <0.75 – 0.5 × LLN or 25 - <50% decrease from baseline | <0.5 × 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 – 80 g/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 × ULN; >1 – 1.5 times above baseline if on anticoagulation | >1.5 – 2.5 × ULN; >1.5 – 2.5 tmes above baseline if on anticoagulation | >2.5 × ULN; >2.5 times above baseline if on anticoagulation |
| Lymphocyte count decreased | <LLN – 800/mm$^3$; <LLN – 0.8 × 10$^9$/L | <800 – 500/mm$^3$; <0.8 – 0.5 × 10$^9$/L | <500/mm$^3$; <0.5 × 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 × 10$^9$/L | <1500 – 1000/mm$^3$; <1.5 – 1.0 × 10$^9$/L | <1000/mm$^3$; <1.0 × 10$^9$/L |
| Platelet count decreased | <LLN – 75,000/mm$^3$; <LLN – 75.0 × 10$^9$/L | <75,000 – 50,000/mm$^3$; <75.0 – 50.0 × 10$^9$/L | <50,000/mm$^3$; <50.0 × 10$^9$/L |
| White blood cell decreased | <LLN – 3000/mm$^3$; <LLN – 3.0 × 10$^9$/L | <3000 – 2000/mm$^3$; <3.0 – 2.0 × 10$^9$/L | <2000/mm$^3$; <2.0 × 10$^9$/L |
| **Chemistry** | | | |
| Acidosis | pH <normal, but ≥7.3 | - | pH <7.3 |
| Alanine aminotransferase increased | >ULN – 3.0 × ULN | >3.0 – 5.0 × ULN | >5.0 × ULN |
| Alkaline phosphatase increased | >ULN – 2.5 × ULN | >2.5 – 5.0 × ULN | >5.0 × ULN |
| Alkalosis | pH >normal, but ≤7.5 | - | pH >7.5 |
| Aspartate aminotransferase increased | >ULN – 3.0 × ULN | >3.0 – 5.0 × ULN | >5.0 × ULN |

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| Blood bilirubin increased | >ULN – 1.5 × ULN | >1.5 – 3.0 × ULN | >3.0 × 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 |
| 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 × 10$^9$/L | <500 – 200/mm$^3$; <0.5 – 0.2 × 10$^9$/L | <200/mm$^3$; <0.2 × 10$^9$/L |
| CPK increased* | >ULN - <6 ULN | 6 – 10 × ULN | >10 × ULN |
| Creatinine increased | >1 – 1.5 × baseline; >ULN – 1.5 × ULN | >1.5 – 3.0 × baseline; >1.5 – 3.0 × ULN | >3.0 × baseline; >3.0 × ULN |
| GGT increased | >ULN – 2.5 × ULN | >2.5 – 5.0 × ULN | >5.0 × 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; <20 – 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 – 30 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 |

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| Hypomagnesemia | <LLN – 1.2 mg/dL;<br><LLN – 0.5 mmol/L | <1.2 – 0.9 mg/dL;<br><0.5 – 0.4 mmol/L | <0.9 mg/dL;<br><0.4 mmol/L |
| Hyponatremia | <LLN – 130 mmol/L | - | <130 mmol/L |
| Hypophosphatemia | <LLN – 2.5 mg/dL;<br><LLN – 0.8 mmol/L | <2.5 – 2.0 mg/dL;<br><0.8 – 0.6 mmol/L | <2.0 mg/dL;<br><0.6 mmol/L |
| Lipase increased | >ULN – 1.5 × ULN | >1.5 – 2.0 × ULN | >2.0 × ULN |
| Serum amylase increased | >ULN – 1.5 × ULN | >1.5 – 2.0 × ULN | >2.0 × ULN |
| **Urine** | | | |
| Proteinuria | | | |
| Adults | 1+ protenuria;<br>urinary protein <1.0 g/24 hrs | 2+ proteinuria;<br>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).

# 8. APPENDIX 2: MAJOR PROTOCOL DEVIATIONS

Major Protocol Deviations are defined as any intentional or unintentional change from the IRB-approved protocol that adversely affects the risk/benefit ratio of the study; the rights, safety, or welfare of the participants or others; or the integrity of the study and interferes with evaluation of efficacy or safety of the study drug. The list of Major Protocol Deviations is provided below.

- IRB/IEC approved informed consent not signed and dated prior to initiating any study specific procedures,
- Inclusion/exclusion (I/E) criteria not verified prior to patient enrollment or not met, and patient enrolled despite not meeting I/E criteria
- Misrandomization
- Overdose,
- Use of IP where medication usability is compromised (i.e. expired study drug, study drug that has experienced temperature excursion and has not been approved for use by Sponsor)
- Patient taking/receiving any disallowed concomitant medication or therapy
- Inadequate reporting or documentation of serious adverse events (SAEs),
- Evidence of serious misconduct at the site

# STATISTICAL ANALYSIS PLAN ADDENDUM

## APPROVAL SIGNATURE PAGE

| | |
|---|---|
| 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) |
| Protocol Number: | ISIS 681257-CS6 |
| Document Date: | 06 June 2018 |
| Version: | Final Version 1.0 |
| Sponsor: | Akcea Therapeutics, Inc.<br>55 Cambridge Parkway, Suite 100<br>Cambridge, MA 02142 |

Author Signatory:

[redacted], MS

Signature: [redacted]

Date: 7 June 2018

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

[redacted] MD, PhD

[redacted]

Signature: [redacted]

Date: 6 June 2018

Akcea Therapeutics

## Purpose

The purpose of this document is to define additional, pre-defined supportive efficacy analyses of the primary efficacy endpoint by additional subgroups of interest for study ISIS 681257-CS6. In addition, this document slightly redefines treatment compliance to better capture partial doses received.

## Additional Subgroups

In addition to the subgroups defined in the final statistical analysis plan (SAP v1.0) dated 12 April 2018, the following subgroups are defined:

Baseline Lp(a)
The analyses by baseline Lp(a) will be categorized by quartiles, as well as >70 mg/dL versus ≤70 mg/dL.

Intensity of Statin Therapy
Intensity of statin therapy will be categorized as either High or Moderate/Low, by the use of the following concomitant medication while on-treatment:

- High-intensity: atorvastatin (40-80 mg/day), rosuvastatin (20-40 mg/day), and simvastatin (>40 mg/day). The medication names to be used are the following:
    - ATORVASTATIN
    - ROSUVASTATIN
    - SIMVASTATIN
- Moderate/Low-intensity: atorvastatin (<40 mg/day), rosuvastatin (<20 mg/day), simvastatin (≤40 mg/day), and any other statin medication will be considered low levels. The following medication names, in addition to those above, are to be used:
    - FLUVASTATIN
    - LOVASTATIN
    - PITAVASTATIN
    - PRAVASTATIN
    - INEGY
    - ZETITOR

Patients who do not take any statin medication will also be classified as Moderate/Low-intensity.

Niacin Use
Niacin use will be categorized as either Yes or No, by the use of the concomitant medication 'NICOTINIC ACID' while on-treatment.

PCSK9 Inhibitor Use
PCSK9i use will be categorized as either Yes or No, by the use of the following concomitant medications while on-treatment:

- ALIROCUMAB
- EVOLOCUMAB

## Supportive Efficacy Analyses

In addition to those described in the SAP version 1.0, the change and percent change from baseline in Lp(a) over time will be tabulated by treatment group for all subgroups defined above. Descriptive statistics will be presented (n, mean, std, Q1, median, Q3, min, and max) for all visits. Data will be reported as collected; missing data will not be imputed.

## Percent Compliance

Version 1.0 of the SAP defines treatment compliance in terms of number of infusions received. In order to better account for partial infusions, percent compliance is redefined in terms of volume received as follows:

$$Percent\ Compliance\ (\%) = \frac{Total\ Volume\ of\ Study\ Drug\ Received\ (mL)}{Total\ Volume\ of\ Study\ Drug\ Planned\ Per\ Protocol\ (mL)} \times 100\%$$