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

MINOR Criteria

a. Requirement for high doses of insulin, e.g., requiring ≥ 200 U/day, ≥ 2 U/kg/day, or currently taking U-500 insulin

b. Presence of acanthosis nigricans on physical examination

c. Evidence/history of polycystic ovary syndrome (PCOS) or PCOS-like symptoms (hirsutism, oligomenorrhea, and/or polycystic ovaries)

d. History of pancreatitis associated with hypertriglyceridemia

e. Evidence of non-alcoholic fatty liver disease

- Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease or radiographic evidence of hepatic steatosis (e.g., on ultrasound or CT)

4. A diagnosis of diabetes mellitus, made at least 6 months prior to the Screening, and:

- A HbA1c ≥ 7% to ≤ 12% at Screening,
- On anti-diabetic therapy consisting of:

a. Metformin ≥ 1500 mg/day, or

b. If the dose of metformin is < 1500 mg/day, or metformin is not tolerated, then the patient should be on other oral anti-diabetic drugs (OAD) or an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, or

c. Insulin therapy alone or in combination with other anti-diabetic drugs

5. Hypertriglyceridemia as defined by Fasting TG levels ≥ 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification visits. Patients with the clinical diagnosis of FPL and with Fasting TG levels ≥ 200 (≥ 2.26 mmol/L) to < 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification Visits who meet the genetic or family history criteria for study inclusion may be further screened and enrolled in the study

6. Presence of hepatosteatosis (fatty liver), as evidenced by a Screening MRI indicating a hepatic fat fraction (HFF) ≥ 6.4%

7. Willing to maintain their customary physical activity level and to follow a diet moderate in carbohydrates and fats with a focus on complex carbohydrates and replacing saturated for unsaturated fats

8. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until at least 13 weeks after

STUDY GLOSSARY

Abbreviation	**Definition**
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
ANGPTL3	Angiopoietin-like 3
APL	Acquired Partial Lipodystrophy
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
ASGPR	Asialoglycoprotein Receptor
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	blood pressure
BUN	blood urea nitrogen
C	centigrade
C5a	complement factor C5a (activated complement split product)
C_{max}	maximum concentration
CBC	complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiological Collaboration
CL	systemic clearance
CMV	Cytomegalovirus
CRF	case report form
CRNMB	Clinically-relevant Non-major Bleeding
CRO	Clinical Research Organization
CRP	C-reactive protein
CS	clinically significant
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Manager
DEXA	dual-energy X-ray absorptiometry
dL	deciliter
DLT	dose-limiting toxicity

evaluation and mitigation strategy (REMS) program, which requires prescriber and pharmacy certification and special documentation (Chan et al. 2011; Myalept PI).

At the present time, the Sponsor does not intend to study the generalized forms for which a specific therapy exists (metreleptin) nor the acquired forms of the partial lipodystrophy disorders because of the heterogeneity of etiologies, some iatrogenic, and the high incidence of associated immune disorders in these populations. Therefore, this study will focus only on patients with the congenital form of the partial lipodystrophy disorders and, among those, on the most severe subtype, patients with familial partial lipodystrophy, or FPL.

Familial Partial Lipodystrophy (FPL) is an orphan disease for which no specific pharmacologic treatment currently exists. FPL was described in the 1970s independently by Köbberling and Dunnigan (Dunnigan et al. 1974; Köbberling et al. 1975), and is the most common subtype of inherited PL (National Organization for Rare Disorders [NORD] 2012). It has been estimated that FPL affects approximately 0.2 in 10,000 people in the European Union, which is equivalent to a total of around 10,000 people (Committee for Orphan Medicinal Products 2012). FPL encompasses several subtypes differentiated by the underlying genetic mutation (6 FPL subtypes and mutations in 5 genes have been identified). FPL type 1, Köbberling variety has been reported in a handful of individuals and its molecular basis is unknown. FPL type 2, Dunnigan variety is the most common form and the most well characterized disorder and is due to missense mutations in the A and C LMNA gene. FPL type 3 has been reported in 30 patients and is due to mutations in the PPARγ gene. FPL type 4 has been reported in 5 patients and is due to mutations in the PLIN1 gene. FPL type 5 has been reported in 4 members of a family who presented with insulin resistance and diabetes and is due to mutations in the AKT2 gene. The last subtype, Autosomal Recessive FPL has been identified recently in 1 patient with homozygous mutations in CIDEC. Some individuals with FPL do not have mutations in any of these genes, suggesting that additional, as yet unidentified genes can cause the disorder (Hegele et al. 2007; Garg et al. 2011; National Organization for Rare Disorders [NORD] 2012).

The diagnosis of FPL is mainly clinical and needs to be considered in patients presenting with the triad of insulin resistance (with or without overt diabetes), significant dyslipidemia in the form of hypertriglyceridemia, and fatty liver (Huang-Doran et al. 2010). Patients often present with diabetes and severe insulin resistance requiring high doses of insulin. Other evidence of severe insulin resistance is provided by the presence of acanthosis nigricans and polycystic ovary syndrome (PCOS) (with symptoms like hyperandrogenism and oligomenorrhea). Some patients develop severe hypertriglyceridemia resulting in episodes of pancreatitis. In many patients, the TG levels remain persistently elevated despite fully optimized therapy or diet modifications. Radiographic evidence of hepatic steatosis or steatohepatitis with hepatomegaly and/or elevated transaminases is common (Handelsman et al. 2013). Patients with the Dunnigan variety have a higher risk of coronary artery disease (Hegele 2001). Although very rare, patients with a specific mutation in the LMNA gene are at an increased risk of cardiomyopathy and its associated complications, congestive heart failure and conduction defects.

There is limited natural history data, mostly cross-sectional and derived from publication of baseline characteristics of patients entering a clinical trial (Diker-Cohen CE et al. 2015; Ajluni N et al. 2016; Akinci B et al. 2017; Ahmad Z et al. 2013; Bidault G. et al. 2013). The evidence that FPL progresses over time comes from a prospective, open-label NIH study with ongoing enrollment since 2000 (N = 87). Data analyzed in 2014 showed that metabolic manifestations of the cohort of 32 partial lipodystrophy patients (including 25 FPL) were as severe as those of the cohort of generalized lipodystrophy (N = 55), which is recognized as a more severe form of lipodystrophy (Diker-Cohen CE et al. 2015).

- 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/week 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.
- In the Phase 1 study, there was no elevations in ALT at single dose cohorts up to 120 mg. In multiple dose cohorts, two out of six subjects in the 60 mg weekly dose cohort had a > 2 x ULN increase of ALT, without increase in bilirubin, which was considered a treatment related adverse event (AE) for one by Principal Investigator (PI). There were no other observed clinically significant changes in ALT and liver function in 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 unconjugated 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 decrease in

3.2 Number of Study Centers

This study is planned to be conducted at a single center but will include additional centers if needed.

3.3 Number of Subjects

Approximately 3 subjects will be treated in this study. Initially, 3 subject will be enrolled, but enrollment could be increased to 6 subjects, based on safety profile and efficacy observations.

3.4 Overall Study Duration and Follow-up

The length of subjects' participation in the study may be up to 45 weeks. This includes an up to 6-week screening period, that includes a 4-week diet stabilization / run-in period, a 2-week qualification period, a 26-week treatment period, and a 13-week post-treatment evaluation period.

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/Qualification

Subject eligibility for the study will be determined within 42 days/6 weeks prior to study entry. Potential subjects will report to the Study Center for screening assessments at specified intervals within the 6-week screening period as detailed in the Schedule of Procedures in Appendix A. As part of the screening period, subjects will have a 4-week diet stabilization/run-in period followed by a up to 2-week qualification period. 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. A baseline DEXA scan and MRI will be obtained to assess liver fat content once all other eligibility has been confirmed. MRI results must be available prior to registration and administration of the first dose of study drug.

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. Subsequent administrations of study drug may occur at home or in 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

Subjects are to return to the Study Center for follow-up visits. These visits will take place at 4, 8 and 13 weeks after the Treatment Period (last dose through one dosing interval post last dose). Refer to Schedule of Procedures in Appendix A.

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.

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 for safety and clinical laboratory evaluations. A ± 3-day excursion from the scheduled visit date is permitted for this time period.

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 at least 10 hours. 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. 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 also be collected every 14 days and sent to the central laboratory for analysis for the first 3 months of the study treatment, and monthly thereafter during the Treatment Period per Section 8.5.1.

While on treatment blood and urine samples for renal function testing will also be collected every 14 days and sent to the central laboratory for analysis per 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 laboratory's 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 (Grade 3 or Grade 4) is considered an adverse event of special interest and must be reported in an expedited fashion to the Sponsor as per Section 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 Section 9.4.1.

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

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

6.2.1 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 DEXA Scan

Dual-energy X-ray Absorptiometry (DEXA) scans will be conducted prior to administration of the first dose of Study Drug and repeated at Week 13 and 27 using standardized procedures and settings.

6.2.3 Electrocardiography

Electrocardiography (ECG) will be conducted as indicated in the Schedule of Procedures (Appendix A) at Screening, Day 1 (prior to the first dose of Study Drug), and during the treatment period.

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.

6.2.4 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.

6.2.5 Mixed Meal Test

The Mixed Meal Test (MMT) (Appendix E) will be done at baseline, at week 13 and at week 27. This test consists of having the subject consume a standardized meal in the evening and fast overnight for at least 8 hours. The following morning, before the test, fasting plasma glucose, free fatty acids (FFA), C-peptide, insulin, serum ghrelin, GIP, GLP-1 and PYY as well as incretin hormones are measured. The subject then consumes a liquid standard meal (such as Optifast®) and the same metabolic parameters are

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 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).

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 study procedures and observations at the time of withdrawal (see Appendix A). The Investigator should clarify what type of follow-up the subject is agreeable to: in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records. Wherever possible these subjects should continue to be followed up via the agreed means to collect information on adverse events, concomitant medications and survival status. At the very least, the patient's status at the end of the protocol defined study period should be ascertained and documented.

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 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 (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

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. For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population.

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.

9.3.3.1 Adverse Events of Special Interest

For the purpose of this study severe reductions in platelet count < 50,000 mm^3 are considered as an AE of special interest and should be subject to expediting reporting to the Sponsor following the same requirements as for SAE reporting (Section 9.4.1).

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a 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:INC Research, LLC

Email:INCDrugSafety@INCResearch.com

Fax:1-877-464-7787

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) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 703802) 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) 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) due to the event is characterized by 1 of the following:

- **None:** No changes were made to Study Drug (ISIS 703802) 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

special interest and should be reported in an expedited fashion to the Sponsor as per Sections 9.3.3.1 and 9.4.1).

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

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

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the 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) 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 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 Investigator's 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

- The effect of ISIS 703802 on the percent change from Baseline in fasting triglyceride levels (TG) at week 27

10.1.2 Secondary Endpoints

- Change from Baseline in AUC plasma glucose, serum insulin, serum C-peptide, free fatty acid, serum ghrelin, GIP, GLP-1, and PYY and incretin hormones in response to a mixed meal test (MMT)
- Change from Baseline in lipids and lipoproteins including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), non-HDL-C, apolipoprotein B (apoB), apolipoprotein B-48 (apoB-48), apolipoprotein B-100 (apoB-100), apolipoprotein A-1 (apoA-1), apolipoprotein C-III (apoC-III :total, chylomicron, VLDL, LDL and HDL), Lipoprotein a [Lp(a)], free fatty acids (FFA), and glycerol levels, lipoprotein particle size/number
- Change from Baseline in glycosylated hemoglobin (HbA1c)
- Change from Baseline in homeostasis model assessment-estimated insulin resistance (HOMA-IR)
- Change from Baseline in adiponectin and leptin
- Change from Baseline in hepatic fat fraction (as assessed by magnetic resonance imaging [MRI])
- Changes from Baseline in body fat distribution for various areas in the body as measured by skinfold thickness and DEXA; VAT and SAT as measured by MRI; body weight, waist circumference and waist/hip ratio
- Change from Baseline in quality of life and pain score

10.2 Sample Size Considerations

There is no statistical rationale for the selected sample size. The sample size is selected based upon prior experience with ISIS 703802 to ensure that the safety, tolerability and efficacy of ISIS 703802 can be explored in an ultra-rare condition before enrolling subjects in a larger study.

10.3 Populations

Safety Set: All subjects who are enrolled and receive at least 1 dose of Study Drug. PK Set: All subjects who receive at least 1 dose of Study Drug and have at least 1 evaluable PK sample.

10.4 Definition of Baseline

For fasting lipid measurements, the Baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

For other measurements, Baseline will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis and Early Stopping Guidelines

Since the study is open labeled no interim analysis will be performed to inform early stopping guidelines.

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.

All eCRF data, lab data, and any outcomes derived from the data will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

10.6.1 Demographic and Baseline Characteristics

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

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

10.6.2.1 Adverse Events

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

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

10.6.2.2 Clinical Laboratory Data

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, complement, etc., will be summarized by study visit. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug administration, as appropriate. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be listed.

10.6.2.3 Vital Signs and Examinations

Vital signs, weight, and ECG measures will be summarized by study visit.

10.6.3 Efficacy Analysis

Change at week 27 relative to Baseline will be summarized for:

- Fasting TG
- MTT (plasma glucose, serum insulin, serum C-peptide, FFA, serum ghrelin, GIP, GLP-1 and PYY)
- Glycosylated hemoglobin
- HOMA-IR
- 24-hr glucose
- Adiponectin and leptin
- HFF
- Fat distribution

10.6.4 Pharmacokinetic Analysis

The plasma PK of ISIS 703802 (as total full length oligonucleotides, including, fully conjugated, partially conjugated, and unconjugated ISIS 703802) will be assessed following multiple-dose SC administration. The plasma trough levels of ISIS 703802 during treatment period and those during post-treatment follow up period will be descriptively summarized with stratification by subject immunogenicity status if applicable.

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti- ISIS 703802 antibodies) before, during, and after treatment with ISIS 703802 will be listed. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed and study day.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Appendix A Schedule of Procedures

	Screening		Treatment Period								Follow-up Period		
	Diet Run-in[#]	Qual[†]											
Study Week	**-6 to -1**	**-1 to 0**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27/ET**	**4***	**8***	**13***
Study Day	**-42 to -1**	**-7 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	***Post Last Dose of Study Drug**		
Visit and Testing Window +/- Days	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**3**	**3**	**3**
Informed Consent	X												
Outpatient Visit	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 [a]	X		X	X		X				X	X		X
Body Weight and Height [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist and hip circumference	X									X			
DEXA Scan	X[d]					X				X			
12- lead ECG (triplicate)	X		X	X		X		X		X	X	X	X
Ultrasound	X												
Mixed Meal Test [c]		X				X				X			
MRI	X[d]					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
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

Appendix C PK Sampling Schedule

	Treatment Period								Follow-up Period		
Study Week	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**	**4***	**8***	**13***
Study Day	**D1**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	***Post Last Dose of Study Drug**		
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime

Note: D, Day

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

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 monkeys 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.

Appendix A Schedule of Procedures

	Screening		Treatment Period								Follow-up Period		
	Run-in[#]	Qual[†]											
Study Week	**-6 to -1**	**-1 to 0**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27/ET**	**4***	**8***	**13***
Study Day	**-42 to -1**	**-7 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	***Weeks from the end of treatment period[o]**		
Visit and Testing Window +/- Days	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**3**	**3**	**3**
Informed Consent	X												
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X	X										
Medical History	X												
Genetic Testing[p]	X												
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X
Physical Examination [a]	X		X	X		X				X	X		X
Body Weight and Height [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist and hip circumference	X									X			
DEXA Scan	X[d]					X				X			
12- lead ECG (triplicate)	X		X	X		X		X		X	X	X	X
Ultrasound	X												
Mixed Meal Test [c]		X				X				X			
MRI	X[d]					X				X			
24-Hour Urine for Creatinine Clearance and Protein[q]		X											
Extended Urinalysis [e]	X		EVERY 14 DAYS (+/- 2 days) [e, f]				X	X	X	X	X	X	X
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

Appendix C PK Sampling Schedule

	Treatment Period								Follow-up Period		
Study Week	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27**	**4***	**8***	**13***
Study Day	**D1**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	*** Weeks from the end of treatment period[1]**		
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime	Anytime	Anytime

Note: D, Day

1 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

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 F 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

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 monkeys 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

	the last dose of Study Drug administration. b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing 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 Study Drug administration. *Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception). Exclusion Criteria 1. A diagnosis of generalized lipodystrophy 2. A diagnosis of acquired partial lipodystrophy (APL) 3. Acute pancreatitis within 4 weeks of Screening 4. History within 6 months of Screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack, or unstable congestive heart failure requiring a change in medication 5. Major surgery within 3 months of Screening 6. History of heart failure with New York Heart Association functional classification (NYHA) greater than Class II 7. Uncontrolled hypertension (blood pressure [BP] > 160 mm Hg systolic and/or 100 mm Hg diastolic) 8. Clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion, including the following: a. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 1 g/24-hr b. Estimated GFR < 60 mL/min/1.73 m^2 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x ULN d. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL e. Alkaline phosphatase (ALP) > 1.5 X ULN f. Platelet count < LLN 9. Uncontrolled hyper- or hypothyroidism. Subjects on dose stable replacement therapy for at least 3 months prior to Screening will be allowed 10. History within 6 months of Screening of drug or alcohol abuse 11. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening

ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	End of Treatment
FFA	Free Fatty Acid
FHBL2	Familial combined hypolipidemia
FPG	Fasting Plasma Glucose
FPL	Familial Partial Lipodystrophy
FSH	follicle-stimulating hormone
g	gram
GalNAc	N-acetyl galactosamine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GIP	Gastric Inhibitory Polypeptide
GLP-1	Glucagon-like Peptide 1
HAV	hepatitis A virus
Hb	Hemoglobin
HBA1c	Glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
HDL	High Density Lipoprotein
HFF	Hepatic Fat Fraction
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	Homeostasis Model Assessment-estimated Insulin Resistance
HR	heart rate
hr, hrs	hour(s)
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
IgM	immunoglobulin M
IL-1β	interleukin-1 beta
IL-6	interleukin-6
INR	international normalized ratio
IRB	Institutional Review Board

Patients with FPL have both a partial loss and maldistribution of adipose tissue leading to their distinct phenotype. In many of these patients mutations in proteins involved in adipocyte differentiation, fatty acid uptake by adipocytes, triglyceride synthesis, or lipid droplet formation have been identified (Garg et al. 2011, Handelsman et al. 2013). Due to this severe dysfunction of adipose tissue FPL patients have much lower TG storage capacity than patients with hypertriglyceridemia without FPL, highlighting the importance of TGs in the pathophysiology of FPL. Plasma TG levels in FPL patients varied across studies from mean (25-75 percentile) 483 mg/dL (232, 856) (Diker-Cohen CE et al. 2015), median (25-75 percentile) 342 mg/dL (279, 801) (Akinci B et al. 2017), mean 383 mg/dL (Bidault G et al. 2013), median 389 mg/dL (155-3455) (Ahmad Z et al. 2013) and mean 1058 mg/dL (Ajluni N et al. 2016). It is estimated that 1/4 to 1/5 of patients with FPL may have TG levels > 500 mg/dL.

Due to inability of adipose tissue to accommodate excess TGs, TGs are deposited in higher amounts in organs other than adipose tissue that are less well adapted to excess lipid storage ("ectopic fat") (Garg et al. 2011, Handelsman et al. 2013; Robbins et al. 2015; Nolis 2014; Huang-Doran et al. 2010). This ectopic fat accumulation has been found in and around many organs and is most clearly associated with metabolic abnormalities in the liver, pancreas and skeletal muscle contributing to severe insulin resistance, hepatic steatosis, diabetes and hypertriglyceridemia and increased risk of pancreatitis, non-alcoholic steatohepatitis and cirrhosis (Robbins et al. 2015; Nolis 2014; Huang-Doran et al. 2010; Vatier et al. 2013; Sleigh A et al. 2012).

Careful clinical assessment of fat distribution through visual and physical examination can confirm the diagnosis. Patients with FPL have reduced subcutaneous fat in the limbs and truncal regions and may have excess subcutaneous fat deposition in neck, face and intra-abdominal regions. Patients with the Dunnigan variety have normal body fat distribution in childhood and gradually lose subcutaneous fat from the extremities and trunk around the time of puberty. In women, the loss of fat may be most striking in the buttocks and hips. At the same time these patients accumulate fat on the face ("double chin"), neck and upper back ("Cushingoid appearance with buffalo hump"). The extent of adipose tissue loss usually determines the severity of the metabolic abnormalities. Patients display prominent muscularity and phlebomegaly (enlarged veins) in the extremities and complain of disproportionate hyperphagia. The condition in females is more easily recognized than in men, and so is reported more often. Patients may also have a family history of similar physical appearance and/or fat loss.

Genetic testing, when available, is confirmatory. (Hegele et al. 2007; Huang-Doran et al. 2010; Garg et al. 2011).

Current treatment includes lifestyle modification such as reducing caloric intake and increasing energy expenditure via exercise. Conventional therapies used to treat severe insulin resistance (metformin, thiazolidinediones, Glucagon-like peptide 1s [GLP-1], insulin), and/or high TGs (dietary fat restriction, fibrates, fish oils) are not very efficacious in these patients (Chan and Oral 2010).

Familial Partial Lipodystrophy is an ultra-orphan indication for which there is a significant unmet medical need. Diabetes, hepatic steatosis, and hypertriglyceridemia associated with this condition can lead to serious complications (Handelsman et al. 2013) such as:

- Acute pancreatitis, especially when triglyceride levels are > 1,000 mg/dL
- Accelerated microvascular complications from uncontrolled diabetes
- Accelerated cardiovascular disease from lipid abnormalities and insulin resistance

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% and LDL-C by more than 30% in the Phase 1 study in healthy volunteers. The objective of this study is to assess the effect of TG lowering in FPL patients. 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 these patients. 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 FPL patients.

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.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2 open-label multiple-dose study of approximately 3 subjects with FPL that will be treated with ISIS 703802. Initially, 3 subject will be enrolled, but enrollment could be increased to 6 subjects, based on safety profile and efficacy observations.

Subjects will be evaluated for study eligibility during Screening and Qualification, which takes place up to 6 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 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 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 and DEXA scan will be obtained during Screening once all other eligibility criteria are met to assess liver fat content. MRI results must be available prior to registration and administration of the first dose of study drug.

Subjects meeting eligibility criteria at qualification will return to the clinic on Day 1 for their first dose of ISIS 703802 by subcutaneous (SC) injection. During the treatment period subjects will receive ISIS 703802 (20 mg) administered every week for 26 weeks.

Subjects will return regularly for outpatient visits throughout the treatment period according to the Schedule of Procedures (Appendix A). The primary safety and efficacy analysis time point is at Week 27.

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 schedule.

Subjects must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered screened into the Study and will be assigned a unique subject identification 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. The patient identification number must remain constant throughout the entire trial. Subject identification numbers, once assigned, will not be reused.

4.2 Registration

Subjects will be registered after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. Once a subject is registered for the study, they are considered enrolled into the study. No subject may begin treatment prior to assignment of a unique subject identification number nor confirmation of eligibility.

4.3 Replacement of Subjects

Due to the small number of subjects participating in the study, subjects who withdraw from the study may be replaced by allowing a new subject to be screened and enrolled. The subjects who withdrew for safety reasons will not be replaced.

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 42 days of treatment Day 1 or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at the time of informed consent
3. Clinical diagnosis of familial partial lipodystrophy plus diagnosis of type 2 diabetes mellitus and hypertriglyceridemia.

   Diagnosis of lipodystrophy is based on deficiency of subcutaneous body fat in a partial fashion assessed by physical examination and low skinfold thickness in anterior thigh by caliper measurement: men (≤ 10 mm) and women (≤ 22 mm), and at least 1 of the following:
   - Genetic diagnosis of familial PL (e.g., mutations in LMNA, PPAR-γ, AKT2, CIDEC, PLIN1 genes)

   OR

   - Family history of FPL or family history of abnormal and similar fat distribution plus 1 Minor Criteria

   OR

   - 2 Minor Criteria (In the absence of FPL-associated genetic variant or family history) and BMI< 35 kg/m^2

   MINOR Criteria

   a. Requirement for high doses of insulin, e.g., requiring ≥ 200 U/day, ≥ 2 U/kg/day, or currently taking U-500 insulin
   b. Presence of acanthosis nigricans on physical examination

measured again over the course of 300 minutes at 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 minutes. In addition, a validated visual analogue scale (VAS) will be used to measure the subject's perception of hunger.

6.2.6 MRI

An MRI to determine liver fat fraction will be done during Screening after all other eligibility criteria are met , and again at Week 13 and Week 27.

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

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 a 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.

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.

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. In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of

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 1 of the following: **AE Persists:** Subject terminates from the trial and the AE continues:

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

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

- **Persists (as non-serious AE):** Subject has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Subject recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **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. All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3. Any case of a platelet count reduction to levels below 50,000/mm^3 (Grade 3 or Grade 4) is considered an adverse event of

10.6.5 Pharmacodynamic Analysis

The following parameters will be measured throughout the trial and change at week 27 relative to Baseline will be summarized:

- ANGPTL3
- HDL-C
- LDL-C
- TC
- VLDL-C
- non-HDL-C
- apoB
- apoB-48
- apoB-100
- apoA-1
- apoC-III
- Lp(a)
- FFA
- Glycerol levels
- Lipoprotein particle size/number

10.6.6 Additional Analyses

Additional analyses may be performed not specified in this open label study protocol from the data available.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a 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 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

Appendix A Schedule of Procedures *Continued*

Visit and Testing Window +/- Days	0	0	0	2	2	2	3	3	3	0	3	3	3
Hematology	X		EVERY 14 DAYS (+/- 2 days) [f]								X[h]	X[h]	X[h]
Coagulation	X		X							X			
Hepatitis B, C, HIV	X												
Thyroid Panel	X												
Inflammatory			X			X				X			X
Liver Biomarkers			X			X				X			X
Plasma PK - ISIS 703802 [l]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	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
PD Panel [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
Quality of Life Assessment		X				X				X			
Widespread Pain Diary		X	TO BE DONE AT OUTPATIENT VISITS								X	X	X
Study Drug: SC Injection			WEEKLY SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 26/Day 176)										
Adverse Events	TO BE COLLECTED FROM TIME OF INFORMED CONSENT TO END OF FOLLOW-UP PERIOD												
Concomitant Medication	TO BE COLLECTED FROM TIME OF INFORMED CONSENT TO END OF FOLLOW-UP PERIOD												

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.

† Qual =Qualification

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

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

b Height only required at Screening

c Mixed Meal Test-refer to Appendix E for further details

d MRI and DEXA scan will only be performed after subjects have met initial screening eligibility. MRI and DEXA scan should be performed as close to anticipated Day 1 date as possible and to allow time for result reporting and analysis.

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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 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

Appendix A Schedule of Procedures *Continued*

	Screening		Treatment Period								Follow-up Period		
	Run-in[#]	Qual[†]											
Study Week	**-6 to -1**	**-1 to 0**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**27/ET**	**4***	**8***	**13***
Study Day	**-42 to -1**	**-7 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	***Weeks from the end of treatment period[o]**		
Visit and Testing Window +/- Days	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**0**	**3**	**3**	**3**
Hematology	X		EVERY 14 DAYS (+/- 2 days) [f]								X[h]	X[h]	X[h]
Coagulation	X		X							X			
Hepatitis B, C, HIV	X												
Thyroid Panel	X												
Inflammatory			X			X				X			X
Liver Biomarkers			X			X				X			X
Plasma PK - ISIS 703802 [l]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	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
PD Panel [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
Quality of Life Assessment		X				X				X			
Widespread Pain Diary		X	TO BE DONE AT OUTPATIENT VISITS								X	X	X
Study Drug: SC Injection			WEEKLY SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 26/Day 176)										
Adverse Events	TO BE COLLECTED FROM TIME OF INFORMED CONSENT TO END OF FOLLOW-UP PERIOD												
Concomitant Medication	TO BE COLLECTED FROM TIME OF INFORMED CONSENT TO END OF FOLLOW-UP PERIOD												

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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ISIS 703802-CS05: Administrative Clarification Letter 1 to Protocol Amendment 1

11 September 2018

RE: Protocol ISIS 703802-CS5: An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-LRx) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy, Protocol Amendment 1 dated 16 February 2018

Dear Investigators:

The following administrative clarifications are being issued for Protocol ISIS 703802-CS5 Amendment 1.

Administrative Clarification 1 – Section 6.2.1 Physical Exams and Vital Signs

Current Text:

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.

*Clarification: (new text indicated in **bold**)*

Physical exams, vital signs, **and skin fold measurements** 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. **Skinfold measurements will be recorded as per the Schedule of Procedures (Appendix A) starting at Day 1 Pre-dose. Skinfold measurements will be collected from each subject's right mid anterior thigh and right tricep.**

Rationale:

The secondary endpoints include "Changes from Baseline in body fat distribution for various areas in the body as measured by skinfold thickness and DEXA." The purpose of this clarification it to provide omitted details regarding the collection of skinfold measurements that were missing from Section 6: Study Procedures. This measurement will occur at every visit in which a physical exam (full or abbreviated) occurs.

Administrative Clarification 2 – Appendix A Schedule of Procedures – Skinfold Measurements

Current Text:

None.