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- Original Protocol, dated 09 Nov 2017
- Protocol Amendment No. 1, dated 16 Feb 2018
- Administrative Clarification Letter 1, dated 11 Sep 2018
- Administrative Clarification Letter 2, dated 02 Oct 2018
- Administrative Clarification Letter 3, dated 02 Jul 2019

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ISIS 703802-CS5

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Original Protocol – 09 November 2017

ISIS 703802-CS05

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Original Protocol – 09 November 2017

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ISIS 703802

Ionis Protocol Number ISIS 703802-CS05

Original Protocol

Clinical Phase: 2

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

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Date: 09 NOVEMBER 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 703802-CS05
Protocol Title:	**An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy**
Amendment:	Original Protocol
Date:	09 November 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy" dated 09 November 2017, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

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

_____

Investigator's Signature

_____ _____

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

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PROTOCOL SYNOPSIS

Protocol Title	An Open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy
Study Phase	2
Indication	Familial Partial Lipodystrophy (FPL)
Primary Objective	To assess the effect of ISIS 703802 on reduction in fasting triglycerides (TG).
Secondary Objectives	To evaluate the safety and tolerability of ISIS 703802 To evaluate the effect of ISIS 703802 on changes from Baseline to end of treatment on: • Plasma glucose, serum insulin, serum C-peptide and free fatty acid (FFA) in responses to a mixed meal test (MMT) • Lipids, lipoproteins and lipid metabolism • Glycosylated hemoglobin (HbA1c) • Liver fat and body fat distribution • Quality of life and pain score To evaluate pharmacokinetics (PK) of ISIS 703802
Study Design	This is a single-center, open-label study. The study will comprise the following periods: **Screening period**: Up to 6 weeks (including an up to 4 week run-in diet period) **Treatment Period**: 26 weeks **Post-treatment Follow-up Period**: 13 weeks The primary safety and efficacy analysis time point is at Week 27.
Number of Subjects	Approximately 3
Study Population	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 <u>MINOR Criteria</u>

	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 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

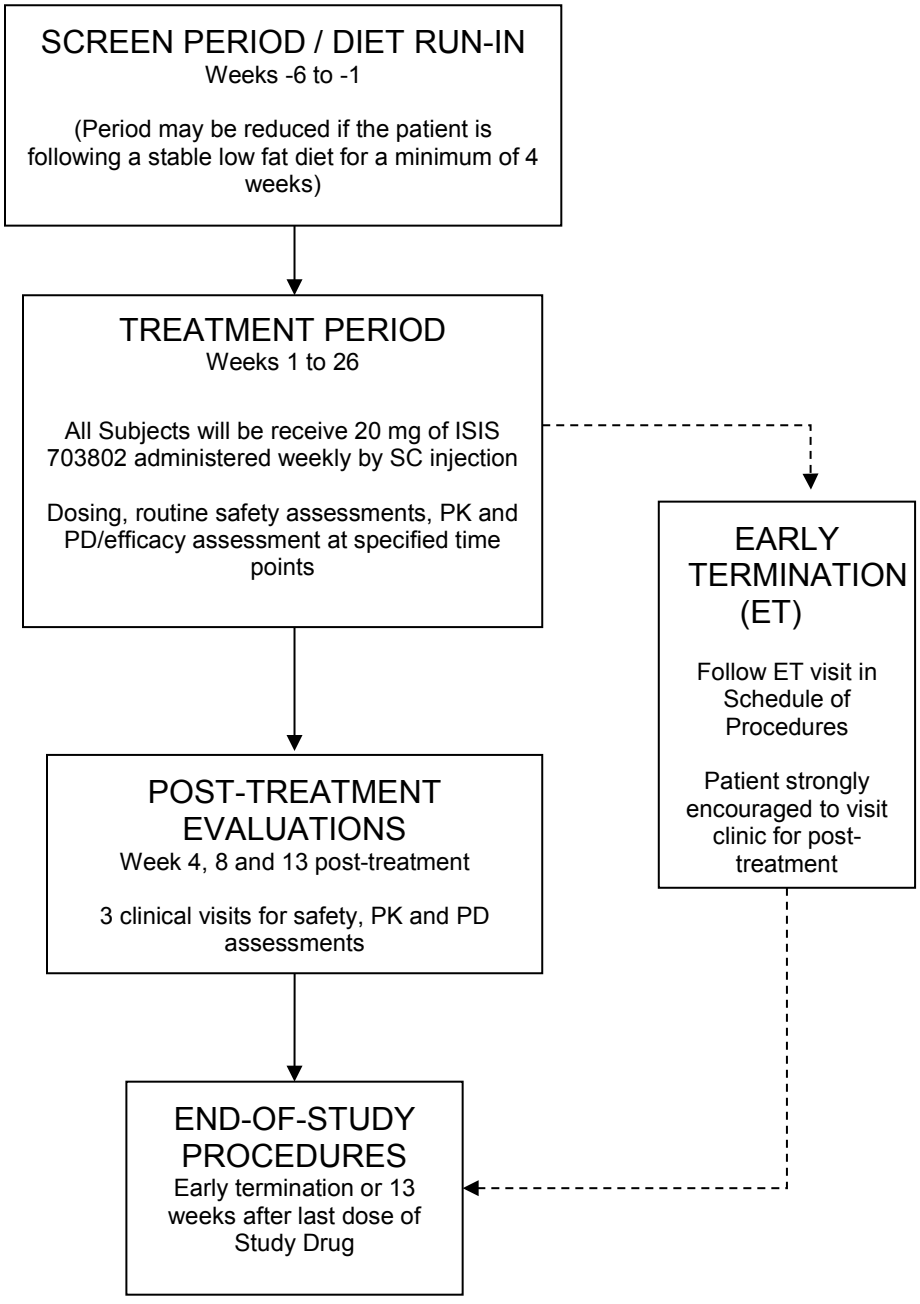
	utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug administration. *Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual 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 or unstable congestive cardiac failure requiring a change in medication 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 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance 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 12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 14. Malignancy within 5 years, except for basal or squamous cell

	carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer 16. Unwilling to comply with lifestyle requirements (see Section 6.3) 17. Use of any of the following: a. Metreleptin within the last 3 months prior to Screening b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to Screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to Screening are also eligible c. Insulin unless on a stable daily basal insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Screening f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor Medical Monitor g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Screening and dose and regimen expected to remain constant throughout the study i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), and lorcaserin (Belviq), phentermine, amphetamines, herbal preparations] within 12 weeks prior to Screening (except liraglutide [rDNA origin] injection (Saxenda) if on stable therapy for more than 6 weeks prior to Screening). k. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 19. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Groups	Single Group, open-label treatment with 20 mg of ISIS 703802 SC weekly
Study Drug Dosage and Administration	The Sponsor will provide ISIS 703802 in a single vial with a concentration of 100 mg/mL 20 mg every week of ISIS 703802 (0.2 mL). The study dose of 20 mg (0.2 mL) of ISIS 703802 will be administered every week during the treatment period for a total of 26 weekly doses. All doses will be given by SC injection. Self-administration will be allowed

	after appropriate training of subject and/or caregiver.
Rationale for Dose and Schedule Selection	A 20 mg weekly dose was selected as being the lowest dose that provided maximum TG lowering of approximately 60%, based on the TG lowering effect of ISIS 703802 observed in healthy volunteers with elevated TGs.
Adjustment of Dose or Treatment Schedule	Dose adjustments, including dose interruptions, and/or decreasing the dose and dose frequency may be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures are outlined in Section 6, Appendices A and C. The study for an individual subject will generally consist of the following periods: • An up to 6-week Screening period, including a 4-week diet stabilization phase for subjects not already on a stable diet • A 26-week treatment period during which Study Drug will be administered weekly by SC injection • A 13-week post-treatment follow-up period During the Screening period, subject will be advised to maintain diet and exercise routines, and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening period, subjects may have 4 weeks of diet run-in and final eligibility will be determined during qualification. 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. TGs will be measured and MRI will be obtained to assess liver fat content. For subjects who are already on a stable diet and are known to the site, the diet stabilization period can be omitted and subject can move directly to qualification. Subjects meeting eligibility criteria at Screening and having a qualifying MRI, defined as having at least 6.4% liver fat assessed by MRI-PDFF (via central reviewer) will return to the clinic on Day 1. In addition, TG will be measured at qualification and results of TG and MRI must be available prior to registration and administration of the first dose of study drug. Blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B shows a list of analytes required for the study and Appendix C details the PK sample schedules. The Mixed Meal Test (MMT) 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 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.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: AEs, vital signs and weight, physical examinations, clinical laboratory tests, ECGs, use of concomitant medications.

Efficacy Evaluations	**Primary Endpoint:** • The effect of ISIS 703802 on the percent change from Baseline in fasting triglyceride levels (TG) at week 27 **Secondary Endpoints:** • Change from Baseline in AUC plasma glucose, serum insulin, serum C-peptide, free fatty acid, serum ghrelin, GIP, GLP-1, and PYY 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 dual-energy X-ray absorptiometry (DEXA); visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) as measured by MRI; body weight, waist circumference and waist/hip ratio • Changes from Baseline in quality of life and pain score
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 703802 trough levels throughout treatment and levels during the post-treatment Follow-up period. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Pharmacodynamic Evaluations	Plasma angiopoietin-like 3 (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
Statistical Considerations	There is no statistical rationale for the selected sample size.
Sponsor/Collaborator	Ionis Pharmaceuticals, Inc./ Akcea Therapeutics, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
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
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
ISIS 703802	antisense inhibitor of ANGPTL3
IV	Intravenous(ly)
kg	kilogram
L	liter
LDL-C	Low Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
m^2	square meter
MAD	multiple ascending dose
MB	Major Bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
mm	millimeter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

MMT	Mixed Meal Test
MTD	maximum tolerated dose
NAFLD	Nonalcoholic Fatty Liver Disease
NEFA	Non-esterified Fatty Acids
NOAEL	No Adverse Effect Level
NCS	not clinically significant
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
on study	The *insert* [subject] *or* [patient] is 'on study' from signing of the informed consent until their last study visit
OAD	Oral Antidiabetic Drugs
OTC	Over the Counter
PCOS	Polycystic OvarySyndrome
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLT	Platelet
pRBC	packed red blood cells
PT	prothrombin time
PYY	Peptide Tyrosine Tyrosine
RBC	Red Blood Cells
REMS	Risk Evaluation ad Mitigation Strategy
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAT	Subcutaneous Adipose Tissue
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
SMBG	Self Monitored Blood Glucose
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 703802

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TG	Triglycerides
T_{max}	time to maximal concentration
TNF-α	tumor necrosis factor-alpha
T2DM	Type 2 Diabetes
ULN	upper limit of normal
UACR	Urine albumin/creatinine ratio
UPCR	Urine Protein Creatinine Ratio
VAT	Visceral Adipose Tissue
VLDL	Very Low Density Lipoprotein
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to assess the effect of ISIS 703802 on reduction in fasting triglycerides (TG).

1.2 Secondary Objective(s)

The secondary objectives are:

- To evaluate the safety and tolerability of ISIS 703802
- To evaluate the effect of ISIS 703802 on changes from Baseline to end of treatment on:
  - Plasma glucose, serum insulin, serum C-peptide and free fatty acid (FFA) in responses to a mixed meal test (MMT)
  - Lipids, lipoproteins and lipid metabolism
  - Glycosylated hemoglobin (HbA1c)
  - Liver fat and body fat distribution
  - Quality of life and pain score
- To evaluate pharmacokinetics (PK) of ISIS 703802.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Lipodystrophy syndromes are a group of rare metabolic diseases characterized by selective loss of adipose tissue that leads to ectopic fat deposition in liver and muscle and the development of insulin resistance, diabetes, dyslipidemia and fatty liver disease (Garg 2004; Chan and Oral 2010; Garg et al. 2011; Shulman et al. 2014).

These syndromes are categorized according to the distribution of fat loss into generalized or partial and according to the underlying etiology as inherited or acquired (Garg 2004; Chan and Oral 2010; Garg et al. 2011).

These syndromes constitute a significant medical unmet need as these patients are refractory to current therapies, mainly used to treat diabetes and elevated TG levels, in an attempt to reduce the risk of serious associated complications (coronary artery disease, diabetic nephropathy, cirrhosis and pancreatitis).

As such, in February 2014, the FDA approved Myalept (metreleptin) as replacement therapy to treat the complications of leptin deficiency in addition to diet in patients with congenital or acquired generalized lipodystrophy. The safety and effectiveness of Myalept was evaluated in 2 open-label studies conducted at the NIH, which included 72 patients (48 with generalized lipodystrophy and 24 with partial lipodystrophy [PL]) with diabetes, high TG, and elevated levels of fasting insulin. The best results were achieved in patients with generalized lipodystrophy who had low leptin levels (mean [SD]: 1.3 [1.1] ng/mL), while patients with

partial lipodystrophy who had a wider range of baseline leptin values (mean [SD]: 4.9 [3.1] ng/mL) had a more varied and attenuated response. Because of the risks associated with the development of neutralizing antibodies and lymphoma, Myalept is available only through a risk 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 PPARg 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; Ahmed 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).

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) (Ahmed 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-Doram 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-Doram 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-Doram 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
- Steatohepatitis that can progress to cirrhosis and an increased risk of hepatocellular carcinoma
- Proteinuric nephropathies which can progress to end stage renal disease

In patients with Generalized Lipodystrophy the metabolic complications are partially related to leptin deficiency, and can be ameliorated in part by leptin replacement. However, leptin deficiency alone cannot explain the severity of metabolic disease in patients with PL who have variable leptin levels.

By reducing ANGPTL3 and TG levels, ISIS 703802 may improve the metabolic profile of patients with FPL and reduce their risk of acute pancreatitis. In addition, reductions in TG could improve hepatic steatosis and reduce cirrhosis risk. Furthermore, this mechanism may also improve insulin sensitivity in these patients and potentially lead to a reduction in the complications associated with diabetes.

2.2 Therapeutic Rationale

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

ANGPTL3 protein is produced exclusively in liver, where its expression is downregulated by leptin and insulin (Inukai et al. 2004). Hepatic specific knock-down of ANGPTL3 mRNA is associated with reduction in plasma triglycerides due to increased lipoprotein lipase activity as well as decreased hepatic VLDL triglyceride secretion. Because ANGPTL3 is produced by the liver only, which does not express LPL, it is thought to function as an endocrine rather than paracrine factor with insulin sensitizing effects that go beyond the liver. In fact, insulin sensitization has been shown in patients with ANGPTL3 gene mutations as well as in ANGPTL3-deficient mice, in which increased uptake of fatty acids into oxidative tissues such as

muscle and brown adipose tissue led to decreased uptake of fatty acids and increased uptake of glucose in white adipose tissue (Wang et al. 2015). Suppression of hepatic ANGPTL3 protein production in mice resulted in significant reductions in levels of triglycerides, LDL cholesterol, non-HDL cholesterol, and VLDL cholesterol and these favorable effects were associated with decreased liver triglyceride content, increases in insulin sensitivity, and a reduction in atherosclerosis progression (Graham et al. 2017).

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

2.3 ISIS 703802

2.3.1 Mechanism of Action

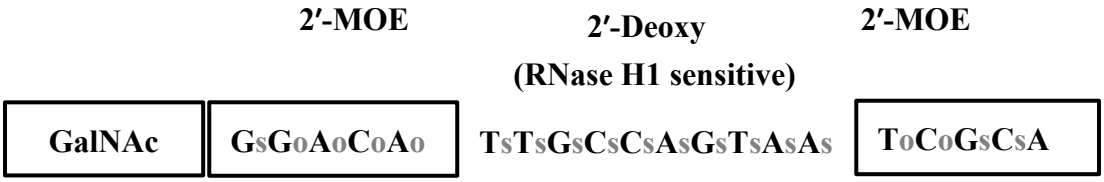
ISIS 703802 is a second-generation ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach results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

2.3.2 Chemistry

Chemically, ISIS 703802 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed backbone design reduces the total number of phosphorothioate linkages in the MOE-modified regions, which reduces non-specific interactions with proteins and further enhances potency of GalNAc conjugated ASOs. The nucleotide sequence of ISIS 703802 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 6 of the ANGPTL3 mRNA coding sequence at position 1169-1188 bp.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first

generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 703802 employs this chimeric structure to enable use of the RNase H1 mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition. The fourth region is comprised of a triantennary cluster of *N*-acetyl galactosamine (GalNAc) sugars which is linked to the 5′ end of ISIS 703802 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the asialoglycoprotein receptor (ASGPR), a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc cluster enhances delivery of ISIS 703802 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release 'free ASO' inside the cell (Prakash et al. 2014).



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

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

2.3.3 Preclinical Experience

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

2.3.3.1 Preclinical Pharmacology

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

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

Reductions in murine ANGPTL3 mRNA and protein were routinely observed in all mouse models treated with a murine-specific ANGPTL3 ASO. Pharmacology studies were done with *Ldlr*$^{-/-}$ mice fed a hypercholesterolemic diet known to develop elevated LDL-C, TG, and atherosclerosis, as well as features of metabolic syndrome (hyperglycemia and hyperinsulinemia) (Huszar et al. 2000; Schreyer et al. 2002; Tsuchiya et al. 2012). Treatment of mice with a murine-specific ANGPTL3 ASO resulted in improvement in all of the aforementioned lipid and metabolic endpoints compared to controls. In all mouse models tested, total plasma cholesterol, LDL-C, TG, and non-esterified fatty acids (NEFA) have been shown to be consistently reduced upon treatment with ANGPTL3 ASOs, while HDL-C is modestly decreased in wild type mice (- 22%), and either stable or increased in others. While a clear mechanistic understanding of HDL-C reductions has not been elucidated, results from *in vitro* reverse cholesterol transport assays suggest that HDL function is maintained.

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

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

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

2.3.3.2 Preclinical Toxicology

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

Pharmacokinetic data confirmed continuous and dose-dependent exposure to ISIS 703802. An estimated liver and plasma terminal elimination half-life values of approximately 1 week and 3-4 weeks for 2 mg/kg and 35 mg/kg, respectively, were observed in monkeys. The most

noteworthy findings observed in mice and monkeys following ISIS 703802 treatment were, in general, non-specific class effects related to the uptake and accumulation of ASO and no toxicologically relevant findings were considered related to the pharmacologic inhibition of hepatic ANGPTL3 expression, either with the present series of studies or with the former development candidate targeting ANGPTL3. There were no test-article related changes in PLT count in either mouse or monkey in both sub-chronic and chronic studies.

The most noteworthy finding in the monkey was the kidney alteration (hypoalbuminemia and proteinuria) seen in one early-sacrifice animal from the 16-week study at 35 mg/kg/week, a dose equivalent to at least ~190-fold of the 40 mg weekly clinical doses by plasma AUC. Non-dose dependent increases in renal protein excretion (up to 2.2-fold in quantitative urine protein, protein/creatinine ratio or urine albumin) were also observed at 8 and/or 35 mg/kg/week (> ~30 to 190-fold of the 40 mg weekly clinical doses by plasma AUC) at the 16-week scheduled terminal necropsy. However, Similar kidney alterations were not seen at the 6-week interim at any doses or in the 39-week chronic monkey study up to 12 mg/kg/week (> ~200-fold of the 20 mg weekly clinical dose by plasma AUC).

Additional findings related to ASO liver accumulation included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) at ≥ 8 mg/kg/week in the 16- and 26-week mouse studies, and were correlated with individual hepatocyte necrosis (minimal to mild) in mouse liver. Those changes were most prominent in the high dose groups (50 and 24 mg/kg/week for the 16- and 26-week studies, respectively). Conversely, no changes in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week. In the 16-week 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

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 approximately dose proportionally. No accumulation based on C_{max} or AUC was observed after 6 weekly doses.

2.3.4.1 ISIS 563580-CS1 Phase 1 SAD/MAD

In a Phase 1 study, ISIS 563580-CS1, healthy volunteers received subcutaneous administration of ISIS 563580, an unconjugated 2′-MOE modified ASO that has the same base sequence as ISIS 703802, from 50 to 400 mg as a single dose, or 100 to 400 mg as multiple doses (8 doses in 36 days). Overall, the safety findings from this study suggest that ISIS 563580 was not associated with any safety concerns. There were 383 adverse events (AE) reported in the ISIS 563580-treated subjects of which 363 (95%) were mild in severity. For the multiple-dose subjects, the most common treatment-emergent adverse events were AEs at the injection site. There was 1 serious adverse event (SAE) in the study of periorbital cellulitis which was considered a medically important event by the Investigator and was also considered unlikely related to Study Drug by the Investigator. Together, the above suggest that ISIS 563580 was well-tolerated at the doses and regimen given, which exceed the dose levels and cumulative exposures to be tested in

the current study. There were no clinically-relevant changes in laboratory assessments and the heparin dose of 80 U/kg was well-tolerated in support of the post-heparin procedures. ISIS 563580 produced dose-dependent reductions in plasma ANGPTL3 (up to 93%; group means up to 84%), TG (up to 63%; group means up to 49%) and TC (up to 46%; group means up to 28%) at Day 36 (Brandt et al. 2015).

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 703802 doses of 10 mg, 20 mg, 40 mg and 60 mg given weekly for 6 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in lipid biomarkers. The dose proposed for the present study will provide the equivalent drug exposure of 20 mg weekly (80 mg monthly) and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from Baseline in TGs of approximately 63% at steady-state.

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

In healthy volunteers, 703802 achieved an equivalent reduction in ANGPTL3 plasma concentration to that of the unconjugated form, at approximately $1/10^{th}$ of the unconjugated ASO (ISIS 563580) dose (Brandt et al. 2015).

2.5 Benefit-Risk Assessment

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

2.5.2 Risk Assessment

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

- In preclinical mouse studies, there were increases in ALT and AST and were correlated with increased incidence and/or severity of necrosis of individual hepatocytes (minimal to mild in severity). Those changes were most prominent in the high dose groups and showed no clear progression over time. No increases in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week (~200-fold of the 20 mg/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 2ꞌ-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 2ꞌ-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 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 exercise routines, and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening period, following 4 weeks of diet run-in, subjects will have a qualification visit and final eligibility assessments will be performed. Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet run-in. At the qualification visit TGs will be measured to qualify and MRI will be obtained 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.

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 5-week screening period, that includes a 4-week diet stabilization / run-in period, a 1-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 subjects will have a baseline DEXA scan and MRI will be obtained to assess liver fat content. 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 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.

Subjects must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled 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. No subject may begin treatment prior to assignment of a unique subject identification number.

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

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

g. Presence of acanthosis nigricans on physical examination

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

i. History of pancreatitis associated with hypertriglyceridemia

j. 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:
     d. Metformin ≥ 1500 mg/day, or
     e. 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
     f. 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 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).

5.2 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 or unstable congestive cardiac failure requiring a change in medication
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 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance
   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
12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Unwilling to comply with lifestyle requirements (see Section 6.3)
17. Use of any of the following:
    a. Metreleptin within the last 3 months prior to Screening
    b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to Screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to Screening are also eligible
    c. Insulin unless on a stable daily basal insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing
    d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis
    e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Screening
    f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor Medical Monitor
    g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Screening and dose and regimen expected to remain constant throughout the study
    i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed
    j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), and lorcaserin (Belviq), phentermine, amphetamines, herbal preparations] within 12 weeks prior to Screening (except liraglutide [rDNA origin] injection (Saxenda) if on stable therapy for more than 6 weeks prior to Screening).

k. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)

18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
19. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

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

All required study procedures are outlined in Appendix A.

6.1.1 Screening/Qualification

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

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

As part of the screening period, subjects not already on a stable diet will have 4 weeks of diet run-in, followed by a qualification visit, during which final eligibility assessments will be performed. Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet run-in. At the qualification visit TGs will be measured and MRI will be obtained to assess liver fat content. MRI results must be available prior to registration and administration of the first dose of study drug.

6.1.2 Treatment Period

Subjects will be managed on an outpatient basis. Safety and clinical laboratory evaluations as well as blood sampling for PK analysis will be performed periodically throughout the treatment period. Any AEs and concomitant medications will be recorded.

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 703802 plasma concentrations, immunogenicity, MRI, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A.

6.1.4 Post-Treatment Period

Each subject will be followed for safety assessments for 13 weeks after the last dose of Study Drug. 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 sent to the central laboratory are received on the next day and processed. Lab Alerts issued as per protocol safety monitoring requirements or stopping rules will indicate the applicable protocol section to facilitate review and will be immediately and simultaneously sent by email to the Investigator, the Sponsor and the CRO Medical Monitors, the Sponsor Drug Safety Physician, and the Clinical Trial Manager (CTM), and should be received by them within 2 days from sample collection. Hematology results from the site's local laboratories are received by the study center staff on the day of sample collection, and should be entered as soon as possible into the eCRF to inform the Sponsor and CRO study monitoring teams.

All platelet count results must be reviewed promptly (within 48 hours of receipt) by the Investigator, or designee, to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the 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 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 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 at Qualification, 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

For female subjects and female partners of male subjects:

- Using 2 of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any

2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository

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

***Note:** **A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.**

6.3.2 Other Requirements

All subjects will be required to fast for at least 10 hours before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 ISIS 703802

Study Drug (ISIS 703802) characteristics are listed in Table 1.

Study Drug (ISIS 703802) will be provided as 0.8 mL deliverable volume in 2 mL stoppered and sealed glass vials as a sterile solution.

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

Table 1 Study Drug Characteristics

Study Drug	ISIS 703802
Strength	100 mg/ mL
Volume/Formulation	0.8 mL/vial
Route of Administration	SC*

* SC = subcutaneous

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 703802) supplies provided by the Sponsor. The subject must return all used and unused Study Drug to the Study Center for accountability. The Study Center must return all used and unused Study Drug to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

Vials are for single use only. Study staff will administer the first dose of Study Drug. Doses will be administered by SC injection, patients or their caregivers may self-administer the study drug following the training given by the study center staff.

Subjects will receive treatment weekly with weeks always defined relative to Study Day 1. For example if a subject receives the first dose on a Monday, subsequent doses should be given on Mondays according to the respective dosing schedule, if possible. If a subject misses an injection, or if dosing on the usual day is not possible, the subject can reschedule the injection provided that 2 doses are administered at least 2 days apart.

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

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

Table 2 Study Drug Dosing Information

Volume to Administer*	Total Dose*
0.20 mL	20 mg (open label)

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

Subjects will continue their lipid-lowering therapy on a stable regimen from the signing of informed consent at Screening through the end of the post-treatment evaluation period.

8.3 Other Protocol-Required Treatment Procedures

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

8.4 Treatment Precautions

No specific treatment precautions are required.

8.5 Safety Monitoring Rules

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

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

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

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

Confirmation Guidance: At any time during the Study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens prior to administering the next dose of Study Drug. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

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

In the event of an initial clinical laboratory result that meets a stopping criterion, subjects must not be re-dosed until a confirmatory test result has been reviewed by the Study Medical Monitor. If any of the stopping criteria described below are met and are confirmed, the subject will be permanently discontinued from further treatment with Study Drug (ISIS 703802), evaluated fully as outlined below and in consultation with the Study Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Study Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate.

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

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the FDA guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009 and adopted to meet the requirements of this protocol and compound to ensure safety of the subjects.

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

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

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

Subjects with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR] and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.5 x ULN.

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

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

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (hepatitis A virus [HAV] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, Cytomegalovirus [CMV] IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

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

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

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

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

8.5.2 Safety Monitoring for Renal Function

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

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

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

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

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

Lab alerts for abnormal renal tests will be issued for: Creatinine clearance (by CKD-EPI formula) decrease from Baseline > 25%, urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or an increase in serum creatinine from Baseline > 0.3 mg/dL).

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

In the event of a confirmed laboratory result meeting one or more of the above criteria, the following supplemental renal tests should be immediately obtained:

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

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

8.5.3 Safety Monitoring Rules for Platelet Count Results

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

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

Any case of a platelet count reduction to levels below 50,000/mm^3 (Grade 3 or Grade 4) is considered an adverse event of special interest and should be reported in an expedited fashion to the Sponsor.

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

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

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

8.5.4 Safety Monitoring for Bleeding Events

Subjects will be evaluated for occurrence of bleeding events continuously after the start of Study Drug treatment (Day 1). Patients will be instructed to promptly report any signs or symptoms of bleeding. Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, or gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, hepatic enzymes, bilirubin and platelet count may be performed.

8.5.5 Safety Monitoring for Constitutional Symptoms

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

8.5.6 Safety Monitoring for Hypoglycemia

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

take immediate action to confirm the subject's glucose level and treat the subject accordingly. Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

Classification of Hypoglycemia

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

Severe Hypoglycemia

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

Documented Symptomatic Hypoglycemia

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

Asymptomatic Hypoglycemia

Not accompanied by typical hypoglycemia symptoms but with measured plasma glucose

≤ 70 mg/dL (≤ 3.9 mmol/L).

Probable Symptomatic Hypoglycemia

Typical hypoglycemia symptoms not accompanied by plasma glucose determination but likely caused by plasma 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 plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

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

8.5.7 Safety Monitoring for Documented Hyperglycemia

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

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

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

- FPG > 270 mg/dL (15.0 mmol/L)

From Week 13 to Week 25/27/ET (including value at Week 25/27/ET) of Randomized Treatment period:

- FPG > 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 FPG/HbA1c above the threshold values, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition
- 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 FPG/HbA1c under the threshold values, rescue medication may be introduced at the Investigator discretion and according to local guidelines.

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

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

8.6 Stopping Rules

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

8.6.1 Stopping Rules for Liver Chemistry Elevations

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

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation**.**

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

8.6.2 Stopping Rules for Renal Function Test Results / Temporary Stopping Rules for Renal Function Test Results

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

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

Dosing of a patient with Study Drug (ISIS 703802) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

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

Irrespective of whether the stopping rule is confirmed or not, the follow-up schedule and frequency of renal function monitoring after the initial event will be determined by the Study Medical Monitor in consultation with the Investigator. The Investigator should consider consulting a local nephrologist for any change of renal function that presents a concern. If a renal biopsy is performed, a sample specimen should be made available for examination by an independent renal pathologist who has been engaged by the Sponsor to review such specimens.

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

8.6.3 Stopping Rule for Platelet Count Results

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

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

Administration of steroids is recommended for subjects whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count < 75,000/mm^3 and > 50,000/mm^3, dosing of a subject with Study Drug should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued, it must be at a reduced dose as shown in Table 1. The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the subject's platelet count, whether any bleeding events were experienced by the subject, and the speed of recovery of platelet count after interruption of dosing.

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

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

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

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

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

Definitions:

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

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 20 g/L (1.24 mmol/L) or more within 24 hours

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

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

Table 3 Actions in Patients with Low Platelet Count

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

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

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

8.7 Adjustment of Dose and/or Treatment Schedule

Dose frequency adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

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

Subjects may have their dose interrupted in response to AEs in consultation with Study Medical Monitor**.**

8.8 Discontinuation of Study Drug/Treatment

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an adverse event (AE) that necessitates permanent discontinuation of Study Drug
- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.3
- When a platelet count of less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 while the patient is on a reduced dose.

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

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

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

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

Any subject who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in Table 3, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 13 weeks after discontinuing Study Drug. If the subject declines or is unable to participate in the above, the early termination visit procedures should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug. In addition, 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.

8.9 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.

Allowed Concomitant Therapy

Ibuprofen may be used for symptomatic pain relief. Any other therapy (including OTC medications) should be approved by the Sponsor Medical Monitor or designee. Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

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 such cases, 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 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. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be 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

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 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.

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 the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

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

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of SAEs occurring at the

Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, subjects should be identified by initials (if permitted by local law) and a subject identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3 Study Documentation and Storage

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

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

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. Case report form entries may be considered source data if the case report form is the site of the original recording (i.e., there is no other written or electronic record of data).

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

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

12.4 Study Monitoring

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

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on subject data received by the Sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

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

12.5 Language

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

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

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 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 A Schedule of Procedures *Continued*

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

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

g Urine samples for renal biomarkers will be collected. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values are taken every 14 days (+/- 2 days) for 6 weeks after last dose of Study Drug, then at Week 8 and Week 13 Follow-up visits.

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

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

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

l Refer to Appendix C for PK Sampling schedule.

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

n Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until completion of the final study report.

Time (time is in reference to Study Drug administration):
1 Pre-dose

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

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

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

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

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

Extended Lipid Panel
- Total Cholesterol (TC)
- LDL cholesterol (LDL-C)
- HDL cholesterol (HDL-C)
- Triglycerides (TG)
- VLDL cholesterol (VLDL-C)
- Non-HDL cholesterol (Non-HDL-C)
- Lp(a)
- FFA
- ApoB
- ApoB-48
- ApoB-100
- Apo A-1
- ApoCIII (total, chylomicron, LDL, HDL, VLDL)
- Delipidated Free Glycerol
- Ceramides
- Sphingolipids
- Diacylglycerol
- Lipoprotein particle analysis

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

Pharmacokinetics[1]
- ISIS 703802 levels in plasma

Immunogenicity
- Anti-ISIS 703802 antibodies

Liver Biomarkers (Biomarkers of liver apoptosis and fibrosis)
- CK18
- PIIINP

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

Genetic Testing
- Genetic sequencing of FPL causing genes[3]

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

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

Mixed Meal Test
- Plasma glucose
- FFA
- C-peptide
- Insulin
- Serum ghrelin
- GIP
- GLP-1
- PYY
- Incretin hormones

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 703802 with plasma constituents

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

3 Blood will be collected to assess genetic evidence of FPL (e.g., mutations in LMNA, PPAR-γ, AKT2, CIDEC, PLIN1 genes). May not be collected if adequate genetic data are available in medical history or if patient does not consent to genetic testing

Appendix C PK Sampling Schedule

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

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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

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

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

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

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

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

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

Appendix E Mixed Meal Test

Appendix E Mixed Meal Test

At Baseline, 3 months and end of study, subjects enrolled will undergo a meal tolerance test (MTT) as follows: subjects will consume a standardized meal the evening before the test (750 kcal; 20% of energy from protein, 30% from fat, and 50% from carbohydrate) and refrain from consuming alcohol for 72 h.

A cannula will be inserted into a forearm vein, and an overnight fasting venous blood sample will be taken between 8:00 AM and 10:00 AM for measurement of plasma glucose, FFA, C-peptide and insulin concentrations and serum ghrelin, GIP, GLP-1, and PYY. Incretin hormones will be measured using a multiplex assay (EMD Millipore, Billerica, MA). The tubes for the incretin hormones will contain Pefabloc SC (Sigma-Aldrich, St. Louis, MO) and DPP-IV inhibitor (EMD Millipore, Billerica, MA) to inhibit DPP-IV and other proteases. The change in ratings from Baseline will be quantified.

Subjects will then consume a liquid load of Optifast (Optifast; Novartis, Minneapolis, MN; 474 ml, 320 kcal, 50% carbohydrate, 35% protein, 15% fat) within a 15-min period. Additional blood samples will be taken at 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min after meal consumption. VAS will be completed at 180 minutes and 300 min. To calculate the insulin sensitivity index (S_I), the oral minimal model for glucose will be used; and to calculate the hepatic insulin extraction, oral minimal model for insulin and c-peptide will be used [Cobelli et al, 2007; Cobelli et al, 2005]. Subjects will complete a validated visual analogue scale (VAS) questionnaire to assess subjective hunger at 0, 180 and 300 minutes [Luscombe-Marsh et al, 2005; Moran et al, 2005].

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

Collaborator:
Ionis Pharmaceuticals, Inc.
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Carlsbad, CA 92010

ISIS 703802-CS5

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Amendment 1 – 16 February 2018

ISIS 703802-CS5

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Amendment 1 – 16 February 2018

Protocol History

Original Protocol 09 November 2017

Protocol Amendment 1 16 February 2018

[redacted] –

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ISIS 703802

Protocol Number ISIS 703802-CS5

Amendment 1

Clinical Phase: 2

An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

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Date: 16 February 2018

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 703802-CS5
Protocol Title:	**An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy**
Amendment:	Amendment 1
Date:	16 February 2018

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy" dated 16 February 2018, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

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

Investigator's Signature

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

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PROTOCOL AMENDMENT

Protocol Number: ISIS 703802-CS5

Protocol Title: An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Amendment Number: Protocol Amendment 1

Amendment Date: 16 February 2018

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 703802-CS5 Original Protocol dated 09 November 2017 intended to clarify inconsistencies, make some administrative updates and add an appendix. The following administrative updates have been made: Akcea Therapeutics, Inc. now appears as the Sponsor and Ionis Pharmaceuticals, Inc. now appears as the Collaborator; ISIS 703802-CS05 is being updated to ISIS 703802-CS5. In addition, the reference list has been updated. The tables being updated are not shown in this summary of changes. Finally, minor updates noted as inconsistencies have been made throughout the document. Note that language in the *Was* section that is being deleted appears as strikethrough and new language in the *Update* section appears as bold:

1. **Synopsis and Section 5.2 *Exclusion Criteria* number 6**

Was:

6. History of heart failure with New York Heart Association functional classification (NYHA) greater than Class II ~~or unstable congestive cardiac failure requiring a change in medication~~

Update:

6. History of heart failure with New York Heart Association functional classification (NYHA) greater than Class II

Rationale:

The portion of exclusion criterion 6 that is being deleted is covered in exclusion criterion 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

2. **The following changes have been made to several sections with respect to MRI and DEXA scan**

Synopsis sections Study Visit Schedule and Procedures

Was:

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. TGs will be measured ~~and~~. MRI will be obtained to assess

liver fat content. ~~For subjects who are already on a stable diet and are known to the site, the diet stabilization period can be omitted and subject can move directly to qualification.~~

Update:

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.

Section 3.1 *Study Design* end of paragraph two

Was:

At the qualification visit TGs will be measured ~~to qualify and~~ MRI will be obtained to assess liver fat content. MRI results must be available prior to registration and administration of the first dose of study drug.

Update:

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.

Section 3.4.1 *Screening/Qualification* end of paragraph one

Was:

At the qualification visit ~~subjects will have~~ a baseline DEXA scan and MRI will be obtained to assess liver fat content. MRI results must be available prior to registration and administration of the first dose of study drug.

Update:

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.

Section 6.1.1 *Screening/Qualification* end of paragraph three

Was:

At the qualification visit TGs will be measured ~~and~~ MRI will be obtained to assess liver fat content. MRI results must be available prior to registration and administration of the first dose of study drug.

Update:

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.

Section 6.2.6 *MRI*

Was:

An MRI to determine liver fat fraction will be done ~~at Qualification~~, Week 13 and Week 27.

Update:

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.

Appendix A Footnote d

Was:

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.~~

Update:

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

Rationale:

The MRI and DEXA scan should be performed after all other eligibility criteria are met and as close to day 1 as possible, allowing for sufficient time to turn around results.

3. Section 4 *Subject Enrollment*

A. Was:

Subjects must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered ~~enrolled~~ into the Study and will be assigned a unique subject identification number before any study procedures, including screening procedures, are performed.

A. Update:

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.

B. Was:

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. No subject may begin treatment prior to assignment of a unique subject identification number.

B. Update:

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**.

Rationale:

These changes are meant to clarify screening and enrollment into the study.

4. Section 6.2 *Study/Laboratory Assessments* paragraph eight

Was:

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

Update:

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.

Rationale:

There could be reasons why samples sent to the central lab are not received the following day. The local laboratory will provide results on specimens tested within its standard timeframe.

5. The following changes have been made to several sections with respect to renal function
Section 8.5.2 *Safety Monitoring for Renal Function* paragraph three and six
A. Was:

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

A. Update:

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

blood cells (RBCs), as well as serum creatinine and cystatin-C which will be monitored every 2 weeks during the first 3-months of the study treatment period, and monthly thereafter. In addition, other biomarkers of acute renal injury may also be measured if a safety signal is seen that warrants further testing. (Appendix B).

B. Was:

Lab alerts for abnormal renal tests will be issued for: ~~Creatinine clearance~~ (by CKD-EPI formula) decrease from Baseline > 25%, urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or an increase in serum creatinine from Baseline > 0.3 mg/dL).

B. Update:

Lab alerts for abnormal renal tests will be issued for: **eGFR** (by CKD-EPI formula) decrease from Baseline > 25%, urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or an increase in serum creatinine from Baseline > 0.3 mg/dL).

Section 8.6.2 *Stopping Rules for Renal Function Test Results/Temporary Stopping Rules for Renal Function Test Results*

Was:

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

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

Update:

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

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

Synopsis and Section 5.2 *Exclusion Criteria* number 8 paragraph b

Was:

Estimated GFR < 60 mL/min (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation ~~for creatinine clearance~~

Update:

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

Rationale:

These changes are made to consistently identify estimated glomerular filtration rate as measured by CKD-EPI formula and avoid confusion with creatinine clearance in the protocol.

6. **The following changes have been made to several sections with respect to platelet monitoring**

Section 8.5.3 *Safety Monitoring Rules for Platelet Count Results* paragraph three and six

A. Was:

Any case of a platelet count reduction to levels below 50,000/mm^3 (Grade 3 or Grade 4) is considered an adverse event of special interest and should be reported in an expedited fashion to the Sponsor.

A. Update:

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

B. Was:

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

B. Update:

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

Section 8.6.3 *Stopping Rule for Platelet Count Results*

The greater than or equal sign (≥) has been added to a couple of places in the fourth paragraph in order to align with updates in Table 3. In addition, paragraph six:

Was:

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

Update:

Once a subject commences weekly monitoring, this frequency of monitoring should continue **until the platelet count returns to the normal range (≥140,000/mm^3) for 2 successive values.**

Table 3 *Actions in Subjects with Low Platelet Count during Treatment or Post-Treatment Period*

Was:

Footnote: Once a subject commences weekly monitoring this frequency of monitoring should continue ~~irrespective of whether the platelet count rises into the normal range~~.

Update:

Footnote: Once a subject commences weekly monitoring this frequency of monitoring should continue **until the platelet count returns to the normal range (≥ 140,000/mm^3) for 2 successive values.**

Rationale:

Several changes have been made to Table 3 in order to clarify normal ranges, to clarify the need to refer Grade 3 and 4 low platelet counts to a hematologist and to clarify when to start and when to discontinue weekly platelet monitoring.

Appendix F Additional testing for low platelet count

Addition of a table outlining tests to be performed on patients that experience a single occurrence of platelets <100,000/mm^3.

Rationale:

Changes have been made in order to clarify normal ranges, to clarify the need to refer Grade 3 and 4 low platelet counts to a hematologist, and to clarify when to start and when to discontinue weekly platelet monitoring. These changes are expected to help better understand the reasons for platelet count reductions, were they to occur, and ensure close monitoring of subjects if a single platelet count reduction <100,000/mm^3 is observed. These changes are also expected to ensure continuity of safety monitoring for subjects with a decreased platelet count.

7. Section 8.5.4 *Safety Monitoring for Bleeding Events* and Section 8.6.3 *Stopping Rule for Platelet Count Results*

These sections have been re-arranged in such a way that monitoring of bleeding events has been taken out of Section 8.6.3 and added to Section 8.5.4.

The following has been deleted from Section 8.5.4 due to the redundancy resulting from the re-arrangement above:

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

The following was deleted from Section 8.5.4 to avoid protocol deviations:

~~Patients will be instructed to promptly report any signs or symptoms of bleeding.~~

In addition, Section 8.5.4 has an additional phrase and sentence:

Was:
Subjects will be evaluated for occurrence of bleeding events continuously after the start of Study Drug treatment (Day 1)

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

Rationale:
Monitoring and the monitoring period have been clarified and clarification that bleeding events are to be considered adverse events has been added.

8. Section 8.5.6 *Safety Monitoring for Hypoglycemia*

Was:

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

Severe Hypoglycemia

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

Documented Symptomatic Hypoglycemia

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

Asymptomatic Hypoglycemia

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

Probable Symptomatic Hypoglycemia

Typical hypoglycemia symptoms not accompanied by ~~plasma~~ glucose determination but likely caused by ~~plasma~~ 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 ~~plasma~~ glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

Update:

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.

Rationale:

Determination of severe hypoglycemia can be measured by glucometer. Therefore, the language has been made more generic.

9. Section 8.5.7 *Safety Monitoring for Documented Hyperglycemia*

A. Was:

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

- ~~FPG~~ > 270 mg/dL (15.0 mmol/L)

From Week 13 to ~~Week 25/27/ET (including value at Week 25/27/ET) of Randomized Treatment period~~:

- ~~FPG~~ > 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 ~~FPL~~/HbA1c above the threshold values, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- ~~Plasma~~ glucose was actually measured in the fasting condition

A. Update:

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

B. Was:

If none from the above-mentioned reason can be found, or if appropriate action fails to decrease ~~FPG~~/HbA1c under the threshold values, rescue

B. Update:

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

Rationale:

Monitoring for hyperglycemia did not include the post-treatment period. This change now incorporates that period. Fasting plasma glucose(FPG) has been updated to the more generic term "blood glucose" for this section to allow for measurements made with a glucometer.

10. Follow-up Period Post-Treatment

Section 3.4.3 *Post-Treatment*

Was:

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 ~~last dose~~. Refer to Schedule of Procedures in Appendix A.

Update:

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.

Section 6.1.3 Post-Treatment Period

Was:

Each subject will be followed for safety assessments for 13 weeks after the ~~last dose of Study Drug~~.

Update:

Each subject will be followed for safety assessments for 13 weeks after the **Treatment Period (last dose through one dosing interval post last dose).**

Section 8.8.1 *Follow-up Visits for Early Termination from Treatment Period or from Post-Treatment Follow-up Period*
Was:

Any subject who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. ~~Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that subjects are monitored for at least 13 weeks after discontinuing Study Drug.~~

Update:

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

Appendix A Schedule of Procedures and Appendix C PK Sampling Schedule
The follow-up period after treatment period has been clarified in both tables and a footnote has been added to both appendices.

Rationale:

The follow-up period is meant to start after the last dose through one dosing interval post last dose. The prior language could be interpreted to not include the dosing interval post last dose.

11. Section 9.4.1 *Serious Adverse Events*

Was:

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. ~~When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message.~~ An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Update:

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.

Rationale:

To ensure that all pertinent information is reported, Akcea requires all clinical SAEs to be reported via two methods:

1. Email: INCdrugsafety@incresearch.com (monitored 24/7)
2. Fax: +1 877-464-7787

Reporting SAEs only by Email and Fax ensures all information required for a valid and comprehensive case is received with proper documentation.

12. Appendix E Mixed Meal Test

A. Was:

At ~~Baseline~~, 3 months and end of study,…

A. Update:

At **Qualification**, 3 months and end of study,…

B. Was:

A cannula will be inserted into a forearm vein, and an overnight fasting venous blood sample will be taken…

B. Update:

A cannula will be inserted into a forearm vein, and an overnight fasting **(minimum 10 hours)** venous blood sample will be taken…

Rationale:

Procedure is to be done at Qualification and more detail is provided by specifying the minimum fasting time.

PROTOCOL SYNOPSIS

Protocol Title	An Open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy
Study Phase	2
Indication	Familial Partial Lipodystrophy (FPL)
Primary Objective	To assess the effect of ISIS 703802 on reduction in fasting triglycerides (TG).
Secondary Objectives	To evaluate the safety and tolerability of ISIS 703802 To evaluate the effect of ISIS 703802 on changes from Baseline to end of treatment on: • Plasma glucose, serum insulin, serum C-peptide and free fatty acid (FFA) in responses to a mixed meal test (MMT) • Lipids, lipoproteins and lipid metabolism • Glycosylated hemoglobin (HbA1c) • Liver fat and body fat distribution • Quality of life and pain score To evaluate pharmacokinetics (PK) of ISIS 703802
Study Design	This is a single-center, open-label study. The study will comprise the following periods: **Screening period**: Up to 6 weeks (including an up to 4 week run-in diet period) **Treatment Period**: 26 weeks **Post-treatment Follow-up Period**: 13 weeks The primary safety and efficacy analysis time point is at Week 27.
Number of Subjects	Approximately 3
Study Population	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

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

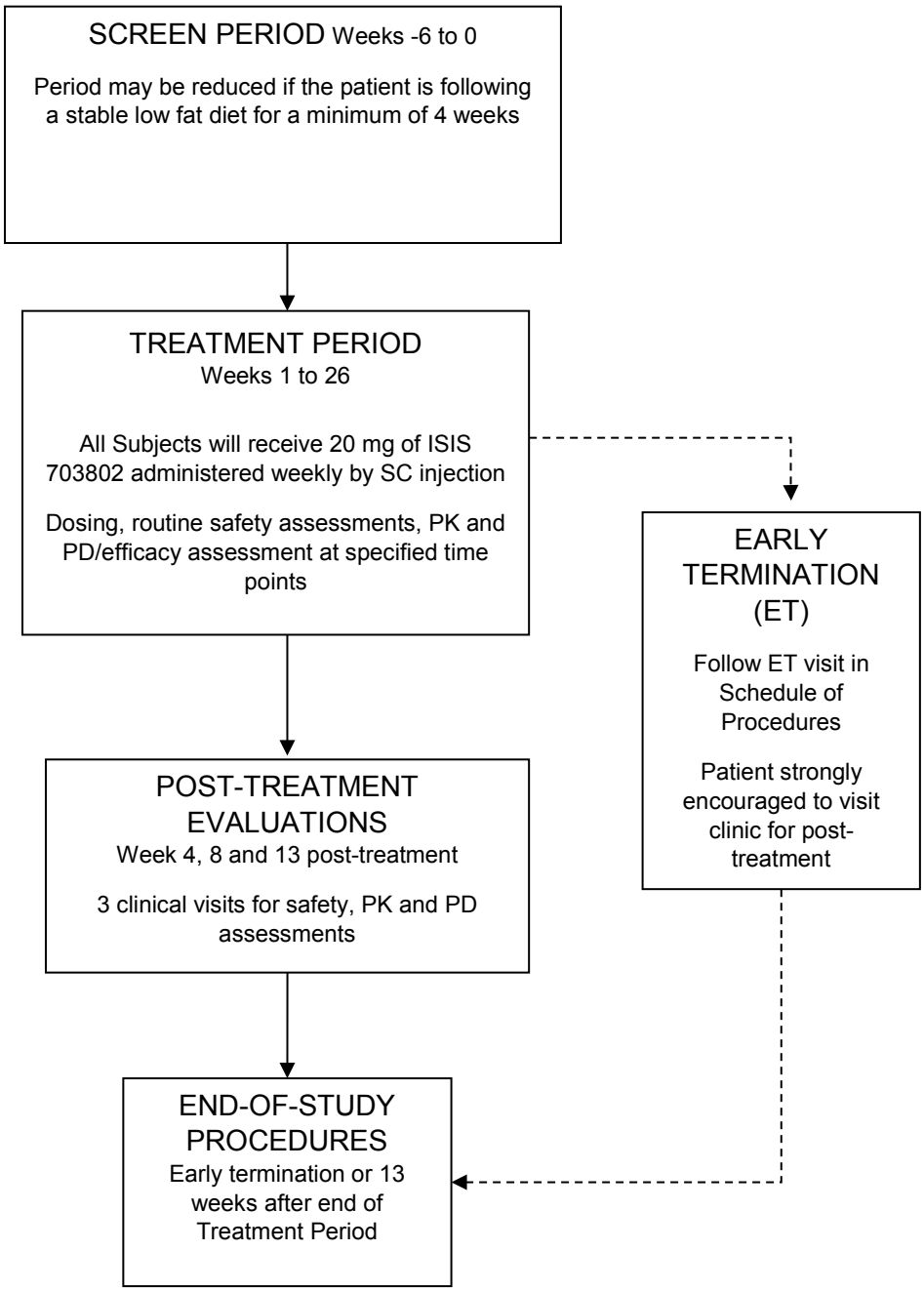
	the last dose of Study Drug administration. b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at 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

	12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer 16. Unwilling to comply with lifestyle requirements (see Section 6.3) 17. Use of any of the following: a. Metreleptin within the last 3 months prior to Screening b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to Screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to Screening are also eligible c. Insulin unless on a stable daily basal insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Screening f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor Medical Monitor g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Screening and dose and regimen expected to remain constant throughout the study i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), and lorcaserin (Belviq), phentermine, amphetamines, herbal preparations] within 12 weeks prior to Screening (except liraglutide [rDNA origin] injection (Saxenda) if on stable therapy for more than 6 weeks prior to Screening). k. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 19. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could

	interfere with the patient participating in or completing the study
Treatment Groups	Single Group, open-label treatment with 20 mg of ISIS 703802 SC weekly
Study Drug Dosage and Administration	The Sponsor will provide ISIS 703802 in a single vial with a concentration of 100 mg/mL 20 mg every week of ISIS 703802 (0.2 mL). The study dose of 20 mg (0.2 mL) of ISIS 703802 will be administered every week during the treatment period for a total of 26 weekly doses. All doses will be given by SC injection. Self-administration will be allowed after appropriate training of subject and/or caregiver.
Rationale for Dose and Schedule Selection	A 20 mg weekly dose was selected as being the lowest dose that provided maximum TG lowering of approximately 60%, based on the TG lowering effect of ISIS 703802 observed in healthy volunteers with elevated TGs.
Adjustment of Dose or Treatment Schedule	Dose adjustments, including dose interruptions, and/or decreasing the dose and dose frequency may be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures are outlined in Section 6, Appendices A and C. The study for an individual subject will generally consist of the following periods: • An up to 6-week Screening period, including a 4-week diet stabilization phase for subjects not already on a stable diet • A 26-week treatment period during which Study Drug will be administered weekly by SC injection • A 13-week post-treatment follow-up period During the Screening period, subject will be advised to maintain diet and exercise routines, and remain on a stable regimen of diabetes and lipid medications (if they are already taking any). As part of the Screening period, subjects may have 4 weeks of diet run-in and final eligibility will be determined during qualification. 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. Subjects meeting eligibility criteria at Screening and having a qualifying MRI, defined as having at least 6.4% liver fat assessed by MRI-PDFF (via central reviewer) will return to the clinic on Day 1. In addition, TG will be measured at qualification and results of TG and MRI must be available prior to registration and administration of the first dose of study drug. Blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B shows a list of analytes required for the study and Appendix C details the PK sample schedules. The Mixed Meal Test (MMT) 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 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.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: AEs, vital signs and weight, physical examinations, clinical laboratory tests, ECGs, use of concomitant medications.
Efficacy Evaluations	**Primary Endpoint:** • The effect of ISIS 703802 on the percent change from Baseline in fasting triglyceride levels (TG) at week 27 **Secondary Endpoints:** • Change from Baseline in AUC plasma glucose, serum insulin, serum C-peptide, free fatty acid, serum ghrelin, GIP, GLP-1, and PYY 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 dual-energy X-ray absorptiometry (DEXA); visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) as measured by MRI; body weight, waist circumference and waist/hip ratio • Changes from Baseline in quality of life and pain score
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 703802 trough levels throughout treatment and levels during the post-treatment Follow-up period. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Pharmacodynamic Evaluations	Plasma angiopoietin-like 3 (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
Statistical Considerations	There is no statistical rationale for the selected sample size.
Sponsor/Collaborator	Akcea Therapeutics, Inc./ Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	**Definition**
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
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

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

ISIS 703802	antisense inhibitor of ANGPTL3
IV	Intravenous(ly)
kg	kilogram
L	liter
LDL-C	Low Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
m^2	square meter
MAD	multiple ascending dose
MB	Major Bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
mm	millimeter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MMT	Mixed Meal Test
MTD	maximum tolerated dose
NAFLD	Nonalcoholic Fatty Liver Disease
NEFA	Non-esterified Fatty Acids
NOAEL	No Adverse Effect Level
NCS	not clinically significant
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
on study	The *insert* [subject] *or* [patient] is 'on study' from signing of the informed consent until their last study visit
OAD	Oral Antidiabetic Drugs
OTC	Over the Counter
PCOS	Polycystic OvarySyndrome
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PLT	Platelet
pRBC	packed red blood cells
PT	prothrombin time
PYY	Peptide Tyrosine Tyrosine

RBC	Red Blood Cells
REMS	Risk Evaluation ad Mitigation Strategy
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAT	Subcutaneous Adipose Tissue
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
SMBG	Self Monitored Blood Glucose
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 703802
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TG	Triglycerides
T_{max}	time to maximal concentration
TNF-α	tumor necrosis factor-alpha
T2DM	Type 2 Diabetes
ULN	upper limit of normal
UACR	Urine albumin/creatinine ratio
UPCR	Urine Protein Creatinine Ratio
VAT	Visceral Adipose Tissue
VLDL	Very Low Density Lipoprotein
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to assess the effect of ISIS 703802 on reduction in fasting triglycerides (TG).

1.2 Secondary Objective(s)

The secondary objectives are:

- To evaluate the safety and tolerability of ISIS 703802
- To evaluate the effect of ISIS 703802 on changes from Baseline to end of treatment on:
  - Plasma glucose, serum insulin, serum C-peptide and free fatty acid (FFA) in responses to a mixed meal test (MMT)
  - Lipids, lipoproteins and lipid metabolism
  - Glycosylated hemoglobin (HbA1c)
  - Liver fat and body fat distribution
  - Quality of life and pain score
- To evaluate pharmacokinetics (PK) of ISIS 703802.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Lipodystrophy syndromes are a group of rare metabolic diseases characterized by selective loss of adipose tissue that leads to ectopic fat deposition in liver and muscle and the development of insulin resistance, diabetes, dyslipidemia and fatty liver disease (Garg 2004; Chan and Oral 2010; Garg et al. 2011; Shulman et al. 2014).

These syndromes are categorized according to the distribution of fat loss into generalized or partial and according to the underlying etiology as inherited or acquired (Garg 2004; Chan and Oral 2010; Garg et al. 2011).

These syndromes constitute a significant medical unmet need as these patients are refractory to current therapies, mainly used to treat diabetes and elevated TG levels, in an attempt to reduce the risk of serious associated complications (coronary artery disease, diabetic nephropathy, cirrhosis and pancreatitis).

As such, in February 2014, the FDA approved Myalept (metreleptin) as replacement therapy to treat the complications of leptin deficiency in addition to diet in patients with congenital or acquired generalized lipodystrophy. The safety and effectiveness of Myalept was evaluated in 2 open-label studies conducted at the NIH, which included 72 patients (48 with generalized lipodystrophy and 24 with partial lipodystrophy [PL]) with diabetes, high TG, and elevated levels of fasting insulin. The best results were achieved in patients with generalized lipodystrophy who had low leptin levels (mean [SD]: 1.3 [1.1] ng/mL), while patients with partial lipodystrophy who had a wider range of baseline leptin values (mean [SD]: 4.9 [3.1] ng/mL) had a more varied and attenuated response. Because of the risks associated with the development of neutralizing antibodies and lymphoma, Myalept is available only through a risk

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).

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

- Steatohepatitis that can progress to cirrhosis and an increased risk of hepatocellular carcinoma
- Proteinuric nephropathies which can progress to end stage renal disease

In patients with Generalized Lipodystrophy the metabolic complications are partially related to leptin deficiency, and can be ameliorated in part by leptin replacement. However, leptin deficiency alone cannot explain the severity of metabolic disease in patients with PL who have variable leptin levels.

By reducing ANGPTL3 and TG levels, ISIS 703802 may improve the metabolic profile of patients with FPL and reduce their risk of acute pancreatitis. In addition, reductions in TG could improve hepatic steatosis and reduce cirrhosis risk. Furthermore, this mechanism may also improve insulin sensitivity in these patients and potentially lead to a reduction in the complications associated with diabetes.

2.2 Therapeutic Rationale

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

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

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

2.3 ISIS 703802

2.3.1 Mechanism of Action

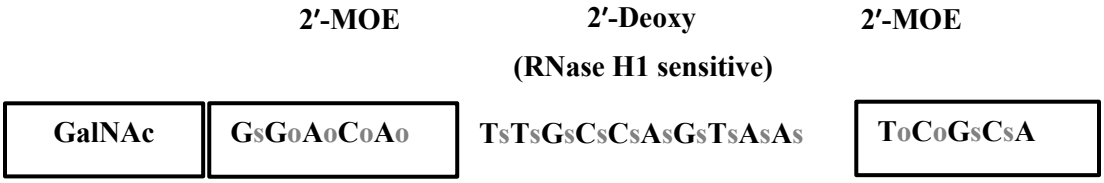
ISIS 703802 is a second-generation ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has

increased ASO potency by approximately 10-fold in mice (Prakash et al. 2014). The ASO portion of ISIS 703802 is complementary to a region within the ANGPTL3 messenger ribonucleic acid (RNA) (mRNA) coding sequence, and binds to the mRNA via Watson and Crick base pairing. The hybridization (binding) of ISIS 703802 to the cognate mRNA results in the Ribonuclease H1 (RNase H1)-mediated degradation of the ANGPTL3 mRNA, thus preventing production of the ANGPTL3 protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, ISIS 703802 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The mixed backbone design reduces the total number of phosphorothioate linkages in the MOE-modified regions, which reduces non-specific interactions with proteins and further enhances potency of GalNAc conjugated ASOs. The nucleotide sequence of ISIS 703802 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 6 of the ANGPTL3 mRNA coding sequence at position 1169-1188 bp.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity for the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 703802 employs this chimeric structure to enable use of the RNase H1 mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition. The fourth region is comprised of a triantennary cluster of *N*-acetyl galactosamine (GalNAc) sugars which is linked to the 5′ end of ISIS 703802 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the asialoglycoprotein receptor (ASGPR), a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc cluster enhances delivery of ISIS 703802 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release ‘free ASO’ inside the cell (Prakash et al. 2014).



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

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

2.3.3 Preclinical Experience

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

2.3.3.1 Preclinical Pharmacology

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

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

Reductions in murine ANGPTL3 mRNA and protein were routinely observed in all mouse models treated with a murine-specific ANGPTL3 ASO. Pharmacology studies were done with *Ldlr*$^{-/-}$ mice fed a hypercholesterolemic diet known to develop elevated LDL-C, TG, and atherosclerosis, as well as features of metabolic syndrome (hyperglycemia and hyperinsulinemia) (Huszar et al. 2000; Schreyer et al. 2002; Tsuchiya et al. 2012). Treatment of mice with a murine-specific ANGPTL3 ASO resulted in improvement in all of the aforementioned lipid and metabolic endpoints compared to controls. In all mouse models tested, total plasma cholesterol, LDL-C, TG, and non-esterified fatty acids (NEFA) have been shown to be consistently reduced upon treatment with ANGPTL3 ASOs, while HDL-C is modestly decreased in wild type mice (- 22%), and either stable or increased in others. While a clear mechanistic understanding of HDL-C reductions has not been elucidated, results from *in vitro* reverse cholesterol transport assays suggest that HDL function is maintained.

Administration of ISIS 703802, a human specific, GalNAc conjugated, ANGPTL3 ASO, to human *ANGPTL3* transgenic mice led to significant, dose-dependent reductions in hepatic ANGPTL3 mRNA. In diet challenged mice, administration of ISIS 731875, a mouse-specific and GalNAc-modified ASO targeting ANGPTL3, led to dose-dependent reductions in both hepatic ANGPTL3 mRNA and plasma

ANGPTL3 with concomitant reductions in plasma TG and cholesterol. Importantly, the potency and the lipid-lowering effects of the ANGPTL3 ASO were independent of diet.

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

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

2.3.3.2 Preclinical Toxicology

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

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

The most noteworthy finding in the monkey was the kidney alteration (hypoalbuminemia and proteinuria) seen in one early-sacrifice animal from the 16-week study at 35 mg/kg/week, a dose equivalent to at least ~190-fold of the 40 mg weekly clinical doses by plasma AUC. Non-dose dependent increases in renal protein excretion (up to 2.2-fold in quantitative urine protein, protein/creatinine ratio or urine albumin) were also observed at 8 and/or 35 mg/kg/week (> ~30 to 190-fold of the 40 mg weekly clinical doses by plasma AUC) at the 16-week scheduled terminal necropsy. However, Similar kidney alterations were not seen at the 6-week interim at any doses or in the 39-week chronic monkey study up to 12 mg/kg/week (> ~200-fold of the 20 mg weekly clinical dose by plasma AUC).

Additional findings related to ASO liver accumulation included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) at ≥ 8 mg/kg/week in the 16- and 26-week mouse studies, and were correlated with individual hepatocyte necrosis (minimal to mild) in mouse liver. Those changes were most prominent in the high dose groups (50 and 24 mg/kg/week for the 16- and 26-week studies, respectively). Conversely, no changes in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week. In the 16-week 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 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

approximately dose proportionally. No accumulation based on C_{max} or AUC was observed after 6 weekly doses.

2.3.4.1 ISIS 563580-CS1 Phase 1 SAD/MAD

In a Phase 1 study, ISIS 563580-CS1, healthy volunteers received subcutaneous administration of ISIS 563580, an unconjugated 2′-MOE modified ASO that has the same base sequence as ISIS 703802, from 50 to 400 mg as a single dose, or 100 to 400 mg as multiple doses (8 doses in 36 days). Overall, the safety findings from this study suggest that ISIS 563580 was not associated with any safety concerns. There were 383 adverse events (AE) reported in the ISIS 563580-treated subjects of which 363 (95%) were mild in severity. For the multiple-dose subjects, the most common treatment-emergent adverse events were AEs at the injection site. There was 1 serious adverse event (SAE) in the study of periorbital cellulitis which was considered a medically important event by the Investigator and was also considered unlikely related to Study Drug by the Investigator. Together, the above suggest that ISIS 563580 was well-tolerated at the doses and regimen given, which exceed the dose levels and cumulative exposures to be tested in the current study. There were no clinically-relevant changes in laboratory assessments and the heparin dose of 80 U/kg was well-tolerated in support of the post-heparin procedures. ISIS 563580 produced dose-dependent reductions in plasma ANGPTL3 (up to 93%; group means up to 84%), TG (up to 63%; group means up to 49%) and TC (up to 46%; group means up to 28%) at Day 36 (Brandt et al. 2015).

2.4 Rationale for Dose and Schedule of Administration

The Phase 1 program evaluated ISIS 703802 doses of 10 mg, 20 mg, 40 mg and 60 mg given weekly for 6 weeks that were found to be generally well-tolerated and to induce clinically-relevant reductions in lipid biomarkers. The dose proposed for the present study will provide the equivalent drug exposure of 20 mg weekly (80 mg monthly) and is predicted (based on modelling of PK/PD data obtained in Phase 1 study) to result in mean reductions from Baseline in TGs of approximately 63% at steady-state.

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

In healthy volunteers, 703802 achieved an equivalent reduction in ANGPTL3 plasma concentration to that of the unconjugated form, at approximately $1/10^{th}$ of the unconjugated ASO (ISIS 563580) dose (Brandt et al. 2015).

2.5 Benefit-Risk Assessment

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

2.5.2 Risk Assessment

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

- In preclinical mouse studies, there were increases in ALT and AST and were correlated with increased incidence and/or severity of necrosis of individual hepatocytes (minimal to mild in severity). Those changes were most prominent in the high dose groups and showed no clear progression over time. No increases in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week (~200-fold of the 20 mg/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

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.

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.

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

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 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).

5.2 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
12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Unwilling to comply with lifestyle requirements (see Section 6.3)
17. Use of any of the following:
    a. Metreleptin within the last 3 months prior to Screening
    b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to Screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to Screening are also eligible
    c. Insulin unless on a stable daily basal insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing
    d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis
    e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Screening
    f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor Medical Monitor
    g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Screening and dose and regimen expected to remain constant throughout the study
    i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed
    j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), and lorcaserin (Belviq), phentermine, amphetamines, herbal

preparations] within 12 weeks prior to Screening (except liraglutide [rDNA origin] injection (Saxenda) if on stable therapy for more than 6 weeks prior to Screening).

k. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)

18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening

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

6. STUDY PROCEDURES

6.1 Study Schedule

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

All required study procedures are outlined in Appendix A.

6.1.1 Screening/Qualification

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. A 6-week period is provided for completing screening assessments and determining subject eligibility for the study. During the screening period, subject will be advised to maintain diet and exercise routines, and remain on a stable regimen of diabetes and lipid medications (if they are already taking any).

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

As part of the screening period, subjects not already on a stable diet will have 4 weeks of diet run-in, followed by a qualification visit, during which final eligibility assessments will be performed. Subjects on stable diet known to the investigator and followed at the site may go from Screening to qualification without a 4-week diet run-in. At the qualification visit TGs will be measured. MRI 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.

6.1.2 Treatment Period

Subjects will be managed on an outpatient basis. Safety and clinical laboratory evaluations as well as blood sampling for PK analysis will be performed periodically throughout the treatment period. Any AEs and concomitant medications will be recorded.

Collection and measurement of vital signs, physical examination results, ECGs, clinical laboratory parameters (Appendix B), ISIS 703802 plasma concentrations, immunogenicity, MRI, AEs and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A.

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

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

For female subjects and female partners of male subjects:

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

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

***Note:** **A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.**

6.3.2 Other Requirements

All subjects will be required to fast for at least 10 hours before visits requiring fasted blood sampling.

7. STUDY DRUG

7.1 ISIS 703802

Study Drug (ISIS 703802) characteristics are listed in Table 1.

Study Drug (ISIS 703802) will be provided as 0.8 mL deliverable volume in 2 mL stoppered and sealed glass vials as a sterile solution.

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

Table 1 Study Drug Characteristics

Study Drug	ISIS 703802
Strength	100 mg/ mL
Volume/Formulation	0.8 mL/vial
Route of Administration	SC*

* SC = subcutaneous

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 703802) supplies provided by the Sponsor. The subject must return all used and unused Study Drug to the Study Center for accountability. The Study Center must return all used and unused Study Drug to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

Vials are for single use only. Study staff will administer the first dose of Study Drug. Doses will be administered by SC injection, patients or their caregivers may self-administer the study drug following the training given by the study center staff.

Subjects will receive treatment weekly with weeks always defined relative to Study Day 1. For example if a subject receives the first dose on a Monday, subsequent doses should be given on Mondays according to the respective dosing schedule, if possible. If a subject misses an injection, or if dosing on the usual day is not possible, the subject can reschedule the injection provided that 2 doses are administered at least 2 days apart.

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

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

Table 2 Study Drug Dosing Information

Volume to Administer*	Total Dose*
0.20 mL	20 mg (open label)

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

Subjects will continue their lipid-lowering therapy on a stable regimen from the signing of informed consent at Screening through the end of the post-treatment evaluation period.

8.3 Other Protocol-Required Treatment Procedures

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

8.4 Treatment Precautions

No specific treatment precautions are required.

8.5 Safety Monitoring Rules

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

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

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

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

Confirmation Guidance: At any time during the Study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below must be confirmed by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens prior to administering the next dose of Study Drug. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

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

In the event of an initial clinical laboratory result that meets a stopping criterion, subjects must not be re-dosed until a confirmatory test result has been reviewed by the Study Medical Monitor. If any of the stopping criteria described below are met and are confirmed, the subject will be permanently discontinued from further treatment with Study Drug (ISIS 703802), evaluated fully as outlined below and in consultation with the Study Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Study Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate.

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

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the FDA guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009 and adopted to meet the requirements of this protocol and compound to ensure safety of the subjects.

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

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

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

Subjects with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR] and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.5 x ULN.

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

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

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (hepatitis A virus [HAV] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, Cytomegalovirus [CMV] IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

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

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

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

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

8.5.2 Safety Monitoring for Renal Function

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

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

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

The assessment of serum creatinine, cystatin-C, and urinalysis more frequently than per the Schedule of Procedures in Appendix A will be guided by consultation with the medical monitor. Any decision taken by the Investigator to discontinue study medication will be made taking into account all available and relevant data. In addition, the decision to discontinue Study Drug may also be based on lesser changes in these parameters observed in isolation or in association with other renal-related abnormalities. Any

decision taken to restart study medication will be made in consultation with the Study Medical Monitor taking into account all available and relevant data.

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

Lab alerts for abnormal renal tests will be issued for: eGFR (by CKD-EPI formula) decrease from Baseline > 25%, urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or an increase in serum creatinine from Baseline > 0.3 mg/dL).

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

In the event of a confirmed laboratory result meeting one or more of the above criteria, the following supplemental renal tests should be immediately obtained:

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

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

8.5.3 Safety Monitoring Rules for Platelet Count Results

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

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

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

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

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

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

8.5.4 Safety Monitoring for Bleeding Events

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

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

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

Definitions:

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

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 20 g/L (1.24 mmol/L) or more within 24 hours

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

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

8.5.5 Safety Monitoring for Constitutional Symptoms

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

8.5.6 Safety Monitoring for Hypoglycemia

Subjects will be instructed to monitor and manage hypoglycemic episodes. Subjects will be provided with glucometer and asked to record Self Monitored Blood Glucose (SMBG) levels and report back alert values to the site. Subjects will be instructed to promptly report symptoms of hypoglycemia: headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness,

increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating and weakness. If subjects suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. If a subject presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the subject's glucose level and treat the subject accordingly. Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

Classification of Hypoglycemia

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

Severe Hypoglycemia

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

Documented Symptomatic Hypoglycemia

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

Asymptomatic Hypoglycemia

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

Probable Symptomatic Hypoglycemia

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

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

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

8.5.7 Safety Monitoring for Documented Hyperglycemia

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

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

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

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

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

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

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

- Blood glucose was actually measured in the fasting condition
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency such as unplanned hospitalization (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control. If the measure does not exceed 7 days, then it will not be considered a rescue. If the measure lasts beyond 7 days then it will be treated as a rescue
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

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

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

8.6 Stopping Rules

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

8.6.1 Stopping Rules for Liver Chemistry Elevations

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

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation**.**

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

8.6.2 Stopping Rules for Renal Function Test Results / Temporary Stopping Rules for Renal Function Test Results

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

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

Dosing of a patient with Study Drug (ISIS 703802) will be stopped permanently if 24-hour urine testing confirms any of the following values in the absence of an alternative explanation:

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

Irrespective of whether the stopping rule is confirmed or not, the follow-up schedule and frequency of renal function monitoring after the initial event will be determined by the Study Medical Monitor in consultation with the Investigator. The Investigator should consider consulting a local nephrologist for any change of renal function that presents a concern. If a renal biopsy is performed, a sample specimen should be made available for examination by an independent renal pathologist who has been engaged by the Sponsor to review such specimens.

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

8.6.3 Stopping Rule for Platelet Count Results

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

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

Administration of steroids is recommended for subjects whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days
(**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count < 75,000/mm^3 and ≥ 50,000/mm^3, dosing of a subject with Study Drug should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. If dosing is continued, it must be at a reduced dose as shown in Table 3. The suitability of the subject for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the subject's platelet count, whether any bleeding events were experienced by the subject, and the speed of recovery of platelet count after interruption of dosing.

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

Once a subject commences weekly monitoring, this frequency of monitoring should continue until the platelet count returns to the normal range (≥140,000/mm^3) for 2 successive values.

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

Table 3 Actions in Subjects with Low Platelet Count

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

* Once a subject commences weekly monitoring this frequency of monitoring should continue until the platelet count returns to the normal range (≥ 140,000/mm^3) for 2 successive values.

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

8.7 Adjustment of Dose and/or Treatment Schedule

Dose frequency adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

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

Subjects may have their dose interrupted in response to AEs in consultation with Study Medical Monitor**.**

8.8 Discontinuation of Study Drug/Treatment

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an adverse event (AE) that necessitates permanent discontinuation of Study Drug
- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.3
- When a platelet count of less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 while the patient is on a reduced dose.

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

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

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

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

Any subject who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug and then at 8 and 13 weeks post end of treatment period (as per visit schedule). If the subject declines or is unable to participate in the above, the early termination visit procedures should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug. In addition, 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.

8.9 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.

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

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

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

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.

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

the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

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

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, subjects should be identified by initials (if permitted by local law) and a subject identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3 Study Documentation and Storage

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

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

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. Case report form entries may be considered source data if the case report form is the site of the original recording (i.e., there is no other written or electronic record of data).

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

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

12.4 Study Monitoring

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

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on subject data received by the Sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

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

12.5 Language

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

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

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 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 A Schedule of Procedures *Continued*

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

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

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

g Urine samples for renal biomarkers will be collected. Sample analysis will be conducted in accordance with Safety Monitoring for Renal Function (Section 8.5.2).

h During follow-up period, hematology sampling for platelet values are taken every 14 days (+/- 2 days) for 6 weeks after last dose of Study Drug, then at Week 8 and Week 13 Follow-up visits.

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

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

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

l Refer to Appendix C for PK Sampling schedule.

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

n Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) and will be retained until completion of the final study report.

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

p Genetic testing will only be performed for eligibility if there is no documented genetic testing in medical history.

q 24-hour urine sample for creatinine clearance and protein should also be obtained in the event of an eGFR (CKD-EPI) value meeting criteria specified in Sections 8.5.2 and 8.6.2.

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

1 Pre-dose

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Clinical Chemistry Panel

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

PD Panel

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

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Screening Tests

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

Extended Lipid Panel

- Total Cholesterol (TC)
- LDL cholesterol (LDL-C)
- HDL cholesterol (HDL-C)
- Triglycerides (TG)
- VLDL cholesterol (VLDL-C)
- Non-HDL cholesterol (Non-HDL-C)
- Lp(a)
- FFA
- ApoB
- ApoB-48
- ApoB-100
- Apo A-1
- ApoCIII (total, chylomicron, LDL, HDL, VLDL)
- Delipidated Free Glycerol
- Ceramides
- Sphingolipids
- Diacylglycerol
- Lipoprotein particle analysis

Hematology

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

Pharmacokinetics[1]

- ISIS 703802 levels in plasma

Immunogenicity

- Anti-ISIS 703802 antibodies

Liver Biomarkers (Biomarkers of liver apoptosis and fibrosis)

- CK18
- PIIINP

Inflammatory

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

Genetic Testing

- Genetic sequencing of FPL causing genes[3]

Extended Urinalysis

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

24-Hour Urine Test

- Creatinine clearance
- Protein
- Albumin

Mixed Meal Test

- Plasma glucose
- FFA
- C-peptide
- Insulin
- Serum ghrelin
- GIP
- GLP-1
- PYY
- Incretin hormones

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 703802 with plasma constituents

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

3 Blood will be collected to assess genetic evidence of FPL (e.g., mutations in LMNA, PPAR-γ, AKT2, CIDEC, PLIN1 genes). May not be collected if adequate genetic data are available in medical history or if patient does not consent to genetic testing

Appendix C PK Sampling Schedule

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

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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

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

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

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

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

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

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

Appendix E Mixed Meal Test

Appendix E Mixed Meal Test

At Qualification, 3 months and end of study, subjects enrolled will undergo a meal tolerance test (MTT) as follows: subjects will consume a standardized meal the evening before the test (750 kcal; 20% of energy from protein, 30% from fat, and 50% from carbohydrate) and refrain from consuming alcohol for 72 h.

A cannula will be inserted into a forearm vein, and an overnight fasting (minimum 10 hours) venous blood sample will be taken between 8:00 AM and 10:00 AM for measurement of plasma glucose, FFA, C-peptide and insulin concentrations and serum ghrelin, GIP, GLP-1, and PYY. Incretin hormones will be measured using a multiplex assay (EMD Millipore, Billerica, MA). The tubes for the incretin hormones will contain Pefabloc SC (Sigma-Aldrich, St. Louis, MO) and DPP-IV inhibitor (EMD Millipore, Billerica, MA) to inhibit DPP-IV and other proteases. The change in ratings from Baseline will be quantified.

Subjects will then consume a liquid load of Optifast (Optifast; Novartis, Minneapolis, MN; 474 ml, 320 kcal, 50% carbohydrate, 35% protein, 15% fat) within a 15-min period. Additional blood samples will be taken at 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min after meal consumption. VAS will be completed at 180 minutes and 300 min. To calculate the insulin sensitivity index (S_I), the oral minimal model for glucose will be used; and to calculate the hepatic insulin extraction, oral minimal model for insulin and c-peptide will be used [Cobelli et al, 2007]. Subjects will complete a validated visual analogue scale (VAS) questionnaire to assess subjective hunger at 0, 180 and 300 minutes [Luscombe-Marsh et al, 2005; Moran et al, 2005].

Appendix F Laboratory Tests to Be Performed in the Event of a Platelet Count < 100,000/mm^3

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

AKCEA THERAPEUTICS

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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.

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

Skinfold Measurements: Performed at Study Day 1 (Pre-dose) and at Weeks 5, 13 and 27/ET, and during the Follow Up Period at Weeks 4 and 13.

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." It has come to our attention that the details of the collection and specific timepoints of collecting skinfold measurements were missing from Appendix A: Schedule of Procedures. Skin fold measurements will occur as part of the physical exam and therefore, this measurement will occur at every visit in which a physical exam (full or abbreviated) occurs.

Summary

This Administrative Clarification Letter serves to align the planned secondary endpoints with Section 6: Study Procedures and Appendix A: Schedule of Procedures. It is noted that no safety assessments or procedures have been added or removed. This clarification does not affect the rights, safety, or well-being of study participants.

Sincerely,

[redacted]

[redacted]

[redacted]
Akcea Therapeutics, Inc.

cc: ISIS 703802-CS5 Study Coordinators, ISIS 703802-CS5 TMF

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ISIS 703802-CS5: Administrative Clarification Letter 2 to Protocol Amendment 1

02 October 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 – Appendix A Schedule of Procedures – Footnote H

Current Text:

During follow-up period, hematology sampling for platelet values are taken every 14 days (+/- 2 days) for 6 weeks after last dose of Study Drug, then at Week 8 and Week 13 Follow-up visits.

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

During **the treatment** period, hematology sampling for platelet values are taken every 14 days (+/- 2 days) **from first dose through** 6 weeks **post treatment period**, then at Week 8, and Week 13 Follow-up visits.

Rationale:

Clarification to footnote H of the Schedule of Procedures in order to align with the timing for hematology sampling following the treatment period.

Summary

This Administrative Clarification Letter serves to align the timing for hematology sampling as outlined in the Schedule of Events Table in Appendix A. It is noted that no safety assessments or procedures have been added or removed. This clarification does not affect the rights, safety, or well-being of study participants.

Sincerely,

[redacted]

[redacted]

[redacted]

Akcea Therapeutics, Inc.

cc: ISIS 703802-CS5 Study Coordinators, ISIS 703802-CS5 TMF

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Administrative Clarification Letter 3 to Protocol Amendment 1

02 July 2019

RE: Protocol ISIS 703802-CS5: An open-label Phase 2 Study of ISIS 703802 (AKCEA-ANGPTL3-L_{Rx}) Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Dear Dr. Oral:

The following administrative clarification is being issued for Protocol ISIS 703802-CS5 Protocol Amendment 1.

Administrative Clarification:

Appendix B: List of Laboratory Analytes

Current Text:

Extended Lipid Panel: Ceramides, Sphingolipids, Diacyglycerol

Clarification Text:

Remove: Ceramides, Sphingolipids, Diacyglycerol

Rationale:

Akcea Therapeutics Inc. uses protocol template language as part of its process on developing study protocols. When writing the ISIS 703802-CS5 Protocol, the analytes Ceramides, Sphingolipids, and Diacyglycerol were included in the text of Appendix B as part of template language and were unintentionally left in the List of Laboratory Analytes at protocol finalization. There was never an intention to run those analytes in this study or within this patient population.

Summary

This Administrative Clarification Letter serves to clarify the intended analytes to be studies as listed in the Appendix B List of Laboratory Analytes. Safety assessments, inclusion, or exclusion were not added or removed. This clarification does not affect the rights, safety, or well-being of study participants.

Sincerely

[redacted]

Akcea Therapeutics, Inc.