**Official Title:** A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-LRx) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

**NCT Number:** NCT03371355

**Document Dates:** Protocol Amendment 3 – 21 March 2019

Sponsor:
Akcea Therapeutics, Inc.
22 Boston Wharf Road, 9th Floor
Boston, MA 02210

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

# ISIS 703802-CS2

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

**Protocol Amendment 3– 21 March 2019**

# ISIS 703802-CS2

## A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

**Protocol Amendment 3 – 21 March 2019**

| Protocol History | |
|---|---|
| Original Protocol | 22 September 2017 |
| Protocol Amendment 1 | 14 February 2018 |
| Protocol Amendment 2 | 25 October 2018 |
| Protocol Amendment 3 | 21 March 2019 |

**Approved by:**

[redacted]

[redacted] MD

[redacted]

Akcea Therapeutics, Inc.
22 Boston Wharf Road, 9th Floor
Boston, MA 02210
Telephone: (617) 207-8558

# ISIS 703802-CS2

## Protocol Number ISIS 703802-CS2

## Protocol Amendment 3

## Clinical Phase: 2

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

Trial Sponsor: Akcea Therapeutics, Inc.
22 Boston Wharf Road, 9th Floor
Boston, MA 02210

Key sponsor contact: [redacted] - Akcea Therapeutics, Inc.
22 Boston Wharf Road, 9th Floor
Boston, MA 02210

Phone: [redacted]
E-mail: [redacted]

Sponsor Medical Monitor: [redacted] MD - Akcea Therapeutics, Inc.
22 Boston Wharf Road, 9th Floor
Boston, MA 02210

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

Date: 21 March 2019

## Confidentiality Statement

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

# Protocol Signature Page

**Protocol Number:** **ISIS 703802-CS2**

**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

**Amendment:** Protocol Amendment 3

**Date:** 21 March 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (ISIS 703802) Administered Subcutaneously to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD) dated 21 March 2019, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6R2) and with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2013).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc., and Akcea Therapeutics, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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## PROTOCOL AMENDMENT

**Protocol Number:** ISIS 703802-CS2

**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously (SC) to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD)

**Amendment Number:** Protocol Amendment 3

**Amendment Date:** 21 March 2019

The following modifications to the Protocol ISIS 703802-CS2 Amendment 2 have been made.

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

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

| Protocol Section | Description of Change | Rationale |
|---|---|---|
| Title Pages | Update the Sponsor Approval and Sponsor Medical Monitor to [redacted] MD. | Change in Medical Monitor for the study |
| Throughout (including Synopsis) | Revise sample size for study to 96 randomized. The new per Cohort sample size is 32 randomized. This results in 24 patients receiving active drug and 8 patients receiving placebo. | Sponsor decision to revise sample size in order to accelerate further development for populations with serious hepatic steatosis. With the changes in sample size, the study remains adequately powered to provide the desired information on the primary objective and the key secondary objectives relevant to this population. |
| Appendix A Schedule of Procedures – Weekly Dosing (Cohort A) | Updated Cohort A Appendix A Footer H text to read: "During follow-up period, hematology sampling for platelet values are taken every 14 days (+/- 2 days) for 5 weeks after last dose of Study Drug, then at Week 8 and Week 13 Follow-up visits." | The intent of Cohort A Schedule of Procedures Footer H is to clarify that hematology samples for platelet values should continue to be taken every 14 days (+/- 2 days) after dosing stops. During the Treatment Period, Hematology samples are being drawn every two weeks starting at Week 1 and continuing through W27/ET. It is important to note that even though Week 27 is the last Treatment Period visit, the last dose of IP is actually given at Week 26 for Cohort A. Therefore, bi-weekly hematology testing for platelet values should continue after dosing stops and taken |

| Protocol Section | Description of Change | Rationale |
|---|---|---|
| | | at the following visits: Follow-up Week 2; which is actually 3 weeks post last dose), Follow-up Week 4; which is actually 5 weeks post last dose), then at Follow-up Week 8 and Follow-up Week 13. |
| Appendix A Schedule of Procedures – Every 4-Week Dosing (Cohorts B & C) | Updated Cohorts B & C Appendix A Footer H text to read: "Cohorts B & C Footer H: During the follow-up period, hematology sampling for platelet values should continue to be taken every 14 days (+/- 2 days) for 6 weeks after Week 27/EOT, then at Week 4, Week 8 and Week 13 Follow-up visits" | To clarify the language used in Footer H of Appendix A Schedule of Procedures. As the Follow-Up Visits are already defined in the table, Footer H served as an aid to help explain the timing of the hematology samples when transitioning from Treatment Period to Follow-up period. |
| Section 4.4 Unblinding of Treatment Assignment | The Sponsor will be blinded throughout the study up until the last subject complets the treatment period. | To provide more specific information on when the Sponsor will become unblinded. |
| 8.5.2 Safety Monitoring For Renal Function | The following Lab alerts for abnormal renal tests were updated:<br>• UACR > 165 mg/g<br>• UPCR > 325 mg/g<br>• New onset hematuria defined as ≥ 5 RBC/hpf (except for menstruating females)<br>• Abnormal test results should now be repeated.<br>• Supplemental renal tests should now be obtained within 7 days, and additional laboratory studies may be performed to identify if other potential etiologies may be casual factor<br>• The 24-hour urine sample, urine albumin, and urine protein were removed from the supplemental rental tests. | To align the renal monitoring criteria in this study with the criteria used in clinical studies of other anti-sense oligonucleotides conducted by the Sponsor |
| 8.6.2 Stopping Rules for Renal Function Test Results | The following updates were made to 8.6.2:<br>• 24-hour urine sample removed<br>• eGFR criteria updated to: decrease of > 25% from baseline<br>• Added criteria:<br>o UACR > 165 mg/g<br>o UPCR > 325 mg/g<br>o New onset of hematuria (defined as ≥ 5 RBC/hpf) | To align the renal stopping rules in this study with the rules used in clinical studies of other anti-sense oligonucleotides conducted by the Sponsor |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Protocol Title** | A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study of ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) Administered Subcutaneously (SC) to Subjects with Hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM), and Nonalcoholic Fatty Liver Disease (NAFLD) |
| **Study Phase** | 2 |
| **Indication** | Subjects with Hypertriglyceridemia |
| **Primary Objective(s)** | To assess the effect of different doses and dosing regimens of ISIS 703802 on reduction in fasting triglycerides (TG) |
| **Secondary Objective(s)** | To evaluate the safety and tolerability of ISIS 703802<br><br>To evaluate the effect of ISIS 703802 on changes from Baseline at End-of-Treatment on glucose and lipid metabolism, and liver fat<br><br>To evaluate pharmacokinetics (PK) of ISIS 703802 across different doses and dose regimens<br><br>To evaluate the effect of ISIS 703802 on changes from Baseline on biomarkers related to liver inflammation, adipokines and body composition |
| **Study Design** | This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 96 subjects will be randomized in a 3:1 ratio to receive ISIS 703802 or placebo. The sample size was determined to provide statistical power for efficacy assessments. Study Drug (ISIS 703802 or placebo) will be administered SC every week or every 4 weeks, depending on cohort assignment, for 26 weekly doses, or 6 doses every 4-weeks.<br><br>Following end-of-treatment assessments, all subjects will then enter a 13-week post-treatment follow-up period.<br><br>The primary safety and efficacy analysis time point is at Week 27 for subjects who received weekly dosing (Cohort A) and at Week 25 for subjects who received every 4-week dosing (Cohorts B and C). |
| **Number of Subjects** | Approximately 96 |
| **Study Population** | <u>Inclusion Criteria</u><br>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<br><br>2. Males or females aged ≥ 18 and ≤ 70 years old at the time of informed consent<br><br>3. Plasma TG at Screening > 150 mg/dL and at qualification of > 150 mg/dL<br><br>4. Documented history of hepatic steatosis as determined by imaging (CT scan, MRI, FibroScan, or US) suggesting liver fat > 8%, or positive ultrasound at Screening<br><br>5. Baseline MRI indicating hepatic fat fraction (HFF) > 8%<br><br>6. Clinically confirmed diagnosis of T2DM<br><br>a. Hemoglobin A1c > 6.5 and ≤ 10% at Screening<br><br>b. On a stable dose of oral glucose-lowering medication (ie metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors) for at least 3 months before Screening and plan to remain on the same medication for the duration of the study |

7. Body mass index between 27- 40 kg/m$^2$, inclusive, at Screening

8. If taking lipid lowering medication, subjects must be on a stable dose for at least 3 months before first dose of study drug and plan to remain on the same medication for the duration of the study

9. Females: must be non-pregnant and non-lactating and either;

    a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);

    b. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);

    c. Abstinent* or;

    d. if engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 703802 or placebo)

    * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the subject. 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

10. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 703802

<u>Exclusion Criteria</u>

1. Type 1 diabetes mellitus
2. Active chronic liver disease, alcoholic liver disease, Wilson's disease hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, genetic hemochromatosis, known or suspected hepatocellular carcinoma, history of or planned liver transplant for end-stage liver disease of any etiology
3. Documented history of advanced liver fibrosis
4. History of cirrhosis and/or hepatic decompensation including ascites, hepatic encephalopathy, or variceal bleeding
5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
6. History of acute kidney injury within 12 months of Screening
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Subjects with a history of major bleed or high-risk of bleeding diathesis
9. Clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion, including the following:

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

| | |
|---|---|
| | b. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. 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<br>c. Estimated GFR < 60 mL/min/1.73 $m^2$ (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation)<br>d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN<br>e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL<br>f. Alkaline phosphatase (ALP) > 1.5 x ULN<br>g. Platelet count < LLN<br>10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B<br>11. Uncontrolled hyper- or hypothyroidism. Subjects on dose stable replacement therapy for at least 3 months prior to Screening will be allowed<br>12. History of clinically significant acute cardiac event within 6 months before Screening (includes stroke, transient ischemic attack, and coronary heart disease [angina pectoris, myocardial infarction, revascularization procedures])<br>13. History of heart failure with NYHA greater than Class II<br>14. Current acute or chronic inflammatory disease<br>15. Hypersensitivity to the active substance or to any of the excipients<br>16. Active untreated mental disorder or depression. Subjects who are on a stable dose of medication (excluding atypical antipsychotics) for at least 6 months before screening and whose treating physicians consider them to be mentally stable may be enrolled<br>17. Any major surgery including bariatric surgery within 3 months of Screening<br>18. Weight change > 5% within 3 months before Screening or during diet run in period<br>19. Currently taking parenteral or chronic oral corticosteroids, amiodarone, tamoxifen, obeticholic acid, atypical antipsychotics, HIV protease inhibitors, or ursodeoxycholic acid<br>20. Alcohol consumption > 21 units of alcohol per week for men and > 14 units of alcohol per week for women over a two-year time frame prior to the Baseline MRI eligibility (One drink "unit" or one standard drink is equivalent to a 12 ounce beer, a 4 ounce glass of wine, or a 1 ounce shot of hard liquor)<br>21. 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<br>22. Use of warfarin or other coumarins, direct thrombin inhibitors or Factor Xa inhibitors<br>23. Use of anti-platelet therapies unless the dose has been stable for 4 weeks prior to the first dose of ANGPTL3-$L_{Rx}$ and will remain on a stable regimen through the end of the Post-Treatment Follow-up Period, during which regular clinical monitoring will be performed<br>24. Use of insulin or insulin analogs, GLP-1 agonists, and PPAR$\gamma$ agonists (pioglitazone or rosiglitazone)<br>25. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer |

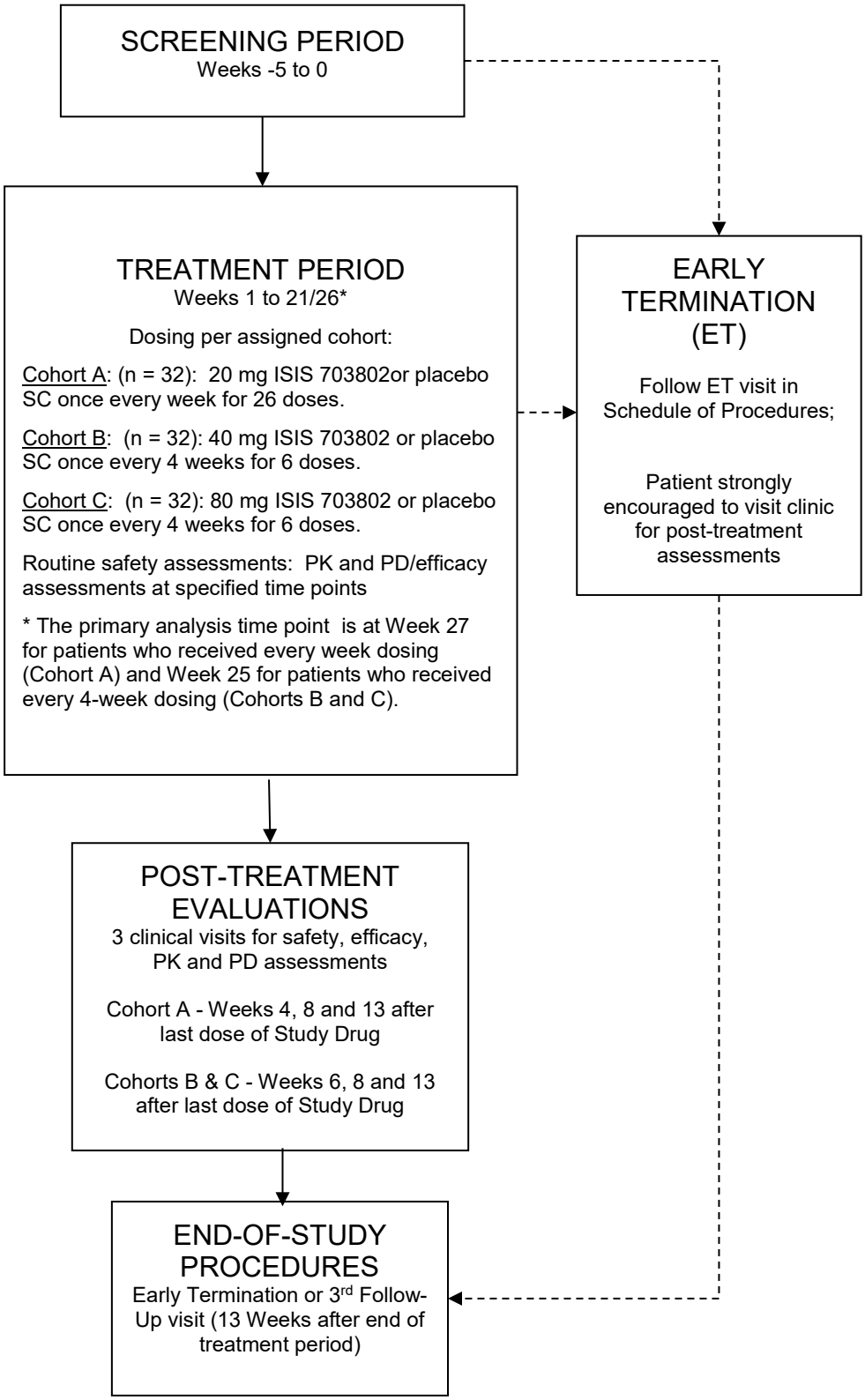
<table>
<tr><td></td><td>
26. Treatment with any non-Akcea/non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Subjects that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months have elapsed since dosing<br>
27. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening<br>
28. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator<br>
29. Subjects with conditions contraindicated for MRI procedures including subjects who have any metal implant (e.g., heart pacemaker, rods, screws, aneurysm clips) that contraindicates MRI procedures<br>
30. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study
</td></tr>
<tr><td>Treatment Groups</td><td>
Subjects will be randomized to 3 parallel cohorts:<br><br>
Cohort A (n = 32): Subjects will be randomized 3:1 to receive 20 mg ISIS 703802 or placebo SC once every week for 26 doses.<br><br>
Cohort B (n = 32): Subjects will be randomized 3:1 to receive 40 mg ISIS 703802 or placebo SC once every 4 weeks for 6 doses.<br><br>
Cohort C (n = 32): Subjects will be randomized 3:1 to receive 80 mg ISIS 703802 or placebo SC once every 4 weeks for 6 doses.
<table>
<tr><th>Cohort</th><th>Treatment</th><th># Doses</th><th>Total Study Drug</th></tr>
<tr><td>A</td><td>20 mg ISIS 703802 or placebo (Every week)</td><td>26</td><td>520 mg</td></tr>
<tr><td>B</td><td>40 mg ISIS 703802 or placebo (Every 4 weeks)</td><td>6</td><td>240 mg</td></tr>
<tr><td>C</td><td>80 mg ISIS 703802 or placebo (Every 4 weeks)</td><td>6</td><td>480 mg</td></tr>
</table>
</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>
The Sponsor will provide ISIS 703802 in a single use vial with a concentration of 100 mg/mL and matching volume placebo:<br><br>
Cohort A: 20 mg every week of ISIS 703802 or placebo (0.2 mL)<br><br>
Cohort B: 40 mg every 4 weeks of ISIS 703802 or placebo (0.4 mL)<br><br>
Cohort C: 80 mg every 4 weeks of ISIS 703802 or placebo (0.8 mL)<br><br>
All doses will be given by SC injection. Self-administration will be allowed after appropriate training of subject and/or caregiver.
</td></tr>
<tr><td>Rationale for Dose and Schedule Selection</td><td>The Phase 1 program evaluated ISIS 703802 doses of 10 mg, 20 mg, 40 mg and 60 mg given weekly for 6 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in lipid parameters. The range of dosing proposed for the present study will provide the equivalent drug exposure of 10 mg (from 40 mg monthly), and 20 mg (from 20 mg weekly and 80 mg monthly) 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 TGs ranging from approximately 45 to 55% at steady-state.</td></tr>
<tr><td>Adjustment of Dose or Treatment Schedule</td><td>Dose adjustments, including dose interruptions, and/or decreasing the dose and dose frequency may be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.</td></tr>
</table>

| | |
|---|---|
| **Study Visit Schedule and Procedures** | Detailed information regarding the study procedures are outlined in Section 6, Appendices A and C.<br><br>All subjects enrolled will be randomized to 6 months of treatment in 1 of 3 treatment cohorts.<br><br>The study for an individual subject will generally consist of the following periods:<br><br>• A Screening Period (up to 5 weeks), including a 4-week diet stabilization phase, where appropriate<br>• A Treatment Period (26 weeks) during which Study Drug will be administered per assigned cohort by SC injection<br>• A Post-treatment Follow-up Period (13 weeks)<br><br>During the Screening Period, subject will be advised to maintain diet and exercise routines and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening Period, subjects not already on a stable diet will have 4 weeks of diet run-in, followed by a qualification visit during which final eligibility assessments will be performed. Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet stabilization phase. At the qualification visit TGs will be measured. MRI will be obtained during screening once all other eligibility criteria are met to assess liver fat content.<br><br>Subjects meeting eligibility criteria at Screening and having a qualifying TG and MRI, defined as having greater than 8% liver fat assessed by MRI-PDFF (via central reviewer) will return to the clinic on Day 1. TG and MRI results must be available prior to randomization and administration of the first dose of study drug.<br><br>Subjects assigned to Cohort A will receive a single SC dose of ISIS 703802 or placebo every week for a total of 26 doses. Subjects assigned to Cohorts B and C will receive a single SC dose of ISIS 703802 or placebo every 4 weeks for a total of 6 doses. Subjects will return regularly for outpatient visits throughout the treatment period according to the Schedule of Procedures (Appendix A).<br><br>Following the end of the treatment period, subjects will then enter a 13-week Post-Treatment Follow-up Period and will return to the Study Center for outpatient evaluations according to the Schedule of Procedures (Appendix A).<br><br>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.<br><br>Safety and tolerability results in patients dosed with ISIS 703802 will be compared with those dosed with placebo. |

| | |
|---|---|
| **Efficacy and Safety Evaluations** | The primary analysis time point is at Week 27 for subjects who received every week dosing (Cohort A) and Week 25 for subjects who received every 4-week dosing (Cohorts B and C).<br><br>**Primary endpoint:**<br><br>• Percent change in fasting TG level from Baseline at the primary analysis time point<br><br>**Secondary endpoints**: Evaluate the effect of ISIS 703802 on changes from Baseline at the primary analysis timepoint in:<br><br>• Absolute and percentage change in ANGPTL3 protein, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoCIII, ApoAI, FFA, Lp(a)<br>• Absolute change in fasting plasma glucose, HbA1c, fasting insulin HOMA-IR, fructosamine and glycated albumin<br>• Absolute and percent change in weight, SBP and DBP<br>• Absolute and percent change in hepatic fat fraction (HFF) by MRI-PDFF<br>• Proportion of subjects reaching hepatic fat fraction (HFF) ≤ 8% by MRI-PDFF<br>• Absolute change in Fatty Liver Index (FLI)<br>• Absolute change in ALT and AST<br>• Adipokines and related metabolic markers such as leptin, adiponectin, phospholipids (e.g. ceramides, sphingolipids, diacylglycerol)<br>• Body composition as measured by single slice MRI of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), waist circumference, WHR (waist-to-hip ratio), and BMI<br><br>[redacted] |
| **Pharmacokinetic Evaluations** | Plasma samples will be taken from all subjects for the measurement of ISIS 703802 plasma trough levels throughout treatment and during the post-treatment follow-up period. Plasma sample collection time points are detailed in Appendix A and C. In addition, in a subset of subjects (approximately 12 subjects per cohort), more frequent plasma samples will be taken following the first administration and Day 176 (for Cohort A) or Day 141 (for Cohorts B and C) dose to determine PK parameters. Plasma sample collection time points are detailed in Appendix A and C.<br><br>The plasma ISIS 703802 levels over time will be descriptively summarized by treatment with stratification by subject immunogenicity status, if applicable. Apparent terminal elimination half-life will be calculated in subjects who received ISIS 703802 treatment using a non-compartmental method, if data permitted.<br><br>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 TG between ISIS 703802 treated groups and placebo group in the Full Analysis Set.<br><br>The data will be analyzed using an ANCOVA model with the Baseline TG level as a covariate.<br><br>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 TG levels. Safety will be evaluated on the basis of incidence of expected and unexpected treatment-related SAEs, and other specific safety considerations including the incidence of platelet reductions.<br><br>Sample Size Considerations:<br><br>Subjects in the placebo arm will be pooled for the statistical analysis in order to compare active and control arms. Therefore, each of the 4 arms will have 24 patients. Considering 10% dropouts, 21 patients per group are expected to complete the study.<br><br>A sample size of 21 patients per arm will be able to detect:<br><br>• *A treatment difference in mean triglycerides of 50% based on a between-patient standard deviation of 46% (Jani et al. 2014) and a two-sample t-test with an unadjusted alpha level of 0.05 with 93% power.*<br>• A treatment difference in mean liver fat of 4.75% based on a between-patient standard deviation of 3.96% (Tiikkainen et al. 2004) and a two-sample t-test with an unadjusted alpha level of 0.05 with 96% power. |
| **Sponsor/Collaborator** | Akcea Therapeutics, Inc./Ionis Pharmaceuticals, Inc. |

## STUDY DESIGN AND TREATMENT SCHEMA



## STUDY GLOSSARY

| Abbreviation | Definition |
|---|---|
| 2′-MOE | 2′-*O*-(2-methoxyethyl) |
| AE | adverse event |
| ISIS 703802 | Antisense inhibitor of ANGPTL3 |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase (SGPT) |
| ANA | antinuclear antibody |
| ANCOVA | Analysis of Covariance |
| ANGPTL3 | Angiopoietin like 3 |
| aPTT | activated partial thromboplastin time |
| 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 |
| Bb | complement Factor Bb (activated complement split product) |
| βhCG | beta-subunit of human chorionic gonadotropin (pregnancy test) |
| bp | Base pair |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| C | Centigrade |
| C5a | complement Factor C5a (activated complement split product) |
| $C_{max}$ | maximum concentration |
| CBC | complete blood count |
| CL | systemic clearance |
| CMV | Cytomegalovirus |
| CRF | case report form |
| CRP | C-reactive protein |
| CS | clinically significant |
| CT | computed tomography |

| **Abbreviation** | **Definition** |
|---|---|
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVD | Cardio Vascular Disease |
| dL | Deciliter |
| DLT | dose-limiting toxicity |
| DSMB | Data And Safety Monitoring Board |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EDC | electronic data capture |
| ESR | erythrocyte sedimentation rate |
| FHBL2 | Familial Combined Hypolipidemia |
| FLI | Fatty Liver Index |
| g | Gram |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| HAV | hepatitis A virus |
| Hb | Hemoglobin |
| HBsAg | hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCT | Hematocrit |
| HCV | hepatitis C virus |
| HDL-C | High density lipoprotein cholesterol |
| HFF | Hepatic Fat Fraction |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HOMA-IR | Homeostatic Model Assessment Insulin Resistance |
| HR | heart rate |
| hr, hrs | hour(s) |
| hsCRP | CRP measured by high sensitivity assay |
| ICH | International Conference on Harmonization |

| Abbreviation | Definition |
|---|---|
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IFN-γ | interferon-gamma |
| IgM | immunoglobulin M |
| IL-1β | interleukin-1 beta |
| IL-1RA | interleukin-1 receptor antagonist |
| IL-6 | interleukin-6 |
| IL-8 | interleukin-8 |
| IL-10 | interleukin-10 |
| IL-12 | interleukin-12 |
| IL-12p40p70 | interleukin-12 p40 (40 kDa) and p70 (70 kDa) subunits |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| ISIS 703802 | antisense inhibitor of ANGPTL3 |
| IV | Intravenous(ly) |
| IXRS | Interactive voice/internet response system |
| kg | Kilogram |
| L | Liter |
| LDH | lactate dehydrogenase |
| LDL-C | Low Density Lipoprotein Cholesterol |
| LDLR | Low Density Lipoprotein Receptor |
| Lp(a) | Lipoprotein (a) |
| LVEF | left ventricular ejection fraction |
| $m^2$ | square meter |
| MAD | multiple ascending dose |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA™ | Medical Dictionary for Regulatory Activities |
| mg | milligram |

| **Abbreviation** | **Definition** |
|---|---|
| min | minute |
| mL | milliliter |
| mm | millimeter |
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| MTD | maximum tolerated dose |
| NAFLD | Non Alcoholic Fatty Liver Disease |
| NASH | Non Alcoholic Steatohepatitis |
| NCS | not clinically significant |
| NSAID | non-steroidal anti-inflammatory drug |
| NYHA | New York Heart Association |
| on study | The patient is 'on study' from signing of the informed consent until their last study visit |
| OTC | Over the Counter |
| PC | personal computer |
| pH | measure of the acidity or basicity of a solution |
| PK | pharmacokinetic(s) |
| pRBC | packed red blood cells |
| PT | prothrombin time |
| QoL | quality of life |
| RNase H1 | an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SAT | Subcutaneous Adipose Tissue |
| siRNA | small interfering ribonucleic acid |
| SC | subcutaneous(ly) |
| sTNF-R1 | soluble tumor necrosis Factor receptor 1 |
| Study Day 1 | defined as the first day Study Drug product is administered to the patient |

| **Abbreviation** | **Definition** |
|---|---|
| Study Drug | ISIS 703802 or placebo |
| SUSAR | suspected unexpected serious adverse reaction |
| T2DM | Type 2 Diabetes Mellitus |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to maximal concentration |
| TC | Total Cholesterol |
| TG | Triglyceride |
| TNF-α | tumor necrosis Factor-alpha |
| TNFR | tumor necrosis factor receptor |
| TNF-RI | tumor necrosis factor receptor I |
| TNF-RII | tumor necrosis factor receptor II |
| UACR | Urine Albumin Creatinine Ratio |
| ULN | upper limit of normal |
| UPCR | Urine Protein Creatinine Ratio |
| US | Ultrasound |
| VAT | Visceral Adipose Tissue |
| VLDL-C | Very Low Density |
| WBC | white blood cell |
| WHO | World Health Organization |
| WHR | Waist Hip Ratio |
| WMA | World Medical Association |

# 1. OBJECTIVES

## 1.1 Primary Objective(s)

To assess the effect of different doses and dosing regimens of ISIS 703802 on reduction in fasting triglycerides (TG).

## 1.2 Secondary Objective(s)

To evaluate the safety and tolerability of ISIS 703802.

To evaluate the effect of ISIS 703802 on changes from Baseline at End-of-Treatment on glucose and lipid metabolism, and liver fat.

To evaluate the pharmacokinetics (PK) of ISIS 703802 across different doses and dose regimens.

To evaluate the effect of ISIS 703802 on changes from Baseline on biomarkers related to liver inflammation, adipokines, and body composition.

# 2. BACKGROUND AND RATIONALE

## 2.1 Overview of Disease

Hypertriglyceridemia commonly observed in diabetic dyslipidemia is generally due to hepatic over production of triglyceride-rich very-low-density lipoprotein (VLDL) particles as well as impaired intravascular catabolism as a result of decreased lipoprotein lipase activity (Adiels et al. 2008). Its etiology includes primary factors (i.e., genetic causes, such as a mutation in a receptor protein). Secondary causes of hypertriglyceridemia are far more common and include metabolic syndrome/insulin resistance, obesity, physical inactivity, cigarette smoking, excess alcohol and a diet very high in carbohydrates. The guidelines from both the National Cholesterol Education Program Adult Treatment Panel III (NCEP 2002) and the American Diabetes Association (ADA 2008) recommend a target TG level of less than 150 mg/dL to reduce cardiovascular risk based on evidence from clinical studies demonstrating that elevated TG levels are an independent risk factor for atherosclerotic CVD.

Hypertriglyceridemia associated with insulin resistance and obesity commonly presents with Type 2 diabetes mellitus (T2DM) which affects more than a third of a billion people worldwide and is the leading cause of cardiovascular disease, with estimated annual worldwide health care costs exceeding half a trillion dollars (Dake et al. 2016). Dyslipidemia in individuals with type 2 diabetes is very common and a major contributing factor to the development of atherosclerosis. The phenotype of dyslipidemia in patients with diabetes is that of elevated triglycerides (hypertriglyceridemia), reduced HDL-C, smaller LDL particles, but with relatively similar LDL-C levels compared with the general population.

The association of diabetic dyslipidemia, insulin resistance, and excess lipid storage in the form of visceral obesity and hepatic steatosis has long been recognized (Shulman 2014). Hepatic steatosis also known as non-alcoholic fatty liver disease (NAFLD) results from increased hepatic uptake of free fatty acids derived mainly from the hydrolysis of adipose-tissue triglycerides (increased because of insulin resistance) but also from dietary chylomicrons overload and hepatic lipogenesis. Insulin resistance is one of the key pathogenic factors in the development and

progression of non-alcoholic fatty liver disease and also plays a major role in the development of the metabolic syndrome and cardiovascular disease (Targher et al. 2010). Worldwide prevalence of NAFLD/NASH is reported to range from 6.3% to 33% with a median of 20% in the general population. The estimated prevalence of NASH is lower, ranging from 3 to 5 % (Vernon et al. 2011). In one study the prevalence of NAFLD in high-risk groups such as in T2DM with dyslipidemia was estimated to be as high as 69% (Leite et al. 2009) which was higher than the 50% prevalence reported in patients with dyslipidemia with or without diabetes who attended lipid clinics (Assy et al. 2000). Despite the high prevalence, there are currently no approved pharmacological therapies for NAFLD associated with dyslipidemia in diabetic patients, highlighting the urgent need to develop effective therapeutic strategies for this common condition.

## 2.2 Therapeutic Rationale

In humans, loss of function mutations within the ANGPTL3 gene give rise to familial combined hypolipidemia (FHBL2), characterized by low plasma levels of triglycerides, total cholesterol, LDL-C, and HDL-C (Minicocci et al. 2012). Homozygous individuals with complete ANGPTL3 deficiency showed the full combined hypolipidemic phenotype while individuals with more partial ANGPTL3 deficiency showed a more attenuated phenotype. Of note, FHBL2 homozygous were not affected by diabetes, showed lower plasma levels of insulin and lower degree of insulin resistance as estimated by HOMA-IR (Robciuc et al. 2013).

ANGPTL3 protein is produced exclusively in the liver, where its expression is downregulated by leptin and insulin (Inukai et al. 2004). Hepatic specific knock-down of ANGPTL3 mRNA is associated with a reduction in plasma triglycerides due to increased lipoprotein lipase activity as well as decreased hepatic VLDL triglyceride secretion. Because ANGPTL3 is produced by the liver only, which does not express LPL, it is thought to function as an endocrine rather than paracrine factor with insulin sensitizing effects that go beyond the liver. In fact, insulin sensitization has been shown in patients with ANGPTL3 gene mutations as well as in ANGPTL3-deficient mice, in which increased uptake of fatty acids into oxidative tissues such as muscle and brown adipose tissue led to decreased uptake of fatty acids and increased uptake of glucose in white adipose tissue (Wang et al. 2015). Suppression of hepatic ANGPTL3 protein production in mice resulted in significant reductions in levels of triglycerides, LDL cholesterol, non-HDL cholesterol, and VLDL cholesterol and these favorable effects were associated with decreased liver triglyceride content, increases in insulin sensitivity, and a reduction in atherosclerosis progression (Graham et al. 2017).

Treatment with ISIS 703802 (AKCEA-ANGPTL3-$L_{Rx}$) would be expected to lower the hepatic expression of ANGPTL3 protein and result in lowering of the levels of triglyceride-rich lipoproteins and LDL-C, increased HDL-C, improved glycemic control and ameliorated insulin resistance in T2DM patients, leading to decreased liver fat content in NAFLD and ultimately, reduced overall risk of coronary artery disease.

## 2.3 ISIS 703802

### *2.3.1 Mechanism of Action*

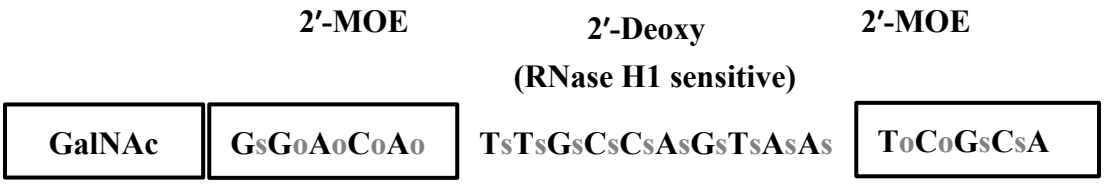
ISIS 703802 is a second-generation ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold in mice (Prakash et al. 2014). The ASO portion of ISIS 703802 is complementary to a region within the ANGPTL3 messenger ribonucleic acid (RNA) (mRNA) coding sequence, and binds to the mRNA via Watson and Crick base pairing. The hybridization (binding) of ISIS 703802 to the cognate mRNA results in the Ribonuclease H1 (RNase H1)-mediated degradation of the ANGPTL3 mRNA, thus preventing production of the ANGPTL3 protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

### *2.3.2 Chemistry*

Chemically, ISIS 703802 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 in the MOE-modified regions, which reduces non-specific interactions with proteins and further enhances the potency of GalNAc conjugated ASOs. The nucleotide sequence of ISIS 703802 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 6 of the ANGPTL3 mRNA coding sequence at position 1169-1188 bp.

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. 2008). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 703802 employs this chimeric structure to enable the use of the 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). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition. The fourth region is comprised of a triantennary cluster of *N*-acetyl galactosamine (GalNAc) sugars which is linked to the 5′ end of ISIS 703802 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the

asialoglycoprotein receptor (ASGPR), a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc cluster enhances delivery of ISIS 703802 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release 'free ASO' inside the cell (Prakash et al. 2014).




**GalNAc = THA-GalNAc cluster**
**2′-MOE = 2′-methoxyethyl RNA**
**2′-Deoxy = DNA**
**s = phosphorothioate linkage**
**o = phosphodiester linkage**

**Figure 1 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of ISIS 703802 is shown.**

### *2.3.3 Preclinical Experience*

Detailed information concerning the preclinical studies conducted with ANGPTL3 ASOs can be found in the Investigator's Brochure. A summary is included below.

#### *2.3.3.1 Preclinical Pharmacology*

The pharmacology of ANGPTL3 ASOs has been examined in multiple *in vitro* cell lines where specific and dose-dependent reduction of ANGPTL3 mRNA and protein was clearly demonstrated, resulting in reductions in apoB secreted protein. The pharmacology of ISIS 563580, an unconjugated 2′-MOE modified ASO that has the same base sequence as ISIS 703802, has been studied at doses higher than planned for ISIS 703802.

ISIS 563580 has been explored in human ANGPTL3 transgenic mice, wherein liver mRNA and plasma ANGPTL3 protein levels were reduced upon treatment with ISIS 563580.

Reductions in murine ANGPTL3 mRNA and protein were routinely observed in all mouse models treated with a murine-specific ANGPTL3 ASO. Pharmacology studies were done with *Ldlr*$^{-/-}$ mice fed a hypercholesterolemic diet known to develop elevated LDL-C, TG, and atherosclerosis, as well as features of metabolic syndrome (hyperglycemia and hyperinsulinemia) (Huszar et al. 2000; Schreyer et al. 2002; Tsuchiya et al. 2012). Treatment of mice with a murine-specific ANGPTL3 ASO resulted in improvement in all of the aforementioned lipid and metabolic endpoints compared to controls. In all mouse models tested, total plasma cholesterol, LDL-C, TG, and non-esterified fatty acids (NEFA) have been shown to be consistently reduced upon treatment with ANGPTL3 ASOs, while HDL-C is modestly decreased in wild type mice (- 22%), and either stable or increased in others. While a clear mechanistic understanding of

HDL-C reductions has not been elucidated, results from *in vitro* reverse cholesterol transport assays suggest that HDL function is maintained.

Administration of ISIS 703802, a human specific, GalNAc conjugated, ANGPTL3 ASO, to human *ANGPTL3* transgenic mice led to significant, dose-dependent reductions in hepatic ANGPTL3 mRNA. In diet challenged mice, administration of ISIS 731875, a mouse-specific and GalNAc-modified ASO targeting ANGPTL3, led to dose-dependent reductions in both hepatic ANGPTL3 mRNA and plasma ANGPTL3 with concomitant reductions in plasma TG and cholesterol. Importantly, the potency and the lipid-lowering effects of the ANGPTL3 ASO were independent of diet.

Finally, administration of a mouse-specific ANGPTL3 ASO to western diet fed *Ldlr*$^{-/-}$, a mouse model of FH, also led to significant reductions in hepatic ANGPTL3 mRNA and plasma ANGPTL3 protein with concomitant reductions in plasma TG and LDL-C that were similar to what was observed in wild type western diet fed mice, indicating that the absence of Ldlr does not affect the ASOs potency or lipid-lowering effects. This suggests that administration of ANGPTL3 ASO administration is a promising target for clinical study in familial hypercholesterolemia patients.

While formal pharmacology studies have not been conducted in the monkey with the human ANGPTL3 ASO, hepatic mRNA expression has been shown to be reduced by more than 60% in cynomolgus monkeys, the same model used to conduct the toxicology evaluation.

#### *2.3.3.2 Preclinical Toxicology*

General toxicology studies for ISIS 703802 consisted of sub-chronic (16-week) and chronic (26- or 39-week) toxicity studies CD-1 in mice and cynomolgus monkeys. Since ISIS 703802 is not fully complementary to the mouse ANGPTL3 transcript, treatment group receiving a mouse-specific inhibitor (ISIS 731875) was also included in the mouse study. Please refer to the Investigator Brochure for a detailed description of the preclinical toxicology and pharmacokinetics with ISIS 703802.

Pharmacokinetic data confirmed continuous and dose-dependent exposure to ISIS 703802. An estimated liver and plasma terminal elimination half-life values of approximately 1 week and 3-4 weeks for 2 mg/kg and 35 mg/kg, respectively, were observed in monkeys. The most noteworthy findings observed in mice and monkeys following ISIS 703802 treatment were, in general, non-specific class effects related to the uptake and accumulation of ASO and no toxicologically relevant findings were considered related to the pharmacologic inhibition of hepatic ANGPTL3 expression, either with the present series of studies or with the former development candidate targeting ANGPTL3. There were no test-article related changes in PLT count in either mouse or monkey in both sub-chronic and chronic studies.

The most noteworthy finding in the monkey was the kidney alteration (hypoalbuminemia and proteinuria) seen in one early-sacrifice animal from the 16-week study at 35 mg/kg/week, a dose equivalent to at least ~190-fold of the 40 mg weekly clinical doses by plasma AUC. Non-dose dependent increases in renal protein excretion (up to 2.2-fold in quantitative urine protein, protein/creatinine ratio or urine albumin) were also observed at 8 and/or 35 mg/kg/week (> ~ 30 to 190-fold of the 40 mg weekly clinical doses by plasma AUC) at the 16-week

scheduled terminal necropsy. However, Similar kidney alterations were not seen at the 6-week interim at any doses or in the 39-week chronic monkey study up to 12 mg/kg/week (> ~200-fold of the 20 mg weekly clinical dose by plasma AUC).

Additional findings related to ASO liver accumulation included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) at ≥ 8 mg/kg/week in the 16- and 26-week mouse studies and were correlated with individual hepatocyte necrosis (minimal to mild) in mouse liver. Those changes were most prominent in the high dose groups (50 and 24 mg/kg/week for the 16- and 26-week studies, respectively). Conversely, no changes in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week. In the 16-week monkey study, increase in ALT was only evident in one early-sacrifice animal at 35 mg/kg/week, and non-statistically significant increases in ALT (< 2-fold of the prestudy Baseline) were also observed in the interim- and terminal-sacrifice animals at ≥ 8 mg/kg/week but showed no microscopic correlates or dose-dependency.

Given the spectrum and severity of the test article-related clinicopathologic alterations present in monkeys at doses ≤ 12mg/kg/week (> ~100-fold of the 40 mg weekly clinical dose by plasma AUC) during the 39-week treatment phase, none would be regarded to represent an adverse effect (Dorato and Engelhardt 2005; Everds et al. 2013). Considering the monkey to be the most relevant species, these data have characterized the safety profile and established appropriate therapeutic margins for the clinical evaluation of ISIS 703802 in humans.

### *2.3.4 Clinical Experience*

Detailed information concerning the clinical studies conducted with ISIS 703802 can be found in the Investigator's Brochure. A summary is included below.

The Study Drug, ISIS 703802, is being evaluated in Phase 1 in the clinical setting with single doses up to 120 mg and multiple doses up to 60 mg (once per week for 6 weeks). The parent drug ISIS 563580, an unconjugated 2′-MOE modified ASO that has the same base sequence as ISIS 703802, was also evaluated in a blinded, placebo-controlled Phase 1 study.

An interim analysis of ISIS 703802 Phase 1 SAD/MAD Study (ISIS 703802-CS1) was performed in 44 subjects administered single ascending (20, 40 and 80 mg) or multiple ascending doses (10, 20, 40 and 60 mg/week for 6 weeks). Twelve participants were randomly assigned to single-dose groups (9 to active-agent dose groups and 3 to the placebo group) and 32 were randomly assigned to multiple-dose groups (24 to active-agent dose groups and 8 to the placebo group). The main endpoints of the study were safety, tolerability, pharmacokinetics, pharmacodynamics and changes in lipids and lipoproteins. After 6 weeks of treatment, persons in the multiple dose groups treated with ISIS 703802 had dose-dependent reductions in levels of ANGPTL3 protein (reductions of 46.6 to 84.5% from Baseline, P< 0.01 for all doses vs. placebo 1.6%) and in levels of triglycerides (reductions of 33.2 to 63.1% vs placebo 11.4%), LDL cholesterol (1.3 to 32.9% vs placebo 13.6%), very-low-density lipoprotein cholesterol (27.9 to 60.0% vs placebo 4.0%), non–high-density lipoprotein cholesterol (10.0 to 36.6% vs placebo 9.1%), apolipoprotein B (3.4 to 25.7% vs placebo 11.0%), and apolipoprotein C-III (18.9 to 58.8% vs placebo 3.1%). There were no serious adverse events documented during the trial. No protocol-defined injection-site reactions were reported. Of those participants who received the multiple-dose regimen, three reported headache (one who received placebo and two who

received ISIS 703802) and three reported dizziness (two who received placebo and one who received ISIS 703802). There was no clinical evidence of prothrombotic effects, bleeding episodes, significant decreases in platelet count or thrombocytopenia, or significant changes in renal function. One subject in the 60 mg weekly dose cohort had an approximately 5 x ULN increase of ALT, without an increase in bilirubin and a second subject had an ALT of 88 U/L on Day 36 post treatment which returned to normal range by Day 50 and remained normal until the end of the study. One subject in the 20 mg MAD group was lost to follow-up after 5 doses. There were no other discontinuations during the treatment period (Graham et al. 2017 and data on file).

The pharmacokinetics of ISIS 703802 evaluated in Study ISIS 703802-CS1 showed rapid absorption following SC administration, with median time to maximum plasma concentrations ($T_{max}$) ranging from 1 to 6 hours. Similar $T_{max}$ values were observed at all dose levels. After reaching $C_{max}$, plasma concentrations of ISIS 703802 declined in a multi-phasic fashion with a rapid disposition phase, followed by a slower elimination phase with terminal elimination half-life of 3 to 5 weeks. The peak ($C_{max}$) and total exposure (AUC) after a single SC dose increased approximately dose proportionally from 20 to 40 mg, and greater than dose proportionally from 40 to 80 mg, suggesting more efficient tissue uptake at lower doses. After single and multiple SC doses in the range of 10 to 60 mg, the $C_{max}$ and AUC increased approximately dose proportionally. No accumulation based on $C_{max}$ or AUC was observed after 6 weekly doses.

#### *2.3.4.1 ISIS 563580-CS1 Phase 1 SAD/MAD*

In a Phase 1 study, ISIS 563580-CS1, healthy volunteers received subcutaneous administration of ISIS 563580 from 50 to 400 mg as a single dose, or 100 to 400 mg as multiple doses (8 doses in 36 days). Overall, the safety findings from this study suggest that ISIS 563580 was not associated with any safety concerns. There were 383 adverse events (AE) reported in the ISIS 563580-treated subjects of which 363 (95%) were mild in severity. For the multiple-dose subjects, the most common treatment-emergent adverse events were AEs at the injection site. There was 1 serious adverse event (SAE) in the study of periorbital cellulitis which was considered a medically important event by the Investigator and was also considered unlikely related to Study Drug by the Investigator. Together, the above suggest that ISIS 563580 was well-tolerated at the doses and regimen given, which exceed the dose levels and cumulative exposures to be tested in the current study. There were no clinically-relevant changes in laboratory assessments and the heparin dose of 80 U/kg was well-tolerated in support of the post-heparin procedures. ISIS 563580 produced dose-dependent reductions in plasma ANGPTL3 (up to 93%; group means up to 84%), TG (up to 63%; group means up to 49%) and TC (up to 46%; group means up to 28%) at Day 36 (Brandt et al. 2015).

### 2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 703802 doses of 10 mg, 20 mg, 40 mg and 60 mg given weekly for 6 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in lipid biomarkers. The range of dosing proposed for the present study will provide the equivalent drug exposure of 10 mg (from 40 mg monthly), and 20 mg (from 20 mg weekly and 80 mg monthly) 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 TGs ranging from approximately 45 to 55% at steady-state.

Safety data from the available chronic mouse (26-week) and monkey (39-week) studies support once-weekly dosing for chronic administration. The No Adverse Effect Level (NOAEL) for ISIS 703802 in chronic monkey study was determined to be 12 mg/kg/wk.

Preclinical pharmacology experiments in Tg-mice and non-human primates demonstrated that ISIS 703802 achieved an equivalent reduction in ANGPTL3 plasma concentration to that of the unconjugated form, at $1/10^{th}$ of the unconjugated ASO (ISIS 563580) dose.

## 2.5 Benefit-Risk Assessment

### *2.5.1 Benefit Assessment*

The current study is designed to evaluate the safety and tolerance of ISIS 703802 in patients with hypertriglyceridemia, Type 2 Diabetes Mellitus (T2DM) and Nonalcoholic Fatty Liver Disease (NAFLD). The dose selected is expected to reduce ANGPTL3 and result in a reduction of triglyceride levels, reduction of fat content of the liver and improvement of glycemic control in T2DM patients. We do not know if subjects participating in this study would necessarily benefit from the treatment. However, the increased understanding of the effects of ISIS 703802 in this population may potentially result in new treatment options that would ultimately benefit patients with hypertriglyceridemia, T2DM and, NAFLD. Due to the short duration of this trial, any benefit observed is not expected to persist beyond the end of the study.

### *2.5.2 Risk Assessment*

The known potential risks to study participants associated with ISIS 703802 are elaborated on in the Guidance to Investigator section of the Investigator's Brochure.

- In preclinical mouse studies, there were increases in ALT and AST and were correlated with increased incidence and/or severity of necrosis of individual hepatocytes (minimal to mild in severity). Those changes were most prominent in the high dose groups and showed no clear progression over time. No increases in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week (~200-fold of the 20 mg clinical dose by plasma AUC). In the 16-week monkey study, increase in ALT was only evident in 1 early-sacrifice animal at 35 mg/kg/week, no meaningful increase in ALT was observed in the schedule sacrificed animals.

- One subject in the 60 mg weekly dose cohort had an approximately 5 x ULN increase of ALT, without increase in bilirubin, which was considered a treatment related adverse event (AE) by Principal Investigator (PI) a second subject had an ALT of 88 U/L on Day 36 post treatment which returned to normal range by Day 50 and remained normal until the end of the study. There were no other observed clinically significant changes in ALT and liver function in an ongoing Phase 1 human study (data on file).

- However, to evaluate and mitigate the potential for liver enzyme abnormalities, regular liver chemistry monitoring and stopping rules are included in the study as specified in Sections 8.5 and 8.6.

- Injection site adverse events, while not considered safety issues, may affect the ability of the subject to tolerate dosing. Injection site adverse events are the most common side

effects observed following SC administration of 2′-MOE ASOs and are dose and concentration dependent. Erythema is the most prevalent characteristic. Generally, these events are mild and reversible, resolve spontaneously and do not worsen with time. The histologic findings are consistent with a local inflammatory response. Subjects should be informed of the possibility of occurrence of injection site adverse events. Symptomatic interventions such as icing of the injection site or administration of NSAIDs prior to and/or after the SC dosing have been utilized.

- Although no changes in platelet (PLT) counts have been observed in healthy volunteers, mouse or monkey in both sub-chronic and chronic studies with ISIS 703802, reductions in platelet counts to below the lower limit of normal have been observed after administration of other ASOs and some subjects have experienced severe thrombocytopenia following administration of unconjugated 2′-MOE ASOs. To evaluate and mitigate the potential for a reduction in PLT count, monitoring and stopping rules are included in the study as specified in Sections 8.5 and 8.6 (Safety Monitoring Rules and Stopping Rules).

- No significant changes in serum creatinine, electrolytes, BUN, or urinalysis were reported from the interim analysis of the ongoing Phase 1 study (data on file). To evaluate and mitigate the potential for a reduction in renal function, since kidneys are an organ of high distribution for the studied ASO, monitoring and stopping rules are included in the study as specified in Sections 8.5 and 8.6 (Safety Monitoring Rules and Stopping Rules).

While the long-term effects of reducing ANGPTL3 as a target with the Study Drug are not known at this time, there is evidence in literature in humans in whom ANGPTL3 is absent from plasma, due to homozygous or compound heterozygous ANGPTL3 mutations, present a pan-hypobetalipoproteinemia phenotype, with generalized and marked decreases (~50% to 70%) in all apoB-100 containing lipoproteins, including VLDL and LDL, as well as HDL. This clinical phenotype has been termed familial combined hypolipidemia or FHBL2 (Romeo et al. 2009; Musunuru et al. 2010; Martin-Campos et al. 2012; Minicocci et al. 2012; Noto et al. 2012; Pisciotta et al. 2012; Wang et al. 2015). Clinical studies in FHBL2 suggest a trend toward lower glucose and insulin levels and reported a decrease in VLDL. Remarkably, diabetes and cardiovascular disease are reportedly absent from those with homozygous FHBL2 and, no adverse clinical phenotype has been reported to date.

### *2.5.3 Overall Assessment of Benefit: Risk*

ISIS 703802 has demonstrated the ability to reduce ANGPTL3, APOCIII, and TGs by greater than 60% in the Phase 1 study in healthy volunteers. The objective of this study is to assess the effect of TG lowering in these subjects. This study will also investigate the potential of ISIS 703802 in improving the insulin resistance and glucose profile, and decreasing liver and visceral fat content in subjects with high TG levels and T2DM. Although the subjects enrolled in this study will not derive long term benefits due to the short duration of the study, they may derive some short term benefit from improved metabolic health and dietary counselling. The information obtained in the course of this study is critical to further development of ISIS 703802 for hypertriglyceridemia, dyslipidemia, NAFLD and associated metabolic complications and cardiovascular disease.

The protocol identifies that potential risks associated with ISIS 703802 treatment will be mitigated by routine monitoring. Thus, exposure of subjects in this study is justified by the anticipated benefits that may be afforded to the wider population of patients by continued development of ISIS 703802 (see Section 8.5 Safety Monitoring Rules).

# 3. EXPERIMENTAL PLAN

## 3.1 Study Design

This is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Approximately 96 subjects will be randomized in a 3:1 ratio to receive ISIS 703802 or placebo. The sample size was determined to provide statistical power for efficacy assessments. Study Drug (ISIS 703802 or placebo) will be administered SC every week or every 4 weeks, depending on cohort assignment, for 26 weekly doses, or 6 every 4-week doses.

Subjects will be evaluated for study eligibility during Screening and Qualification, which takes place up to 5 weeks prior to Day 1 (the first day of Study Drug administration). During the Screening Period, subjects will be advised to maintain routine diet and exercise routines and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening Period, following 4 weeks of diet run-in, subjects will have a qualification visit and, final eligibility assessments will be performed. Subjects on a stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet run-in. At the qualification visit, TGs will be measured to qualify (≥ 150 mg/dL). MRI will be obtained during screening once all other eligibility criteria are met to assess liver fat content.

Subjects meeting eligibility criteria at Screening and having a qualifying MRI, defined as having greater than 8% liver fat assessed by MRI-PDFF (via central reviewer) will return to the clinic on Day 1. TG and MRI results must be available prior to randomization and administration of the first dose of Study Drug. Subjects who continue to meet all eligibility criteria at Day 1 will be randomized to 1 of the 3 dosing cohorts, with each cohort having a 3:1 ratio to receive ISIS 703802 or matching volume of placebo, respectively, by SC injection.

The primary safety and efficacy analysis time point is at Week 27 for subjects who received weekly dosing (Cohort A) and at Week 25 for subjects who received every 4-week dosing (Cohorts B and C).

Cohort A (n = 32): 20 mg ISIS 703802 or placebo (3:1) SC once every week for 26 doses.

Cohort B (n = 32): 40 mg ISIS 703802 or placebo SC (3:1) once every 4 weeks for 6 doses.

Cohort C (n = 32): 80 mg ISIS 703802 or placebo SC (3:1) once every 4 weeks for 6 doses.

Subjects will return regularly for outpatient visits throughout the treatment period according to the Schedule of Procedures (Appendix A).

Subjects will then enter a 13 week Post-Treatment Follow-up Period and will return to the Study Center for outpatient evaluations 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.

## 3.2 Number of Study Centers

This is a multicenter, multinational study.

## 3.3 Number of Subjects

Approximately 96 subjects are planned to be enrolled in this study.

Approximately 32 subjects will be assigned to each cohort, with 24 subjects receiving ISIS 703802 and 8 receiving placebo.

## 3.4 Overall Study Duration and Follow-up

The length of subjects' participation in the study will be up to 44 weeks, including an up to 5-week Screening Period, that includes a 4-week diet stabilization/run-in period for subjects not already on a stable diet, and a 1-week qualification period, a 26-week treatment period, and a 13-week post-treatment evaluation period. Please refer to the Schedule of Procedures in Appendix A.

Subjects may be required to attend additional visits for monitoring of adverse events 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*

Subject eligibility for the study will be determined within 35 days/5 weeks prior to randomization. Potential subjects will report to the Study Center for screening/qualification assessments at specified intervals within the 5-week Screening Period as detailed in the Schedule of Procedures in Appendix A.

### *3.4.2 Treatment*

Eligible subjects will receive the first dose of Study Drug at the Study Center, at which time they will also be trained on self-administration of Study Drug, if applicable. Subsequent administrations of Study Drug may occur at home or at the Study Center. Eligible subjects will report to the Study Center for assessments at specified intervals throughout the 26-week treatment period as detailed in the Schedule of Procedures in Appendix A.

### *3.4.3 Post-Treatment*

After the dosing with Study Drug is completed, subjects will then enter the 13-week post-treatment follow-up period and will return to the Study Center for 3 follow-up visits according to the Schedule of Procedures in Appendix A.

The final study visit for each subject will be 13 weeks after the Treatment Period (last dose through one dosing interval post last dose).

### 3.5 End-of-Study

The End-of-Study is defined as the last subject's last 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 703802 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 703802, 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 Statistical Analysis Plan (SAP).

## 4. SUBJECT ENROLLMENT

### 4.1 Screening

Before subjects 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 subject information and/or recruitment material.

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

### 4.2 Randomization

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

Using an Interactive Web-Response System (IXRS), eligible subjects will be randomized in a 1:1:1 ratio to 1 of the 3 parallel-dose cohorts (Cohorts A, B, or C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive ISIS 703802 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 Subjects

Subjects who withdraw from the study will not be replaced.

### 4.4 Unblinding of Treatment Assignment

All subjects, monitors, and Study Center personnel related to the study will be blinded throughout the study and until all subjects have completed the study and the database has been locked. The Sponsor will be blinded throughout the study and until all subjects have completed the treatment period. However, if a subject 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 subject, the Investigator will have the ability to unblind the treatment assignment for that subject 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 subject 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. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 5 weeks of Study Day 1 or at the time point specified in the individual eligibility criterion listed.

### 5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females aged ≥ 18 and ≤ 70 years old at the time of informed consent
3. Plasma TG at Screening > 150 mg/dL and at qualification of > 150 mg/dL
4. Documented history of hepatic steatosis as determined by at least one imaging record (CT scan, MRI, FibroScan, or US) suggesting liver fat > 8%, or positive ultrasound at Screening
5. Baseline MRI indicating hepatic fat fraction (HFF) > 8%
6. Clinically confirmed diagnosis of T2DM
    a. Hemoglobin A1c > 6.5 and ≤ 10% at Screening
    b. On a stable dose of oral glucose-lowering medication (i.e. metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors) for at least 3 months before Screening and plan to remain on the same medication for the duration of the study
7. Body mass index between 27- 40 $kg/m^2$, inclusive, at Screening
8. If taking lipid lowering medication, subjects must be on a stable dose for at least 3 months before first dose of Study Drug and plan to remain on the same medication for the duration of the study

9. Females: must be non-pregnant and non-lactating and either;

    a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or;

    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) or;

    c. Abstinent* or;

    d. if engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 703802 or placebo)

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the subject. 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

10. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 703802

## 5.2 Exclusion Criteria

1. Type 1 diabetes mellitus
2. Active chronic liver disease, alcoholic liver disease, Wilson's disease hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, genetic hemochromatosis, known or suspected hepatocellular carcinoma, history of or planned liver transplant for end-stage liver disease of any etiology
3. Documented history of advanced liver fibrosis
4. History of cirrhosis and/or hepatic decompensation including ascites, hepatic encephalopathy, or variceal bleeding
5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
6. History of acute kidney injury within 12 months of Screening
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Subjects with a history of major bleed or high-risk of bleeding diathesis
9. Clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion, including the following:

a. Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
b. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. 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
c. Estimated GFR < 60 mL/min/1.73 $m^2$ (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation)
d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN
e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
f. Alkaline phosphatase (ALP) > 1.5 x ULN
g. Platelet count < LLN

10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Uncontrolled hyper- or hypothyroidism. Subjects on dose stable replacement therapy for at least 3 months prior to Screening will be allowed
12. History of clinically significant acute cardiac event within 6 months before Screening (includes stroke, transient ischemic attack, and coronary heart disease [angina pectoris, myocardial infarction, revascularization procedures])
13. History of heart failure with NYHA greater than Class II
14. Current acute or chronic inflammatory disease
15. Hypersensitivity to the active substance or to any of the excipients
16. Active untreated mental disorder or depression. Subjects who are on a stable dose of medication (excluding atypical antipsychotics) for at least 6 months before Screening and whose treating physicians consider them to be mentally stable may be enrolled
17. Any major surgery including bariatric surgery within 3 months of Screening
18. Weight change > 5% within 3 months before Screening or during diet run in period
19. Currently taking parenteral or chronic oral corticosteroids, amiodarone, tamoxifen, obeticholic acid, atypical antipsychotics, HIV protease inhibitors, or ursodeoxycholic acid
20. Alcohol consumption > 21 units of alcohol per week for men and > 14 units of alcohol per week for women over a two year time frame prior to the Baseline MRI eligibility (One drink "unit" or one standard drink is equivalent to a 12 ounce beer, a 4 ounce glass of wine, or a 1 ounce shot of hard liquor)
21. 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
22. Use of warfarin or other coumarins, direct thrombin inhibitors or Factor Xa inhibitors

23. Use of anti-platelet therapies unless the dose has been stable for 4 weeks prior to the first dose of ANGPTL3-$L_{Rx}$ and will remain on a stable regimen through the end of the Post-Treatment Follow-up Period, during which regular clinical monitoring will be performed
24. Use of Insulin or insulin analogs, GLP-1 agonists, and PPAR$^{\gamma}$ agonists (pioglitazone or rosiglitazone)
25. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
26. Treatment with any non-Akcea/non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Subjects 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 have elapsed since dosing
27. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
28. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
29. Subjects with conditions contraindicated for MRI procedures including subjects who have any metal implant (e.g., heart pacemaker, rods, screws, aneurysm clips) that contraindicates MRI procedures.
30. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study

# 6. STUDY PROCEDURES

## 6.1 Study Schedule

The study will consist of a Screening Period, a Treatment period and a Post-treatment follow-up period. These periods are described below.

All required study procedures are outlined in Appendix A.

### *6.1.1 Screening*

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. An up to 5-week period is provided for completing screening assessments and determining subject eligibility for the study. During the Screening Period, subject will be advised to maintain diet and exercise routines and remain on a stable regimen of diabetes and lipid medications (if they are already taking any).

Subjects will undergo a medical history, including collection of race and ethnicity, physical examination including vital signs, 12-lead ECG, and have blood and urine samples taken for clinical laboratory testing. Subjects will be screened for HIV, hepatitis B, and hepatitis C. Safety labs may be retested for determination of subject eligibility after consultation with the Sponsor Medical Monitor.

As part of the Screening Period, subjects not already on a stable diet will have 4 weeks of diet run-in, followed by a qualification visit, during which final eligibility assessments will be performed. Subjects on stable diet known to the investigator and followed at the site may go from screening to qualification without a 4-week diet run-in. At the qualification visit TGs will be measured. MRI will be obtained during screening once all other eligibility criteria are met to assess liver fat content.

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

### *6.1.2 Treatment Period*

During the treatment period, eligible subjects will be randomized and report to the Study Center for clinic visits. Subjects will be randomized to 1 of 3 dose cohorts and receive 20 mg doses of Study Drug administered by SC injection once per week (weekly) for 26 weeks in Cohort A, 40 mg doses of Study Drug administered by SC injection once every 4 weeks for 21 weeks in Cohort B, and 80 mg doses of Study Drug administered by SC injection once every 4 weeks for 21 weeks in Cohort C (Section 8.1).

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 703802 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 subjects, who will consent to voluntary extensive PK sampling, will undergo additional PK sampling, in what is referred to as the PK Subgroup in this study. Subjects in this subgroup will have additional PK sampling time points in order to evaluate the plasma PK parameters of ISIS 703802. Subjects in this subgroup will have additional visits to the clinic during the treatment period in order to collect blood samples for PK assessment (Appendix A and C).

### *6.1.3 Post-Treatment Period*

Each subject will be followed for safety assessments for 13 weeks after the Treatment Period (last dose through one dosing interval post last dose). During the post-treatment evaluation period, subjects will return to the Study Center for outpatient visits as outlined in Appendix A for safety and clinical laboratory evaluations.

## 6.2 Study/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 after fasting for 10 hours. Any confirmatory test, or test taken for safety reasons, may be taken at any time, irrespective of fasting status. During this time subjects can drink water and should ensure that they consume sufficient water to not become dehydrated.

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

While on treatment hematology samples will be collected every 14 days +/- 2 days. Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local samples are unreportable (e.g., due to hemolyzed or clumped blood samples), subject 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 subject to hold dosing until a new platelet count is obtained and reviewed.

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

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

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

All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the subject could be approaching the dose interruption rule of 75,000/$mm^3$ as specified in Section 8.6.3. Any case of a platelet count reduction to levels below 50,000/$mm^3$ is considered an adverse event of special interest and must be reported in an expedited fashion to the Sponsor as per Sections 9.3.3 and 9.4.1.

All liver and renal function tests must also be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the result has not met the stopping rule. Any event meeting renal stopping rules criteria described in Section 8.6.2 is considered an adverse event of special interest and must be reported in an expedited fashion to the Sponsor as per Sections 9.3.3 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 platelet 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.

### *6.2.1 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 subject 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.

### *6.2.2 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:

- Cohort A at Weeks 5, 13, 21, and 27/ET
- Cohorts B and C at Weeks 5, 13, 21 and 25/ET

In all cohorts, ECGs will be conducted during the post-treatment follow-up period at scheduled visits.

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

### *6.2.3 PK Sampling*

Blood samples for the determination of plasma ISIS 703802 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, subjects 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 Subjects

### *6.3.1 Contraception Requirements*

All male subjects 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 a period of 13 weeks after their last dose of study treatment.

Male subjects 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 a period of 13 weeks after the subject'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 one of the following conditions:

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

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

For male subjects:

- 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 subjects with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug

For female subjects and female partners of male subjects:

- 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 subject. 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 two can result in either or both products failing.**

### *6.3.2 Other Requirements*

All subjects 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 703802 or Placebo) characteristics are listed in Table 1.

Study Drug (ISIS 703802 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 703802 (ISIS 703802)*

ISIS 703802 vials contain 100 mg/mL ISIS 703802 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 703802 vials.

**Table 1 Study Drug Characteristics**

| Study Drug | ISIS 703802 | Placebo |
|---|---|---|
| **Strength** | 100 mg/ mL | Not Applicable |
| **Volume/Formulation** | 0.8 mL/ per 2.0 mL vial | 0.8 mL/ 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 703802 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 703802 or placebo) supplies provided by the Sponsor. The subject 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. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

## 8. TREATMENT OF SUBJECTS

### 8.1 Study Drug Administration

Study Drug (ISIS 703802 or placebo) will be administered to subjects by Study Center staff as follows:

Cohort A: a single SC dose of 20 mg every week (weekly) for 26 weeks and 26 doses

Cohort B: a single SC dose of 40 mg once every 4 weeks for 21 weeks and 6 doses

Cohort C: a single SC dose of 80 mg once every 4 weeks for 21 weeks and 6 doses

Self-administration, if applicable, will be allowed after appropriate training of subject and/or caregiver.

Subjects in Cohort A receive 1 dose per week, and subjects in Cohorts B and C should receive 1 dose every 4 weeks with weeks always defined relative to Study Day 1. For example, if a

subject receives the first dose on a Monday, subsequent doses should be given on Mondays according to the respective dosing schedule, if possible. If a subject misses an injection, or if dosing on the usual day is not possible, the subject 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.

Volumes to be administered are shown in Table 2. Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 703802 or placebo) preparation and administration.

**Table 2 Study Drug Dosing Information**

| Cohort | Treatment | Volume to Administer/Dose | # Doses | Total Study Drug |
|---|---|---|---|---|
| A | 20 mg ISIS 703802 or placebo (Every week) | 0.2 mL | 26 | 520 mg |
| B | 40 mg ISIS 703802 or placebo (Every 4 weeks) | 0.4 mL | 6 | 240 mg |
| C | 80 mg ISIS 703802 or placebo (Every 4 weeks) | 0.8 mL | 6 | 480 mg |

## 8.2 Other Protocol-Required Drugs

No other Study Drug treatments are required by the protocol.

## 8.3 Other Protocol-Required Treatment Procedures

There are no other treatment procedures required by the protocol other than those outlined in the schedule of procedures.

## 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 703802 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 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, subjects 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 subject will be permanently discontinued from further treatment with Study Drug (ISIS 703802 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, subjects 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 subject is appropriate.

Additional Guidance: If possible, a PK sample should be collected as soon as possible after a SAE has occurred (preferably within 2 weeks). In addition, if a subject 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 and adopted to meet the requirements of this protocol and compound to ensure safety of the subjects.

While on treatment, all subjects will have liver chemistry tests monitored every 2 weeks during the first 3-months of the study treatment period, and monthly thereafter. Upon completion of the study treatment period, liver chemistry tests should be monitored per visit schedule in Appendix A.

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

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

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

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history of 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. Repetition of the above evaluations should be considered if a subject's ALT and/or AST levels reach 5 x ULN.

All routine liver function test results will be reviewed on an ongoing basis 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 >1.5x ULN. These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance.

### *8.5.2 Safety Monitoring for Renal Function*

While on treatment all subjects will have renal function tests monitored every 2 weeks during the first 3 months of the study treatment period, and monthly thereafter. Upon completion of the study treatment period, urine renal biomarkers should be monitored as per visit schedule in Appendix A.

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

While on treatment during the course of the study, urinary surveillance may include urinalysis to include urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR) and urinary red blood cells (RBCs), as well as serum creatinine and cystatin-C, which will be monitored every 2 weeks during the first 3-months of the study treatment period, and monthly thereafter. In addition, other biomarkers of acute renal injury may also be measured if a safety signal is seen that warrants further testing (Appendix B).

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than per the Schedule of Procedures in Appendix A, will be guided by consultation with the medical monitor. 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 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 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.

Lab alerts for abnormal renal tests will be issued for: Estimated GFR (eGFR) (by CKD-EPI formula) decrease from Baseline > 25%, urine albumin/creatinine ratio (UACR) > 165 mg/g, urine protein/creatinine ratio (UPCR) > 325mg/g, or an increase in serum creatinine from Baseline > 0.3 mg/dL, or new onset hematuria defined as ≥5 RBC/hpf (except for menstruating females).

These alert levels are set to anticipate and prevent the risk of a medically significant change in renal function while receiving Study Drug.

Abnormal test results should be repeated. In the event of a confirmed laboratory result meeting one or more of the above criteria, the following supplemental renal tests should be obtained within 7 days, and additional laboratory studies may be performed to identify if other potential etiologies may be a causal factor:

Serum creatinine, urine culture, urine microscopy sample with inspection of sediment.

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

### *8.5.3 Safety Monitoring for Platelet Count Results*

All subjects 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 8 and 13 weeks post last dose (as per visit schedule).

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 subject could be approaching the dose interruption rule of 75,000/mm$^3$.

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

Lab alerts related to platelet monitoring/stopping rules are issued when: 1) platelet counts are < 140,000 mm$^3$, 2) platelet count is ≥ 30% decreased from Baseline, or 3) the hematology sample is unreportable. All 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.

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

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

### *8.5.4 Safety Monitoring for Bleeding Events*

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

Bleeding events that are either major or clinically-relevant non-major bleeding (as defined below) will need to be monitored and treated immediately. Subjects with a suspected bleeding event will undergo additional testing if deemed appropriate by the treating physician and an (S)AE case report form will be completed. In addition, if bleeding is considered significant, hemoglobin (Hb), hematocrit (HCT), aPTT, PT, INR, and platelet count are to be obtained. In addition, approximately 2 mL of K2EDTA anticoagulated blood will be collected and resulting plasma must be stored allowing for a centralized assessment of ISIS 703802 concentrations.

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

*Definitions*:

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

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

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

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

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

### *8.5.5 Safety Monitoring for Constitutional Symptoms*

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

### *8.5.6 Safety Monitoring for Hypoglycemia*

Subjects will be instructed to monitor and manage hypoglycemic episodes. Subjects will be provided with a glucometer and asked to record Self Monitored Blood Glucose (SMBG) levels weekly and report back alert values to the site. Subjects will be instructed to promptly report symptoms of hypoglycemia: headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating and, weakness. If subjects suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. If a subject presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the subject's glucose level and treat the subject accordingly. Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

#### *Classification of Hypoglycemia*

The alert value for hypoglycemia is ≤ 70 mg/dL (≤ 3.9 mmol/L) blood glucose concentration.

*Severe Hypoglycemia*

Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Glucose concentrations may not be available during an event. Neurological recovery following glucose levels returning to normal considered sufficient evidence that event was induced by low glucose concentration.

*Documented Symptomatic Hypoglycemia*

Typical hypoglycemia symptoms accompanied by measured blood glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

*Asymptomatic Hypoglycemia*

Not accompanied by typical hypoglycemia symptoms but with measured blood glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

*Probable Symptomatic Hypoglycemia*

Typical hypoglycemia symptoms not accompanied by blood glucose determination but likely caused by blood glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

A **documented severe hypoglycemic event** is defined as one in which the subject requires the assistance of another person to obtain treatment for the event and has a blood glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place subjects at risk for injury to themselves or others.

### *8.5.7 Safety Monitoring for Documented Hyperglycemia*

Subjects will be asked to self-monitor their glucose at least once a week and reviewed by Investigator at each Study Center visit. If the value exceeds the specific glycemic limit specified below, the subject will be instructed to check again during the 2 following days. If all values in 3 consecutive days exceed the specific limit, the subject should contact the Investigator and a central laboratory FPG measurement will be performed).

The threshold values are defined as follows, depending on study period:

From Baseline visit to Week 13 (including value at Week 13) of Randomized Treatment period:

- Blood Glucose > 270 mg/dL (15.0 mmol/L)

From Week 13 to Post-treatment Follow-up (Week 4, 8 and 13 post end of treatment period):

- Blood Glucose > 240 mg/dL (13.3 mmol/L) or
- HbA1c > 9% (for subjects with Baseline HbA1c < 8%) and HbA1c increase of more than 1% from Baseline (for subjects with Baseline HbA1c ≥ 8%)

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

- Blood glucose was actually measured in the fasting condition
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency such as unplanned hospitalization (e.g., surgery, infection), the Investigator

can take appropriate measures for glycemic control. If the measure does not exceed 7 days, then it will not be considered a rescue. If the measure lasts beyond 7 days then it will be treated as a rescue
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should undertake appropriate action, i.e.:

- Investigation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the eCRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations
- Schedule an FPG/HbA1c assessment at the next visit

If none from the above-mentioned reason can be found, or if appropriate action fails to decrease blood glucose/HbA1c under the threshold values, rescue medication may be introduced at the Investigator discretion and according to local guidelines.

All assessments for primary and secondary efficacy and safety parameters planned in final primary endpoint assessment visit should be performed before adding the rescue medication if possible. Then the subject continues the study treatment and stays in the study in order to collect safety information. The planned visits and assessments should occur until the last scheduled visit. (See more details in Appendix A).

Note: After Study Drug discontinuation any treatments are permitted, as deemed necessary by the Investigator.

## 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 subject 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/injury

### *8.6.2 Stopping Rules for Renal Function Test Results*

In the event of an eGFR (by CKD-EPI formula) meeting any of the following criteria, or any change in renal biomarkers deemed by the investigator to require further evaluation, a serum creatinine, urine culture, and urine microscopy sample with inspection of sediment should be immediately obtained.

Dosing of a subject with Study Drug (ISIS 703802 or placebo) will be stopped permanently if testing in any of the following values is confirmed in the absence of an alternative explanation:

1. eGFR (CKD-EPI) decrease of > 25% from Baseline
2. eGFR (CKD-EPI) value < 45 mL/min/1.73 $m^2$
3. UACR >165mg/g
4. UPCR >325mg/g
5. New onset of hematuria (defined as ≥5 RBC/hpf)

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. The Investigator should consider consulting a local nephrologist for any change of renal function that presents a concern. If a renal biopsy is performed, a sample specimen should be made available for examination by an independent renal pathologist who has been engaged by the Sponsor to review such specimens.

### *8.6.3 Stopping Rule for Platelet Count Results*

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

In the event of any platelet count < 50,000/$mm^3$, or a platelet count less than 75,000/$mm^3$ that occurs while the subject is already on reduced dose, dosing of the subject 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 subjects 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/$mm^3$, dosing of a subject 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 subject 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 subject's platelet count, whether any bleeding events were experienced by the subject, 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 subject with Study Drug will be stopped permanently.

Once a subject commences weekly monitoring, this frequency of monitoring should continue until the platelet count returns to the normal range (≥140,000/$mm^3$) 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.

**Table 3 Actions in Subjects with Low Platelet Count**

| Platelet Count on Rx | Drug Dose | Monitoring |
|---|---|---|
| Normal range, ≥ 140K/mm$^3$ | No action | Monitor every 14 days (+/- 2 days) |
| ≥100K to <140K/mm$^3$ | No action | Closer observation<br>Monitor every week* |
| ≥75K to <100K/mm$^3$ | Permanently reduce the dose by 50 % as follows:<br>For Cohort A: reduce to 10 mg every week<br>For Cohort B: reduce to 20 mg every 4 weeks<br>For Cohort C: reduce to 40 mg every 4 weeks | Closer observation<br>Monitor every week* |
| ≥50K to <75K/mm$^3$ | Pause dosing<br>When platelet count returns to > 100K/mm$^3$ restart dosing as follows **only if approved by Sponsor Medical Monitor**:<br>For Cohort A: reduce to 10 mg every week<br>For Cohort B: reduce to 20 mg every 4 weeks<br>For Cohort C: reduce to 40 mg every 4 weeks<br>**or**<br>Permanently discontinue Study Drug if it occurs while on already reduced dose | Closer observation<br>Monitor every 2-3 days until 2 successive values show improvement<br>Consider discontinuation of antiplatelet agents/non-steroidal anti-inflammatory drug (NSAIDS)/ anticoagulant medication |
| ≥25K to <50K/mm$^3$ | Permanently discontinue Study Drug | Closer observation:<br>Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable<br>Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm$^3$ if possible<br>Refer to hematologist to provide diagnostic and therapeutic management |
| < 25K/mm$^3$ | Permanently discontinue Study Drug | Closer observation:<br>Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable<br>Steroids recommended**<br>Consider need for hospitalization<br>Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm$^3$ if possible<br>Refer to hematologist to provide diagnostic and therapeutic management |

* Once a subject commences weekly monitoring this frequency of monitoring should continue until the platelet count returns to the normal range (≥140,000/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 24 weeks for 1-4 cycles; Prednis(ol-)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone).

### *8.6.4 Stopping Rule for Documented Severe Hypoglycemia*

In the event of a first instance of documented severe hypoglycemia, dosing of a subject with Study Drug will be suspended temporarily. The need to adjust the background medication and the suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor. In the event of a second instance of documented severe hypoglycemia, after a re-challenge, dosing of a subject with Study Drug will be stopped permanently.

Dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. **Any proposed adjustments to treatment schedule must be discussed with, and approved by, the Study Medical monitor prior to initiation.**

## 8.7 Adjustment of Dose and/or Treatment Schedule

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 in consultation with the Sponsor Medical Monitor.

Subjects may have their dose interrupted in response to AEs, and the Study Medical Monitor will be informed.

## 8.8 Discontinuation of Study Drug/Treatment

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an adverse event (AE) that necessitates permanent discontinuation of Study Drug
- The subject 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 Treatment must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Subjects who discontinue treatment early should be entered into the post-treatment evaluation period. Every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

If a subject discontinues treatment after only 1 dose, then the post-treatment evaluation procedures cohorts should be followed.

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

Any subject 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, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug and then at 8 (weekly dosing cohort) or 10 (every 4 week dosing cohorts) and 13 weeks post end of treatment period (as per visit schedule).

If the subject declines or is unable to participate in the above, the early termination visit procedures 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 Subjects from the Study

Subjects must be withdrawn from the Study for any of the following:

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

Other reasons for withdrawal of subjects 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 subject who withdraws consent to participate in the Study will be removed from further treatment and study observation immediately upon the date of request. These subjects should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (Appendix A).

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

### *8.10.1 Concomitant Therapy*

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter (OTC) medications, herbal medications and vitamin supplements) administered between Screening and the end of the post-treatment evaluation period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a subject, including changes in the subject's current medications, must be recorded in the subject's source documents and CRF. Subjects taking over the counter omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

#### 8.10.1.1 Allowed Concomitant Therapy

Ibuprofen may be used for symptomatic pain relief. Any other therapy for pain (including OTC medications such as acetaminophen) should be approved by the Sponsor Medical Monitor or designee.

Any medications deemed necessary by the Investigator are allowed in response to an AE that requires drug therapy, except those listed in the disallowed concomitant therapy. In such cases, the Investigator must consult the Sponsor Medical Monitor to decide on subject continuation or withdrawal from the study.

#### 8.10.1.2 Disallowed Concomitant Therapy

The use of prescription and OTC medications including nonsteroidal anti-inflammatory drugs (with the exception of occasional ibuprofen) is prohibited during this study unless the occurrence of an AE requires a drug therapy. In cases when there is no AE, the Investigator must consult the Sponsor Medical Monitor to decide on subject continuation or withdrawal from the study.

The medications and therapy identified in exclusion criteria, Section 5.2 are also disallowed concomitant medications and are prohibited during the course of study, unless there is a safety concern. In those cases, the Medical Monitor needs to be notified and rationale provided by the Investigator.

Concomitant therapy with oral corticosteroids used as replacement therapy for pituitary adrenal disease as well as inhaled steroid therapy (e.g., Pulmicort®), or intra-articular, or topical may be acceptable; however, the subject must be on a stable regimen for at least 4 weeks prior to Screening. All exceptions should be discussed with the Sponsor Medical Monitor.

Subject 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 evaluation period.

## 8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of

study medication. Subjects that are self-administering study medication at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

# 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 serious adverse events (SAEs) including 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. The Data and Safety Monitoring Board (DSMB) will be notified of any SAE as specified in the DSMB charter.

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 regulation. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population. For Study Drug (ISIS 703802 or placebo) "expected" AEs, refer to the Investigator's Brochure.

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

### *9.3.3 Serious Adverse Event (SAE)*

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

## 9.4 Monitoring and Recording of Adverse Events

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

### *9.4.1 Serious Adverse Events*

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will

begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period. An Initial Serious Adverse Event Form should be completed and a copy should be 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. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

### *9.4.2 Non-Serious Adverse Events*

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

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

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

#### *9.4.3.1 Relationship to the Study Drug*

The event's relationship to the Study Drug (ISIS 703802 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 703802 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 703802 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)

- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

#### *9.4.3.2 Severity*

The severity of AEs and SAEs 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 703802 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 703802 or placebo) administration and dose
- **Permanently Discontinued:** Study drug was discontinued and not restarted
- **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

#### *9.4.3.4 Treatment Given for Adverse Event*

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

#### *9.4.3.5 Outcome of the Adverse Event*

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

- **AE Persists:** Subject terminates from the trial and the AE continues
- **Recovered:** Subject recovered completely from the AE

- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

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

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Subject has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Subject recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Subject 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. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

### *9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments*

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the timing of the procedure or treatment

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

### *9.5.3 Dosing Errors*

Study Drug (ISIS 703802 or placebo) errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing eCRF. If the subject takes a dose of Study Drug (ISIS 703802 or placebo) that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

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

### *9.5.4 Contraception and Pregnancy*

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

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

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

Female subjects: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The subject with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the subject 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 study physician will assist the subject 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 subjects: The progress of the pregnancy of a male subject's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may 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

## 10.1 Study Endpoints, Subsets, and Covariates

### *10.1.1 Primary Endpoint*

Percent change in fasting TG level from Baseline at the primary analysis time point.

### *10.1.2 Secondary Endpoints*

- Absolute and percentage change in ANGPTL3 protein, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoCIII, ApoAI, FFA, Lp(a)
- Absolute change in fasting plasma glucose, HbA1c, fasting insulin HOMA-IR, fructosamine and glycated albumin
- Absolute and percent change in weight, SBP and DBP
- Absolute and percent change in hepatic fat fraction (HFF) by MRI-PDFF
- Proportion of subjects reaching hepatic fat fraction (HFF) ≤ 8% by MRI-PDFF
- Absolute change in Fatty Liver Index (FLI)
- Absolute change in ALT and AST

Evaluate the beneficial effect of ISIS 703802 on changes from Baseline at the primary analysis time point on:

- Adipokines and related metabolic markers such as leptin, adiponectin, phospholipids (e.g. ceramides, sphingolipids, diacylglycerol)
- Body composition as measured by single slice MRI of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), waist circumference, WHR (waist-to-hip ratio), and BMI

[redacted]

## 10.2 Sample Size Considerations

Subjects in the placebo arm will be pooled for the statistical analysis in order to compare active and control arms. Therefore, each of the 4 arms will have 24 patients. Considering 10% dropouts, 21 patients per group are expected to complete the study.

A sample size of 21 patients per arm will be able to detect:

- A treatment difference in mean triglycerides of 50% based on a between-patient standard deviation of 46% (Jani et al. 2014) and a two-sample t-test with an unadjusted alpha level of 0.05 with 93% power.
- A treatment difference in mean liver fat of 4.75% based on a between-patient standard deviation of 3.96% (Tiikkainen et al. 2004) and a two-sample t-test with an unadjusted alpha level of 0.05 with 96% power.

A total of approximately 96 subjects (32 subjects per cohort, including 24 subjects per cohort treated with ISIS 703802) will be randomized to ensure that the efficacy of ISIS 703802 will be adequately characterized in the study.

## 10.3 Populations

**Full Analysis Set (FAS)**: All subjects who are randomized, received at least 1 dose of Study Drug (ISIS 703802 or placebo), and have a Baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. This population will be used for the primary analysis of efficacy.

**Per Protocol Set (PPS)**: Subset of the FAS who received within 6 months at least 25 weekly doses of Study Drug for subjects randomized to Cohorts A, and at least 5 monthly doses of Study Drug for subjects randomized to Cohorts B and C, 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 subjects who are randomized and receive at least 1 dose of Study Drug. This population will be used for all safety analyses.

**PK Population:** All subjects who are randomized and received at least 1 dose of ISIS 703802, and have at least 1 evaluable concentration result post first dose. This population will be used for analysis of PK data.

## 10.4 Definition of Baseline

Baseline for TG, ANGPTL3, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoCIII, ApoAI, FFA, Lp(a), and other lipid measurements will be defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 pre-dose assessment. 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 is planned.

## 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 subject data listings. Subject data listings will be presented for all subjects 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 subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

### *10.6.2 Safety Analysis*

#### *10.6.2.1 Adverse Events*

Treatment duration and amount of Study Drug (ISIS 703802 or placebo) received will be summarized by treatment group. Subject 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 703802 or placebo) will be summarized.

#### *10.6.2.2 Clinical Laboratory Data*

Laboratory tests to ensure subject 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 703802 or placebo) administration, as appropriate. In addition, the number of subjects 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 TG between ISIS 703802 treatment groups and pooled placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the Baseline TG as a covariate. Missing data may be handled by LOCF or multiple imputation methods (Schafer 1997; Shaffer 1999).

The primary efficacy analysis will take place after the last subject 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*

- Absolute and percentage change at the primary analysis time point in ANGPTL3 protein, TC, LDL-C, HDL-C, VLDL-C, Non-HDL-C, ApoB (ApoB-48, ApoB-100), ApoCIII, ApoAI, FFA, Lp(a) will be compared between each AKCEA-ANGPTL3-$L_R$ treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute change in fasting plasma glucose, HbA1c, fasting insulin HOMA-IR, fructosamine and glycated albumin will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute and percent change in weight, SBP and DBP will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute and percent change in hepatic fat fraction (HFF) by MRI-PDFF will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Proportion of subjects reaching hepatic fat fraction (HFF) $\leq$ 8% by MRI-PDFF at the primary analysis time point will be compared between each ISIS 703802 treatment group and pooled placebo group using a logistic regression model with Baseline HFF as a covariate.

- Absolute change in Fatty Liver Index (FLI) will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute change in ALT and AST will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute change in Adipokines and related metabolic markers such as leptin, adiponectin, phospholipids (e.g. ceramides, sphingolipids, diacylglycerol) will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate
- Absolute change in Body composition as measured by single slice MRI of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), waist circumference, WHR (waist-to-hip ratio), and BM will be compared between each ISIS 703802 treatment group and pooled placebo group using an ANCOVA model with Baseline as covariate

[redacted]

- [redacted]

[redacted]

### *10.6.4 Pharmacokinetic and Immunogenicity Analysis*

For all subjects, trough and post-treatment concentrations of ISIS 703802 in plasma (as total full-length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated ISIS 703802) will be determined and summarized by treatment with and without stratification by subject immunogenicity (IM) status using descriptive statistics.

In addition, plasma terminal elimination half-life of ISIS 703802 will be calculated using the post-treatment follow-up data if data permits.

Additionally, for subjects in the PK subgroup only, PK parameters will be calculated using non-compartmental methods. The maximum plasma concentration ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$) values will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve (AUC) values after the first dose and last dose 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 subject IM status.

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

The IM of ISIS 703802 will be assessed before, during, and after treatment with Study Drug (ISIS 703802 or placebo). The IM incidence (number) and incidence rate (percent) will be

summarized at each evaluated study time point and at the subject level by treatment and dose, as the total number of and percent of evaluated subjects with antibody negative, positive, and unknown status. Study subjects with positive anti-ISIS 703802 antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or not determinable. Potential relationships of IM with selected efficacy, safety, and PK measures may be evaluated.

Additional details regarding the PK and IM 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 subject population, based on an English version provided by the Sponsor or designee.

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject 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 703802 or placebo) are administered. The subject or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject or legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

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

## 11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP E6R2) 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/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the 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 subjects into the study and shipment of Study Drug.A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of subjects 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 notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. 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. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

### 11.4 Subject Confidentiality

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

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor 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 subjects 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 early termination and send a copy of the notification to the Sponsor or designee.

## 12.3 Study Documentation and Storage

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

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the subject's 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. Case report form entries may be considered source data if the case report form is the site of the original recording (i.e., there is no other written or electronic record of data).

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 (E6R2), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the 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.

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.

## 12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., case report forms and other pertinent data) provided that subject confidentiality is respected.

The Sponsor monitor 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 subject medical records and other study-related records needed to verify the entries on the case report forms.

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (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 subject data received by the Sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor 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.

## 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 subjects and investigative staff must use vocabulary and language that are clearly understood.

## 12.6 Compensation for Injury

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

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## 14. APPENDICES

# Appendix A Schedule of Procedures

Schedule of Procedures – Weekly Dosing

Schedule of Procedures – Every 4-Week Dosing

## Appendix A Schedule of Procedures – Weekly Dosing

| | Screening[r] | | Treatment Period | | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Run-in[#] | Qual[†] | | | | | | | | | | | | | | | |
| **Study Week** | -5 to -1 | -1 to 0 | 1 | 1 | 5 | 9 | 13 | 17 | 21 | 25 | 26 | | | 27/ET | 4* | 8* | 13* |
| **Study Day** | -35 to -8 | -7 to -1 | 1 | 2[a] | 29 | 57 | 85 | 113 | 141 | 169 | 176 | 177[a] | 178[a] | 183 | *Weeks from the end of treatment period[q] | | |
| **Visit and Testing Window +/- Days** | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 0 | 0 | 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 |
| Inclusion/Exclusion Criteria | X | X | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | |
| Vital Signs | X | | X | | X | X | X | X | X | X | X | | | X | X | X | X |
| Physical Examination [b] | X | | X | | X | | X | | | | | | | X | X | X | X |
| Waist circumference/ WHR | | | X | | | | X | | | | | | | X | | | |
| Body Weight and Height [c] | X | X | X | | X | X | X | X | X | X | X | | | X | X | X | X |
| 12- lead ECG (triplicate) | X | | X | | X | | X | | X | | | | | X | X | X | X |
| Ultrasound[p] | X | | | | | | | | | | | | | | | | |
| MRI | X[d, s] | | | | | | X | | | | | | | X | | | |
| 24-Hour Urine for Creatinine Clearance and Protein | | X | | | | | | | | | | | | | | | |
| Extended Urinalysis [e] | X | | EVERY 14 DAYS (+/- 2 days) [e, f] | | | | | X | X | X | | | | X | X | X | X |
| Renal Biomarkers [g] | X | | EVERY 14 DAYS (+/- 2 days) [f, g] | | | | | X | X | X | | | | X | X[h] | X[h] | X[h] |
| Serum Creatinine and Cys-C [i, j, k] | X | | EVERY 14 DAYS (+/- 2 days) [f, i] | | | | | X | X | X | | | | X | X | X | X |
| Chemistry Panel [j, k] | X | | EVERY 14 DAYS (+/- 2 days) [f] | | | | | X | X | X | | | | X | X | X | X |
| Hematology [j, k] | X | | X | HEMATOLOGY PERFORMED EVERY 14 DAYS (+/- 2 days) [f, k] | | | | | | | | | | | X[h] | X[h] | X[h] |
| Coagulation | X | | X | | | | X | | | | | | | X | | | X |
| Hepatitis B, C, HIV | X | | | | | | | | | | | | | | | | |
| Thyroid Panel | X | | | | | | | | | | | | | | | | |

## Appendix A Schedule of Procedures – Weekly Dosing *Continued*

| | Screening[r] | | Treatment Period | | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Run-in# | Qual* | | | | | | | | | | | | | | | |
| **Study Week** | **-5 to -1** | **-1 to 0** | **1** | **1** | **5** | **9** | **13** | **17** | **21** | **25** | **26** | | | **27/ET** | **4*** | **8*** | **13*** |
| **Study Day** | **-35 to -8** | **-7 to -1** | **1** | **2[a]** | **29** | **57** | **85** | **113** | **141** | **169** | **176** | **177[a]** | **178[a]** | **183** | *** Weeks from the end of treatment period[q]** | | |
| **Visit and Testing Window +/- Days** | **0** | **0** | **0** | **0** | **2** | **2** | **2** | **3** | **3** | **3** | **3** | **0** | **0** | **3** | **3** | **3** | **3** |
| Liver Biomarkers | | | X | | | | X | | X | | | | | X | | | X |
| Plasma PK - ISIS 703802 [l] | | | X[3] | X[1] | X | X | X | X | X | | X[3] | X[1] | X[2] | X | X | X | X |
| Anti-ISIS 703802 Antibodies | | | X | | X | X | X | | X | | | | | X | X | | X |
| FSH (women only, if applicable) [j, m] | X | | | | | | | | | | | | | | | | |
| Serum Pregnancy Test [m] | X | | X | | X | X | X | X | X | X | | | | X | X | X | X |
| Archived Serum & Plasma Samples [j, n] | | | X | | | X | | X | X | | | | | X | X | X | X |
| PD Panel and phospholipids [j] | X | X | X | | X | X | X | X | X | | X | | | X | X | X | X |
| Extended Lipid Panel [j] | X | X | X | | X | X | X | X | X | | X | | | X | X | X | X |
| HbA1C [j] | X | | X | | | | X | | | | | | | X | | | X |
| FPG, and delipidated free glycerol, insulin [j] | X | | X | | X | X | X | X | X | | X | | | X | X | X | X |
| Biomarkers of Inflammation | | | X | | | | X | | | | | | | X | | | X |
| Study Drug: SC Injection | | | EVERY WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 26/Day 176) [o] | | | | | | | | | | | | | | |
| Adverse Events | 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 |

[†] Qual =Qualification

# Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without the diet run-in period.

## Appendix A Schedule of Procedures – Weekly Dosing *Continued*

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

a Visit only required for subjects in PK subgroup.

b Full physical exam will be performed at the Screening visit and an abbreviated physical exam will be performed during treatment and follow-up periods.

c Height only required at Screening.

d MRI will only be performed during Screening after all other eligibility criteria are met. MRI should be performed 10 days (+/- 2 days) prior to anticipated Day 1 date to allow time for result reporting and analysis.

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. Subject 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 are taken every 14 days (+/- 2 days) for 5 weeks after last dose of Study Drug, then at Week 8 and Week 13 Follow-up visits.

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

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

k If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator 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 Last dose of Study Drug will be administered at Week 26/Day 176 +/- 3 days.

p Ultrasound to determine positive liver fat at screening will only be performed on patients who do not have documented history of hepatic steatosis as determined .by imaging (CT scan, MRI or US). Ultrasound may be repeated at the discretion of the PI. Results of Ultrasound must be available and confirm eligibility prior to MRI being performed.

q Treatment period is defined as the time from the first dose through one dosing interval post last dose.

r If a subject was screened and failed to meet eligibility under a previous protocol, the subject may be screened under the current protocol.

s If a subject was screened and had an MRI, but failed to meet eligibility under a previous protocol, the MRI during rescreening may not need to be repeated. The need to repeat an MRI for such subjects should be discussed with the Medical Monitor.

**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 for all subjects and pre-dose, 1, 2, 4, 8 hours post SC injection for subjects on PK subgroup.

## Appendix A Schedule of Procedures – Every 4-Week Dosing

| | Screening[r] | | Treatment Period | | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Run-in[#] | Qual[†] | | | | | | | | | | | | | | | |
| **Study Week** | -5 to -1 | -1 to 0 | 1 | 1 | 5 | 9 | 13 | 17 | 21 | | | 22 | 23 | 25/ET | 4* | 8* | 13* |
| **Study Day** | -35 to -8 | -7 to -1 | 1 | 2[a] | 29 | 57 | 85 | 113 | 141 | 142[a] | 143[a] | 148[a] | 155[a] | 169 | * Weeks from the end of treatment period[q] | | |
| **Visit and Testing Window +/- Days** | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | 0 | 0 | 0 | 0 | 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 |
| Inclusion/Exclusion Criteria | X | X | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | |
| Vital Signs | X | | X | | X | X | X | X | X | | | X | | X | X | X | X |
| Physical Examination [b] | X | | X | | X | | X | | | | | | | X | X | X | X |
| Waist circumference/ WHR | | | X | | | | X | | | | | | | X | | | |
| Body Weight and Height [c] | X | X | X | | X | X | X | X | X | | | | | X | X | X | X |
| 12- lead ECG (triplicate) | X | | X | | X | | X | | X | | | | | X | X | X | X |
| Ultrasound[p] | X | | | | | | | | | | | | | | | | |
| MRI | X[d, s] | | | | | | X | | | | | | | X | | | |
| 24-Hour Urine for Creatinine Clearance and Protein | | X | | | | | | | | | | | | | | | |
| Extended Urinalysis [e] | X | | EVERY 14 DAYS (+/- 2 days) [e, f] | | | | | X | X | | | | | X | X | X | X |
| Renal Biomarkers [g] | X | | EVERY 14 DAYS (+/- 2 days) [f, g] | | | | | X | X | | | | | X | X[h] | X[h] | X[h] |
| Serum Creatinine and Cys-C [i, j, k] | X | | EVERY 14 DAYS (+/- 2 days) [f, i] | | | | | X | X | | | | | X | X | X | X |
| Chemistry Panel [j , k] | X | | EVERY 14 DAYS [f] | | | | | X | X | | | | | X | X | X | X |
| Hematology [j, k] | X | | X | HEMATOLOGY PERFORMED EVERY 14 DAYS (+/- 2 days) [f, k] | | | | | | | | | | | X[h] | X[h] | X[h] |
| Coagulation | X | | X | | | | X | | | | | | | X | | | X |
| Hepatitis B, C, HIV | X | | | | | | | | | | | | | | | | |
| Thyroid Panel | X | | | | | | | | | | | | | | | | |

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

| | Screening[r] | | Treatment Period | | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Run-in[#] | Qual* | | | | | | | | | | | | | | | |
| **Study Week** | **-5 to -1** | **-1 to 0** | **1** | **1** | **5** | **9** | **13** | **17** | **21** | | | **22** | **23** | **25/ET** | **4*** | **8*** | **13*** |
| **Study Day** | **-35 to -8** | **-7 to -1** | **1** | **2[a]** | **29** | **57** | **85** | **113** | **141** | **142[a]** | **143[a]** | **148[a]** | **155[a]** | **169** | *** Weeks from the end of treatment period[q]** | | |
| **Visit and Testing Window +/- Days** | **0** | **0** | **0** | **0** | **2** | **2** | **2** | **3** | **3** | **0** | **0** | **0** | **0** | **3** | **3** | **3** | **3** |
| Liver Biomarkers | | | X | | | | X | | X | | | | | X | | | X |
| Plasma PK - ISIS 703802 [l] | | | X[3] | X[1] | X | X | X | X | X[3] | X[1] | X[2] | X | X | X | X | X | X |
| Anti-ISIS 703802 Antibodies | | | X | | X | X | X | | X | | | | | X | X | | X |
| FSH (women only, if applicable) [j, m] | X | | | | | | | | | | | | | | | | |
| Serum Pregnancy Test [m] | X | | X | | X | X | X | X | X | | | | | X | X | X | X |
| Archived Serum & Plasma Samples [j, n] | | | X | | | X | | X | X | | | | | X | X | X | X |
| PD Panel and phospholipids [j] | X | X | X | | X | X | X | X | X | | | | | X | X | X | X |
| Extended Lipid Panel [j] | X | X | X | | X | X | X | X | X | | | | | X | X | X | X |
| HbA1C [j] | X | | X | | | | X | | | | | | | X | | | X |
| FPG, and delipidated free glycerol, insulin [j] | X | | X | | X | X | X | X | X | | | | | X | X | X | X |
| Biomarkers of Inflammation | | | X | | | | X | | | | | | | X | | | X |
| Study Drug: SC Injection | | | EVERY 4-WEEK SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 21/Day 141) [o] | | | | | | | | | | | | | | |
| Adverse Events | 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 |

[†]Qual =Qualification

# Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without the diet run-in period.

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

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

a Visit only required for subjects in PK subgroup.

b Full physical exam will be performed at the Screening visit and an abbreviated physical exam will be performed during treatment and follow-up periods.

c Height only required at Screening.

d MRI will only be performed during Screening after all other eligibility criteria are met. MRI should be performed 10 days (+/- 2 days) prior to anticipated Day 1 date to allow time for result reporting and analysis

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. Subject 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 the follow-up period, hematology sampling for platelet values should continue to be taken every 14 days (+/- 2 days) for 6 weeks after Week 27/EOT, then at Week 4, Week 8, and Week 13 Follow-up visits.

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

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

k If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days). All platelet count results will be reviewed promptly (within 48 hours of receipt) by the Investigator 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 Last dose of Study Drug will be administered at Week 21/Day 141 +/- 3 days.

p Ultrasound to determine positive liver fat at screening will only be performed on patients who do not have a documented history of hepatic steatosis as determined.by imaging (CT scan, MRI or US). Ultrasound may be repeated at the discretion of the PI. Results of Ultrasound must be available and confirm eligibility prior to MRI being performed.

q Treatment period is defined as the time from the first dose through one dosing interval post last dose.

r If a subject was screened and failed to meet eligibility under a previous protocol, the subject may be screened under the current protocol.

s If a subject was screened and had an MRI, but failed to meet eligibility under a previous protocol, the MRI during rescreening may not need to be repeated. The need to repeat an MRI for such subjects should be discussed with the Medical Monitor.

**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 for all subjects and pre-dose, 1, 2, 4, 8 hours post SC injection for subjects on PK subgroup

# Appendix B List of Laboratory Analytes

# Appendix B List of Laboratory Analytes

**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
- Alkaline phosphatase
- Creatinine kinase
- GGT
- Cys-C

**PD Panel**
- ANGPTL3
- Insulin
- Proinsulin
- C-peptide
- Fructosamine
- Glycated albumin
- Delipidated Free Glycerol
- Fasting Plasma Glucose

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

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

**Extended Lipid Panel**
- Total Cholesterol (TC)
- LDL cholesterol (LDL-C)
- HDL cholesterol (HDL-C)
- Non-HDL cholesterol (non-HDL-C)
- Triglycerides (TG)
- VLDL cholesterol (VLDL-C)
- Lp(a)
- FFA
- ApoB-48
- ApoB-100
- ApoB
- ApoCIII
- Apo A-1

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

**Pharmacokinetics[1]**
- ISIS 703802 levels in plasma

**Immunogenicity**
- Anti-ISIS 703802 antibodies

**Liver Biomarkers (apoptosis and fibrosis)**
- CK18
- PIIINP

**Inflammatory**
- hs-CRP
- IL-6
- IFN gamma
- TNF alpha
- Leptin
- Adiponectin

**Extended Urinalysis**
- Routine Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Red Blood Cells
  - 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

**24-Hour Urine Test**
- Creatinine clearance
- Protein
- Albumin

**Phospholipids**
- Ceramides
- Sphingolipids
- Diacyglycerol

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 703802 with plasma constituents

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

# Appendix C PK Sampling Schedule

Sampling Schedule for Weekly Dosing Cohort
Sampling Schedule for Every 4-Week Dosing Cohorts

## Appendix C PK Sampling Schedule for Weekly Dosing Cohort

| | Treatment Period | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | **1** | **1** | **5** | **9** | **13** | **17** | **21** | **26** | | | **27** | **4*** | **8*** | **13*** |
| **Study Day** | **1** | **2** | **29** | **57** | **85** | **113** | **141** | **176** | **177** | **178** | **183** | ***Weeks from the end of treatment period[4]** | | |
| **All Subjects** | Pre-dose | NA | Pre-dose | Pre-dose | Pre-dose | Pre-dose | Pre-dose | Pre-dose | NA | NA | Anytime | 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, 1, 2, 4, & 8-hr[1] | 24-hr[2] | 48-hr[3] | 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
4 Treatment period is defined as the time from the first dose through one dosing interval post last dose

## Appendix C PK Sampling Schedule for Every 4-Week Dosing Cohorts

| | Treatment Period | | | | | | | | | | | Follow-up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week** | **1** | **1** | **5** | **9** | **13** | **17** | **21** | | | **22** | **23** | **25** | **4*** | **8*** | **13*** |
| **Study Day** | **1** | **2** | **29** | **57** | **85** | **113** | **141** | **142** | **143** | **148** | **155** | **169** | ***Weeks from the end of treatment period[4]** | | |
| **All Subjects** | Pre-dose | NA | Pre-dose | Pre-dose | Pre-dose | Pre-dose | Pre-dose | NA | NA | NA | NA | Anytime | Anytime | Anytime | Anytime |
| **PK Sub-group only** | Pre-dose, 1, 2, 4, and 8-hr[1] | 24-hr[2] | Pre-dose | Pre-dose | Pre-dose | Pre-dose | Pre-dose, 1, 2, 4, and 8-hr[1] | 24-hr[2] | 48-hr[3] | Anytime | Anytime | 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
4 Treatment period is defined as the time from the first dose through one dosing interval post last dose

# Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

## Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| **Hematology** | | | |
| aPTT prolonged | >ULN - 1.5 x ULN | >1.5 - 2.5 x ULN | >2.5 x ULN; hemorrhage |
| Eosinophils increased[†] | 650 – 1,500 cell/$mm^3$ | 1,501 - 5,000 cell/$mm^3$ | >5,000 cell/$mm^3$ |
| Fibrinogen decreased | <1.0 - 0.75 x LLN or <25% decrease from baseline | <0.75 - 0.5 x LLN or 25 - <50% decrease from baseline | <0.5 x LLN or ≥50% decrease from baseline |
| Hemoglobin decreased (Anemia) | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated |
| Hemoglobin increased | Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN | Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN | Increase in >4 g/dL above ULN or above baseline if baseline is above ULN |
| INR increased | >1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation | >1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation | >2.5 x ULN; >2.5 times above baseline if on anticoagulation |
| Lymphocyte count decreased | <LLN - 800/$mm^3$; <LLN - 0.8 x $10^9$/L | <800 - 500/$mm^3$; <0.8 - 0.5 x $10^9$ /L | <500 /$mm^3$; <0.5 x $10^9$ /L |
| Lymphocyte count increased | - | >4000/$mm^3$ - 20,000/$mm^3$ | >20,000/$mm^3$ |
| Neutrophil count decreased | <LLN - 1500/$mm^3$; <LLN - 1.5 x $10^9$ /L | <1500 - 1000/$mm^3$; <1.5 - 1.0 x $10^9$ /L | <1000/$mm^3$; <1.0 x $10^9$ /L |
| Platelet count decreased | <LLN - 75,000/$mm^3$; <LLN - 75.0 x $10^9$ /L | <75,000 - 50,000/$mm^3$; <75.0 - 50.0 x $10^9$ /L | <50,000/$mm^3$; <50.0 x $10^9$ /L |
| White blood cell decreased | <LLN - 3000/$mm^3$; <LLN - 3.0 x $10^9$ /L | <3000 - 2000/$mm^3$; <3.0 - 2.0 x $10^9$ /L | <2000/$mm^3$; <2.0 x $10^9$ /L |
| **Chemistry** | | | |
| Acidosis | pH <normal, but **>=**7.3 | - | pH <7.3 |
| Alanine aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 x ULN |
| Alkaline phosphatase increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 x ULN |
| Alkalosis | pH >normal, but ≤7.5 | - | pH >7.5 |
| Aspartate aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 x ULN |
| Blood bilirubin increased | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 x ULN |
| Cardiac troponin I increased | Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer | - | Levels consistent with myocardial infarction as defined by the manufacturer |

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

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| Cardiac troponin T increased | Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer | - | Levels consistent with myocardial infarction as defined by the manufacturer |
| CD4 lymphocytes decreased | <LLN - 500/$mm^3$; <LLN - 0.5 x $10^9$ /L | <500 - 200/$mm^3$; <0.5 - 0.2 x $10^9$ /L | <200/$mm^3$; <0.2 x $10^9$ /L |
| CPK increased* | >ULN - <6 ULN | 6 - 10 x ULN | >10 x ULN |
| Creatinine increased | >1 - 1.5 x baseline; >ULN - 1.5 x ULN | >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | >3.0 x baseline; >3.0 x ULN |
| GGT increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 x ULN |
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L | Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic | Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated |
| Hyperglycemia | Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L | Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L | >250 mg/dL; >13.9 mmol/L; hospitalization indicated |
| Hyperkalemia | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L | >6.0; hospitalization indicated |
| Hypermagnesemia | >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L | - | >3.0 mg/dL; >1.23 mmol/L |
| Hypernatremia | >ULN - 150 mmol/L | >150 - 155 mmol/L | >155 mmol/L; hospitalization indicated |
| Hyperuricemia | >ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences | - | >ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences |
| Hypoalbuminemia | <LLN - 3 g/dL; <LLN - 30 g/L | <3 - 2 g/dL; <30 - 20 g/L | <2 g/dL; <20 g/L |
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic | Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated |
| Hypoglycemia | <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | <55 mg/dL; <3.0 mmol/L | <40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡ |
| Hypokalemia | <LLN - 3.0 mmol/L | <LLN - 3.0 mmol/L; symptomatic; intervention indicated | <3.0 mmol/L; hospitalization indicated |
| Hypomagnesemia | <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L | <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L | <0.9 mg/dL; <0.4 mmol/L |
| Hyponatremia | <LLN - 130 mmol/L | - | <130 mmol/L |
| Hypophosphatemia | <LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L | <2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L | <2.0 mg/dL; <0.6 mmol/L |
| Lipase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 x ULN |
| Serum amylase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 x ULN |

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

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| **Urine** | | | |
| Proteinuria<br>Adults<br>Children | 1+ proteinuria; urinary protein <1.0 g/24 hrs<br>- | 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;<br>Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9 | Urinary protein ≥3.5 g/24 hrs;<br>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 |
| Folate (folic acid) |
| Vitamin B12 |
| Fibrinogen |
| von Willebrand factor |
| Total globulins, total IgA, IgG and IgM |
| Complement: total C3, total C4, Bb, C5a |
| hsCRP |
| Helicobacter pylori (breath test) |
| 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 |