Official Title: A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-LRX (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

NCT Number: NCT03360747

Document Date(s): Protocol Version 1: 20-July-2017

Protocol Amendment Version 1: 26-October-2017

16.1.1 Protocol and Protocol Amendments

Document included:

- Clinical Study Protocol, Version 1.0, dated 20 Jul 2017
- Protocol Amendment No. 1, dated 26 Oct 2017

Sponsor:
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IONIS PHARMACEUTICALS, INC.

ISIS 703802-CS3

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Original Protocol – 20 JULY 2017

ISIS 703802-CS3

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-LRX (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Original Protocol – 20 JULY 2017

Protocol History

Original Protocol: 20 JULY 2017

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ISIS 703802-CS3

Ionis Protocol Number ISIS 703802-CS3

Original Protocol

Clinical Phase: 2

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 20 JULY 2017

Confidentiality Statement

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

Protocol Signature Page

Protocol Number: ISIS 703802-CS3

Protocol Title: **A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)**

Amendment: Original Protocol

Date: 20 JULY 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 2 Open-Label Study of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)" dated 20 JULY 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.

[redacted]

Investigator's Signature

[redacted] MD, PhD, CSPQ

Investigator's Name *(please print)*

2017oct23

Date (DD Month YYYY)

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PROTOCOL SYNOPSIS

Protocol Title	A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L$_{RX}$ (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	2
Indication	*Familial Chylomicronemia Syndrome*
Objectives	The primary objective is to evaluate the efficacy of AKCEA-ANGPTL3-L$_{RX}$ for reduction of triglyceride (TG) levels in patients with FCS *Secondary objectives are:* To evaluate the effect of AKCEA-ANGPTL3-L$_{RX}$ on plasma angiopoietin-like 3 (ANGPTL3) and other lipid parameters. *To evaluate the effect AKCEA-ANGPTL3-L$_{RX}$ on postprandial TG* *To evaluate the pharmacokinetics of AKCEA-ANGPTL3-L$_{RX}$* *To evaluate safety and tolerability of AKCEA-ANGPTL3-L$_{RX}$*
Study Design	*This is an, open-label study in 3 FCS patients. After confirming eligibility for the study during the screening period, patients will enter a 13-week treatment period. Study drug (AKCEA-ANGPTL3-L$_{RX}$) will be administered every week for 13 weeks during the treatment period. The patients will then enter a 13 week post-treatment evaluation follow-up period.*
Number of Subjects	3
Study Population	*Inclusion:* 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements. 2. Males or females aged ≥ 18 years old at the time of informed consent 3. Genetically confirmed homozygote or compound heterozygote for known null loss-of-function mutations in the LPL gene. 4. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening. If the fasting TG < 750 mg/dL up to 2 additional tests may be performed in order to qualify. 5. Willing to follow a diet comprising ≤ 20g fat per day during the study 6. Females: must be non-pregnant and non-lactating and either; i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved); iii. Abstinent* or, iv. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L$_{RX}$)

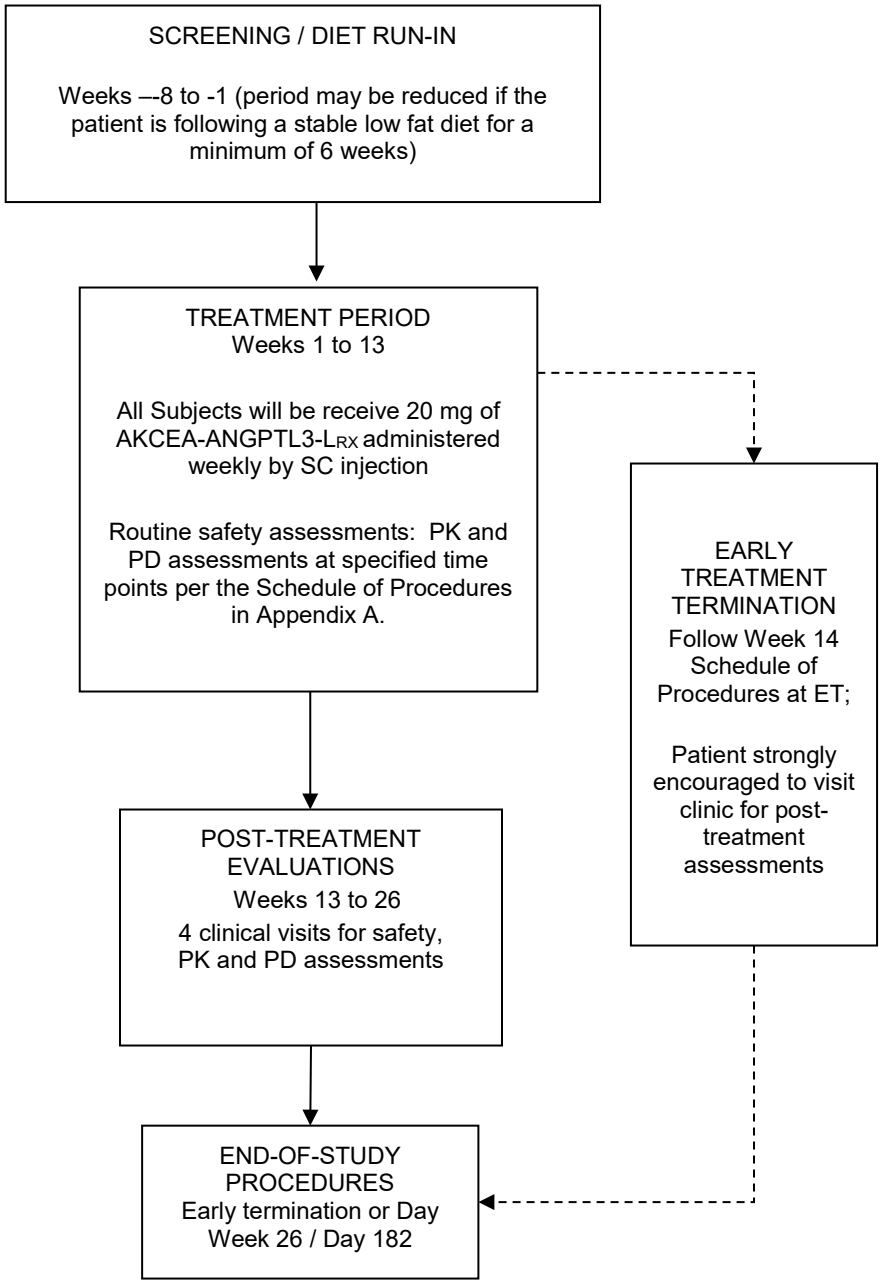
	7. Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L_{RX}) * 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:* 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Current use of GLP-1 agonists 2. Active pancreatitis within 2 weeks prior to screening 3. 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 cardiac failure requiring a change in medication) or major surgery within 3 months of screening 4. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Platelet count < 140,000 mm^3 d. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

	5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg) 6. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 7. History of heart failure with NYHA greater than Class II 8. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 9. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 10. 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 11. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer 12. Unwilling to comply with lifestyle requirements 13. Use of any of the following: a. Statins, omega-3 fatty acids (prescription or OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study. b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed 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 during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study i. Prior exposure to AKCEA-ANGPTL3-L_{RX} j. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 14. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 15. Known hypersensitivity to any of the excipients of the Study Drug

	16. 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 AKCEA-ANGPTL3-L$_{RX}$ by subcutaneous injection at 20 mg weekly*
Study Drug Dosage and Administration	The Sponsor will provide AKCEA-ANGPTL3-L$_{RX}$ in a single use vial with a concentration of 100 mg/mL. The study dose of 20 mg (0.2 mL) of AKCEA-ANGPTL3-L$_{RX}$ will be administered every week during the treatment period. All doses will be given by SC injection. Self-administration will be allowed after appropriate training of patient and/or caregiver.
Rationale for Dose and Schedule Selection	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 AKCEA-ANGPTL3-L$_{RX}$ observed in healthy volunteers with elevated TGs.
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 consist of the following periods: An up to 8-week screening period, including a diet stabilization period of at least 6 weeks A 13 week treatment period during which Study Drug will be administered open label by SC injection A 13-week post-treatment follow-up period Patients will receive up to 13 SC doses of AKCEA-ANGPTL3-L$_{RX}$weekly. Patients will return regularly for outpatient visits throughout the treatment and post-treatment follow-up periods according to the Schedule of Procedures (Appendix A). *Blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B shows a list of analytes required for the study and Appendix C details the PK sample schedules.*
Pharmacodynamic Evaluations	Fasting TGs, plasma angiopoietin-like 3 (ANGPTL3), ANGPTL4, ANGPTL8, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C). total apoC-III, apolipoprotein B-100 (apoB-100), apolipoprotein B-48 (apoB-48), apolipoprotein A-1 (apoA-1), apolipoprotein A-2 (apoA-2), apolipoprotein E (apoE), very-low-density lipoprotein-triglyceride (VLDL-TG), chylomicron-cholesterol (CM-C), chylomicron triglyceride (CM-TG), free fatty acids (FFA), and free glycerol levels
Pharmacokinetic Evaluations	The plasma PK of AKCEA-ANGPTL3-L$_{RX}$ (as total full length oligonucleotides, including, fully conjugated, partially conjugated, and unconjugated AKCEA-ANGPTL3-L$_{RX}$) will be assessed following multiple-dose SC administration. The plasma trough levels of AKCEA-ANGPTL3-L$_{RX}$ during treatment period and those during post-treatment follow up period will be descriptively summarized with stratification by subject immunogenicity status if applicable.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: adverse events, vital signs and weight, physical examinations, clinical laboratory tests, ECGs and use of concomitant medications.

Statistical Considerations	There is no statistical rationale for the selected sample size. The sample size is based on prior experience with second generation and N-acetyl galactosamine (GalNAc)-modified antisense oligonucleotides (ASOs) in healthy volunteers and to ensure that the safety, tolerability, pharmacokinetics, and preliminary pharmacodynamics of AKCEA-ANGPTL3-L_{RX} will be adequately assessed while minimizing unnecessary subject exposure.
Sponsor / Collaborator	Ionis Pharmaceuticals/Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
apoA-I	Apolipoprotein A-I
apoB	Apolipoprotein B
apoC-III	Apolipoprotein C-III
aPTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC_t	Area under the plasma concentration-time curve from zero time (pre-dose) to selected time (t) after Study Drug administration
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CK	Creatine kinase
C_{max}	Maximum observed drug concentration
Day 1	Defined as the first day Study Drug product is administered to the subject
ECG	Electrocardiogram
eCRF	Electronic case report form
FCS	Familial Chylomicronemia Syndrome

Abbreviation/Acronym	Definition
FH	Familial hypercholesterolemia
FHBL	Familial hypobetalipoproteinemia
FHBL2	Familial combined hypolipidemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HoFH	Homozygous familial hypercholesterolemia
HR	Heart rate
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional review board
LDL-C	Low density lipoprotein cholesterol
LDLR	LDL receptor
LLN	Lower limit of normal
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
MedDRA™	Medical Dictionary for Regulatory Activities
MOE	2′-*O*-(2-methoxyethyl)
MRI	Magnetic resonance imaging

Abbreviation/Acronym	Definition
mRNA	messenger ribonucleic acid (RNA)
MTP	Microsomal triglyceride transfer protein
NCS	Not clinically-significant
NEFA	Non-esterified fatty acids
Non-HDL-C	Non-high density lipoprotein cholesterol
OTC	Over-the-counter
P/C	Urine protein/creatinine
PCSK9	Proprotein convertase subtilisin kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time
RBC	Red blood cell
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SC	Subcutaneous
siRNA	Small interfering RNA
Study Drug	AKCEA-ANGPTL3-L_{RX} (ISIS 703802)
SUSAR	Suspected unexpected serious adverse reactions
t	Times
$t_{1/2\lambda z}$	Plasma terminal elimination half-life
TC	Total cholesterol

Abbreviation/Acronym	**Definition**
TG	Triglyceride
T_{max}	Time to reach C_{max}
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol

1. OBJECTIVES

1.1 Primary Objective(s)

- The primary objective is to evaluate the efficacy of AKCEA-ANGPTL3-L_{RX} (also known as ISIS 703802 in this document) for reduction of triglyceride (TG) levels in patients with FCS

1.2 Secondary Objective(s)

- To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on plasma angiopoietin-like 3 (ANGPTL3) and other lipid parameters.
- To evaluate the effect of *AKCEA-ANGPTL3-L_{RX}* on postprandial TG
- To evaluate the pharmacokinetics of *AKCEA-ANGPTL3-L_{RX}*
- To evaluate safety and tolerance of *AKCEA-ANGPTL3-L_{RX}*

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

FCS is characterized by frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and in children, can result in a failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011). Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011).

Patients with FCS often present in infancy or childhood with recurrent episodes of abdominal pain or pancreatitis, eruptive xanthomas or hepatomegaly. The diagnosis of FCS is then established by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, one hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

The preclinical and human genetic studies strongly support a potential role for an ASO approach to lower plasma ANGPTL3 in humans to decrease elevated TG and LDL-C levels in patients that cannot be adequately managed by existing therapies.

Numerous genome-wide association studies have been published in recent years confirming the association of mutations in human ANGPTL3 with reductions in serum lipids in human subjects (Minicocci et al. 2013). The mechanism(s) by which ANGPTL3 affects lipoprotein metabolism appears to be complex, as loss of ANGPTL3 leads to a decrease in multiple atherogenic lipoprotein levels that is hard to ascribe to any 1 single mode of action. ANGPTL3 deficiency in animals accelerates the clearance of VLDL particles from plasma because of increase in lipoprotein lipase (LPL) activity, whereas overexpression or intravenous injection of recombinant ANGPTL3 has opposite effects. These and other observations support a possible role of the LPL enzyme. However, a direct demonstration of this mechanism has not been provided. Understanding the mechanism of action of ANGPTL3 is a present area of active research (Gusarova et al. 2015; Haridas et al 2015; Wang X et al. 2015; Wang Y et al. 2015a; Wang Y et al. 2015b).

The goal of the present protocol is to explore the effects of lowering ANGPTL3 in FCS patients using AKCEA-ANGPTL3-L$_{RX}$ (also known ISIS 703802, using a dose selected on the basis of results in healthy volunteers, to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of AKCEA-ANGPTL3-L$_{RX}$ in these patients.

The known potential risks to study participants associated with AKCEA-ANGPTL3-L$_{RX}$ are further discussed in the Guidance to Investigator section of the Investigator's Brochure.

2.3 AKCEA-ANGPTL3-L$_{RX}$ (ISIS 703802)

2.3.1 Mechanism of Action

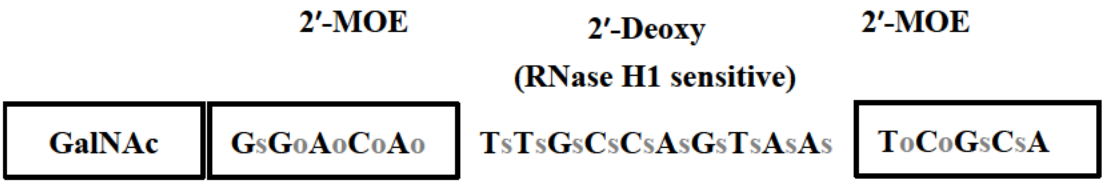
AKCEA-ANGPTL3-L$_{RX}$ is a second-generation ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high-affinity ligand for

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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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, AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} (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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L$_{RX}$ 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 AKCEA-ANGPTL3-L$_{RX}$, at doses higher than planned for AKCEA-ANGPTL3-L$_{RX}$.

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 AKCEA-ANGPTL3-L$_{RX}$, a human specific 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 AKCEA-ANGPTL3-L_{RX} consisted of sub-chronic (16-week) and chronic (26- or 39-week) toxicity studies CD-1 in mice and cynomolgus monkeys. Since AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX}.

Pharmacokinetic data confirmed continuous and dose-dependent exposure to AKCEA-ANGPTL3-L_{RX}. An estimated liver and plasma 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} in humans.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with AKCEA-ANGPTL3-L_{RX} can be found in the Investigator's Brochure. A summary is included below.

The study drug, AKCEA-ANGPTL3-L_{RX}, 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 AKCEA-ANGPTL3-L_{RX}, was also evaluated in a blinded, placebo-controlled Phase 1 study.

AKCEA-ANGPTL3-L_{RX} Phase 1 SAD/MAD interim analysis of 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 AKCEA-ANGPTL3-L_{RX} 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 ANGPTL3-L_{Rx}) and three reported dizziness (two who received placebo and one who received ANGPTL3-L_{Rx}). There was no clinical evidence of prothrombotic effects, bleeding episodes, significant decreases in platelet count or thrombocytopenia, or significant changes in

liver or renal function. 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).

The pharmacokinetics of AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} declined in a multi-phasic fashion with a rapid disposition phase, followed by a slower elimination phase with terminal elimination half-life of 3 to 5 weeks. The peak (C_{max}) and total exposure (AUC) after a single SC dose increased approximately dose proportionally from 20 to 40 mg, and greater than dose proportionally from 40 to 80 mg, suggesting more efficient tissue uptake at lower doses. After single and multiple SC doses in the range of 10 to 60 mg, the C_{max} and AUC increased approximately dose proportionally. No accumulation based on C_{max} or AUC was observed after 6 weekly doses.

2.3.4.1 ISIS 563580-CS1 Phase 1 SAD/MAD

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

2.4 Rationale for Dose and Schedule of Administration

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 AKCEA-ANGPTL3-L_{RX} in chronic monkey study was determined to be 12 mg/kg/wk.

Preclinical pharmacology experiments in Tg-mice and in non-human primates demonstrated that AKCEA-ANGPTL3-L_{RX} achieved an equivalent reduction in ANGPTL3 plasma concentration to that of the unconjugated form, at $1/10^{th}$ of the unconjugated ASO (ISIS 563580) dose. The dose level planned for this study for AKCEA-ANGPTL3-L_{RX} is 20 mg, which is the lowest dose that provided maximum TG lowering of approximately 60% in Study ISIS 703802-CS1 and is approximately 200-fold lower than NOAEL dose in monkey at 12 mg/kg/wk in the 39-week chronic monkey study up to terminal necropsy.

An interim analysis of the phase 1 study completed for all but the 120 mg single dose cohort showed approximately 60% reduction of TG at 20 mg dose. However, at 40 mg and 60 mg dose the TG reduction did not differ significantly from 20 mg dose. Thus, the lower dose was selected for this study for optimal risk to benefit.

2.5 Benefit-Risk Assessment

2.5.1 Benefit Assessment

The current study is designed to evaluate the safety and tolerance of AKCEA-ANGPTL3-L_{RX} in FCS subjects. The dose selected is expected to reduce ANGPTL3 and result in a reduction of the severe hypertriglyceridemia and chylomicronemia that afflicts FCS subjects. Importantly, although we do not know if subjects participating in this study would necessarily benefit from the treatment, the increased understanding of AKCEA-ANGPTL3-L_{RX} in this population is expected to result in improved treatment options that would ultimately benefit all FCS patients, including participants in the study. 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 AKCEA-ANGPTL3-L_{RX} are elaborated on in the Guidance to Investigator section of the Investigator's Brochure.

- In preclinical mouse studies, there were increases in ALT and AST and were correlated with increased incidence and/or severity of necrosis of individual hepatocytes (minimal to mild in severity). Those changes were most prominent in the high dose groups and showed no clear progression over time. No increases in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week (~200-fold of the 20 mg clinical dose by plasma AUC). In the 16-week monkey study, increase in ALT was only evident in 1 early-sacrifice animal at 35 mg/kg/week, no meaningful increase in ALT was observed in the schedule sacrificed animals.
- There were no observed significant changes in ALT and liver function in an ongoing Phase 1 human study (Graham et al. 2017). The risk of observing significant ALT/AST changes in this clinical human study is expected to be relatively low with the proposed 20 mg dose. 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 patient to tolerate dosing. Injection site adverse events are the most common side effects observed following SC administration of 2′-MOE ASOs and are dose and concentration dependent. Erythema is the most prevalent characteristic. Generally, these events are mild and reversible, resolve spontaneously and do not worsen with time. The histologic findings are consistent with a local inflammatory response. While planned doses of AKCEA-ANGPTL3-L_{RX} for clinical evaluation are generally below the doses that are historically associated with these effects, patients 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.

While the long term consequences 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 despite a reported decrease in VLDL production, there is no apparent difference in hepatic fat content compared to controls. 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

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Given the unmet medical need for FCS patients, AKCEA-ANGPTL3-L_{RX} has demonstrated the ability to reduce TGs by 60% in the Phase 1/2 study in healthy volunteers. The objective of this study is to assess the effect of TG lowering in FCS patients. Although the FCS patients enrolled in this study will not derive long term benefits due to the short duration of the study, the information obtained in the course of this study is critical to further development of AKCEA-ANGPTL3-L_{RX} for this disease with an extremely high unmet need. Taking into account the measures taken to minimize risk to subjects participating in this study, the fact that potential risks identified in association with AKCEA-ANGPTL3-L_{RX} are minimal and are manageable by routine monitoring exposure of FCS patients in this study is justified by the anticipated benefits that may be afforded to the wider population of FCS subjects by continued development of AKCEA-ANGPTL3-L_{RX}.

3. EXPERIMENTAL PLAN

3.1 Study Design

This will be a Phase 2 open-label multiple-dose study of approximately 3 subjects with FCS and will be treated with AKCEA-ANGPTL3-L_{RX}.

Subject will receive 20 mg of AKCEA-ANGPTL3-L_{RX} SC weekly.

3.2 Number of Study Centers

This study will be conducted at a single center but could be expanded to more than one center.

3.3 Number of Subjects

Approximately 3 subjects will be treated in this study.

3.4 Overall Study Duration and Follow-up

The study will consist of a screen/ run-in period, study treatment, post-treatment and long term follow-up. Please refer to the Schedule of Procedures in Appendix A.

Subjects may be required to attend additional visits for monitoring of adverse events or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

The length of subjects' participation in the study may be up to 34 weeks, including an up to 8-week screening period, that includes a 6-week diet stabilization / run-in period, a 13-week treatment period, and a 13-week post-treatment evaluation period. Subjects will perform the first dosing at the site, with subsequent dosing occurring at home following training on how to dose. The diet stabilization period may be reduced if the patient is following a stable low fat diet for optimal disease control and disease management prior to screening.

3.4.1 Screening

Subject eligibility for the study will be determined within 56 days/8 weeks prior to study entry.

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 13-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 every four weeks (refer to the Schedule of Procedures in Appendix A). The final study visit will be Study Week 26.

3.5 End-of-Study

The End-of-Study is defined as the last subject's last visit.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the Study, the Sponsor or designee requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

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

screening number and subject identification number must remain constant throughout the entire trial. Screening numbers and subject identification numbers, once assigned, will not be reused.

4.2 Registration

Patients 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 56 days of treatment day 1 or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements.
2. Males or females aged $\geq$ 18 years old at the time of informed consent.
3. Genetically confirmed homozygote or compound heterozygote for known null loss-of-function mutations in the LPL gene.
4. Fasting TG $\geq$ 750 mg/dL (8.4 mmol/L) at Screening. If the fasting TG < 750 mg/dL up to 2 additional tests may be performed in order to qualify.
5. Willing to follow a diet comprising $\leq$ 20g fat per day during the study.
6. Females: must be non-pregnant and non-lactating and either;
   i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);
   ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females $\leq$ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);
   iii. Abstinent* or,
   iv. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L_{RX}).
7. Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing an acceptable contraceptive method (refer to Section 6.3.1)

from the time of signing the informed consent form until at least at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L_{RX}).

* 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. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c ≥ 9.0% at Screening
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])
   d. Current use of GLP-1 agonists
2. Active pancreatitis within 2 weeks prior to screening
3. 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 cardiac failure requiring a change in medication) or major surgery within 3 months of screening
4. Any of the following laboratory values at Screening
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN
   b. Renal:
      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
      - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
      - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)
   c. Platelet count < 140,000 mm^3

d. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
6. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
7. History of heart failure with NYHA greater than Class II
8. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
9. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
10. 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
11. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
12. Unwilling to comply with lifestyle requirements (Section 6.3)
13. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription or OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study.
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to screening
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
    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 during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study
    i. Prior exposure to AKCEA-ANGPTL3-L_{RX}

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

14. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
15. Known hypersensitivity to any of the excipients of the Study Drug
16. 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 period. These periods are described below.

All required study procedures are outlined in Appendix A.

6.1.1 Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. A 4-week period is provided for completing screening assessments and determining subject eligibility for the study. Safety labs may be re-tested for determination of subject eligibility after consultation with the Sponsor Medical Monitor.

During the screening period, 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.

Eligible subjects will be on a stable low-fat diet (according to local clinical guidelines) beginning at least 6 weeks prior to the first dose of Study Drug. The diet stabilization period may be reduced if the patient is following a stable low fat diet for optimal disease control and disease management prior to screening.

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.

Postprandial Assessment (Appendix E): Subjects will consume standardized pre-cooked meals (lunches and dinners (provided) and instructions for breakfasts and snacks) for the 2 days prior to the post-prandial evaluations. Patients will remain fasted after consuming the standardized pre-cooked meal for the dinner on the evening prior to their visit. Alcohol consumption is not allowed for the 2 days prior to the post-prandial evaluations. On each of the post-prandial evaluation days, following the blood draws, patients will consume a standardized liquid meal

(which represents about a third of the daily caloric requirements) with a stable radioisotope tracer, followed by an 8 hour radioisotope infusion and serial blood sampling. Patients will receive a standardized pre-cooked meal 9 hrs after consuming the liquid meal, after which they will fast until the 24 hour blood draw the following day.

6.1.4 Post-Treatment Period

Each subject will be followed for safety assessments for up to 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 on Days 119, 147 and 182 for safety and clinical laboratory evaluations. A ± 1-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 be taken after fasting for approximately 10 hours. During this time subjects can drink water and should ensure that they consume sufficient water to not become dehydrated.

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

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

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

6.3.2 Other Requirements

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

7. STUDY DRUG

7.1 Study Drug Description

7.1.1 AKCEA-ANGPTL3-L$_{RX}$ (ISIS 703802)

Study Drug characteristics are listed in Table 1.

A solution of Study Drug contained in stoppered glass vials will be provided. The Study Drug and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug must be stored securely at 2° to 8° Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	AKCEA-ANGPTL3-LRX (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 supplies provided by the Sponsor. The Study Center must return all used and unused Study Drug to the Sponsor or designee.

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.

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 stable lipid-lowering therapy 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. The medical monitor should be informed.

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described in Section 8.6 are met, the subject will be permanently discontinued from further treatment with Study Drug, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study.

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

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the FDA guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

All patients will have liver chemistry tests monitored every 2 weeks during and treatment and follow-up Period.

- In the event of appearance of symptoms or signs of hepatic injury (jaundice, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, abnormal bleeding or bruising, or eosinophilia > ULN) liver enzymes and bilirubin should be tested as soon as possible. Testing at a lab that is local to the patient is permissible for this purpose.
- In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (treatment or post-treatment period), the initial measurement(s) should be confirmed as described in Section 8.5.
- Patients with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR] and total bilirubin) retested at least once weekly until ALT and AST levels become ≤ 1.2 x ULN.

- All results of liver function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.1. Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN, the following evaluations should be performed:

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

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

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

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

Lab alerts for abnormal liver chemistry tests will be issued for:

1. ALT or AST > 3 x ULN;
2. ALT or AST > 2 x baseline;
3. total bilirubin > ULN;
4. ALP > ULN.

These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance referenced in Section 8.5.1. A more frequent liver function test monitoring may be recommended by the Investigator if warranted. The Investigator should inform the Medical Monitor.

All clinically significant lab alerts for monitoring/ stopping rules as described above are reviewed promptly by the Medical Monitor and communicated with the Investigator and/or the study personnel within 24 hours of receiving an actionable lab alert.

8.5.2 Safety Monitoring for Renal Function

All patients will have renal function tests monitored every 4 weeks throughout the study.

In the event of appearance of symptoms or signs consistent with renal dysfunction such as hematuria, polyuria, anuria, flank pain, new-onset hypertension, nausea and/or anorexia, renal function should be tested as soon as possible.

During the course of the study, urinary surveillance will include urinalysis to include urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR) and urinary red blood cells (RBCs), as well as serum creatinine and cystatin-C to estimate glomerular filtration rate (eGFR), which will be monitored every 4 weeks.

All renal function test results will be reviewed on an ongoing basis at the safety review by the Medical Monitor.

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

Lab alerts for abnormal renal tests will be issued for:

- Creatinine clearance (by CKD-EPI formula) decrease from baseline > 25%,
- Urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or
- An increase in serum creatinine from baseline > 0.3 mg/dL).

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

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

In addition, the following supplemental renal tests should be immediately obtained:

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

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

8.5.3 Safety Monitoring Rules for Platelet Count Results

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

In addition, platelet function may be evaluated by aggregometry, using an approved point-of-care diagnostic device, in all patients at each study site visit.

All platelet count results 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 rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3.

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

Lab alerts related to platelet monitoring/stopping rules are issued when:

1. Platelet counts are < 140,000 mm^3;
2. When platelet count is ≥ 30% decreased from baseline, or
3. When the hematology sample is unreportable.

Actions to be taken in the event of reduced platelet count are shown in Table 3 below. In the event of a platelet count < 100,000/mm^3 the laboratory tests outlined 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.

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

Platelet Count on Rx	Drug Dose	Monitoring
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

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

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

All clinically significant lab alerts for monitoring/stopping rules as described above are reviewed promptly by the Medical Monitor and communicated with the Investigator and/or the study personnel within 24 hours of receiving an actionable lab alert as described in Section 6.2.

8.5.4 Safety Monitoring for Minor Bleeding Events

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

8.6 Stopping Rules

For the purposes of the stopping rules, Baseline is defined as the average of the pre-dose test closest to Day 1 and Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

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

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5

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

8.6.2 Stopping Rules for Renal Function Test Results / 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 (AKCEA-ANGPTL3-L_{RX}) 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.

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.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is already on reduced dose, dosing of the patient with Study Drug will be stopped permanently (Table 3).

Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2

mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count < 75,000/mm^3 and > 50,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with Study Drug should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued it must be at a reduced dose as shown in Table 3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count after interruption of dosing. This will be documented in the patient by the investigator and filed in the TMF.rec.

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

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

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

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

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

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

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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.

Patients 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

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

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

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

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

Any patient who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in Table 3, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

If the patient declines or is unable to participate in the above, the early termination visit procedures should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.9 Withdrawal of Subjects from the Study

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

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

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).

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 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.

Disallowed concomitant therapy are identified in exclusion criteria, Section 5.2, and include the following as specified*:

- Anti-obesity medications (e.g., orlistat, sibutramine), or has discontinued treatment < 12 weeks prior to screening
- Fibrates within 8 weeks of screening
- Systemic corticosteroids or anabolic agents within 6 weeks of screening*
- Treatment with another investigational drug, biological agent, or device within 4 weeks of screening or 5 half-lives of study agent, whichever is longer
- Prior treatment with gene therapy
- No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification.
- Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted.
- Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.
- Other experimental agents during the study including investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. This includes marketed agents at experimental dosages
- Treatment with any non-Ionis oligonucleotide (including siRNA) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of screening. Patients that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months has elapsed since dosing

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

Note: 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.

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 (See Section 9.5.2)
- 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: [redacted]

Email: [redacted]

Fax: [redacted]

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

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

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

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

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug (e.g., confirmation by positive re-challenge test)
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D).
Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities
- **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration and dose
- **Permanently Discontinued:** Study drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Temporarily Interrupted, Restarted Reduced Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the next lower dose

9.4.3.4 Treatment Given for Adverse Event

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

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

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

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

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment (e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia). Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. 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 (AKCEA-ANGPTL3-L_{RX}) 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

For fasting lipid measurements, the values for the Month 3 analysis time point are defined as the average of Week 13 (Day 85) and Week 14 (Day 92) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Percent change and absolute change from baseline in fasting ANGPTL3
- Fasting lipid measurements, including: non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Postprandial TG change from baseline
- Frequency and severity of patient reported abdominal pain during the treatment period

10.1.2 Safety Endpoints

- Adverse events
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Electrocardiograms (ECGs)
- Use of concomitant medications

10.2 Sample Size Considerations

There is no formal statistical justification for the selected sample size. The sample size is selected based upon prior experience with AKCEA-ANGPTL3-L_{RX} to ensure that the safety, tolerability and efficacy of AKCEA-ANGPTL3-L_{RX} can be explored while minimizing unnecessary subject exposure. In 6 healthy volunteers, AKCEA-ANGPTL3-L_{RX} reported a 63% TG reduction after 6 weeks of administration.

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

Definitions of baseline are given below for the purposes of the final analysis.

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 patients 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 tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3 in fasting TG will be summarized. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3 will also be summarized by treatment group for other fasting lipid measures including ANGPTL3, non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

10.6.4 Pharmacokinetic Analysis

The plasma PK of AKCEA-ANGPTL3-L_{RX} (as total full length oligonucleotides, including, fully conjugated, partially conjugated, and unconjugated AKCEA-ANGPTL3-L_{RX}) will be assessed following multiple-dose SC administration. The plasma trough levels of AKCEA-ANGPTL3-L_{RX} during treatment period and those during post-treatment follow up period will be descriptively summarized with stratification by subject immunogenicity status if applicable.

10.6.5 Pharmacodynamic Analysis

The following parameters will be measured throughout the trial: Fasting TGs, plasma angiopoietin-like 3 (ANGPTL3), ANGPTL4, ANGPTL8, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), total apoC-III, apolipoprotein B-100 (apoB-100), apolipoprotein B-48 (apoB-48), apolipoprotein A-1

(apoA-1), apolipoprotein A-2 (apoA-2), apolipoprotein E (apoE), very-low-density lipoprotein-triglyceride (VLDL-TG), chylomicron-cholesterol (CM-C), chylomicron triglyceride (CM-TG), free fatty acids (FFA), and free glycerol levels.

10.6.6 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-AKCEA-ANGPTL3-L_{RX} antibodies) before, during, and after treatment with AKCEA-ANGPTL3-L_{RX} 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.

10.6.7 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 AKCEA-ANGPTL3-L_{RX} 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. The more recent Declaration of Helsinki version from 2013 is not being 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

Study Period		Screen / Run-in [a]	Treatment Period														Post-treatment Follow-up		
Study Week		-8 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14/ET	18	22	26
Study Day		-56 To -1	1 [b]	8	15	22	29	36	43	50	57	64	71	78	85	92	120	148	176
Visit and Testing Window +/- Days		0	0		2		2		2		2		2				3	3	3
Informed Consent		X																	
Inclusion/Exclusion Criteria		X	X																
Medical History		X																	
Height & Weight [c]		X	X				X				X					X			X
Vital Signs		X	X				X				X					X	X	X	X
Physical Examination [d]		X	X				X				X					X			X
12- lead ECG (triplicate)		X	X				X				X					X			X
Urinalysis[m]		X	X				X				X					X	X	X	X
Blood Draw [e]	Chemistry Panel (+ CPK) [f]	X	X		X [g]		X		X [g]		X		X [g]		X [g]		X		X
	CBC with Differential [f]	X	X		X [g]		X		X [g]		X		X [g]		X [g]	X	X [h]	X	X
	Serum Lipid Panel	X	X				X				X				X	X	X	X	X
	PD Panel		X				X				X				X	X	X	X	X
	Coagulation (aPTT, PT, INR)	X	X				X				X					X	X	X	X
	Complement Markers C5A, Bb	X	X													X			
	hsCRP,	X	X				X				X					X			X
	Hepatitis B, C. HIV. TSH. Free T_4	X	X																
	Plasma PK [i]		X[1]				X [1]		X [1]		X [1]		X [1]			X	X	X	X
	Genetic Testing [j]	X																	
	Anti-ANGPTL3-L_{RX} Antibodies		X[1]				X[1]				X[1]					X	X		X
	FSH (women only, if applicable) [k]	X	X																
	Serum Pregnancy Test [k]	X	X				X				X				X	X	X	X	X

Study Period	Screen / Run-in [a]	Treatment Period														Post-treatment Follow-up		
Study Week	**-8 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ET**	**18**	**22**	**26**
Study Day	**-56 To -1**	**1 [b]**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**120**	**148**	**176**
Visit and Testing Window +/- Days	**0**	**0**		**2**		**2**		**2**		**2**		**2**				**3**	**3**	**3**
HbA1C, FPG, and delipidated free glycerol	X	X																
Platelet aggregation	X	X				X				X					X			X
Archived Serum & Plasma [m]		X													X			X
Blood viscosity		X													X			
Post-Prandial Assessment	X[l]														X[l]			
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

a Screening procedures performed on the same day and the subject starts the tightly controlled diet, if needed.

b After 56 days on the controlled diet, patients will have baseline measurements and be assessed for qualification of enrollment.

c Height is only required on Day 1.

d Full physical exam to be given at Screening and abbreviated physical exam to be given during treatment and follow-up period as indicated to assess changes from screening.

e 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.

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

g 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.

h During follow-up period, hematology sampling for platelet values are taken every 14 days for 6 weeks after last dose of Study Drug, then at Week 22 and Week 26 Follow-up visits.

i Refer to Appendix C for PK Sampling schedule.

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

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

l Subjects will be provided standardized meal at Screening visit and will return to the site 2 days later for pre-dose postprandial assessments. Subjects will be provided standardized meal at the Week 14 visit and will return to the site 2 days later for post-dose postprandial assessments.

m Urine, 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

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of AKCEA-ANGPTL3-L_{RX} or other similar oligonucleotides.

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

Fasting Lipid Panel
- Total cholesterol
- Total ApoB
- ApoB-100
- ApoB-48
- LDL cholesterol
- HDL cholesterol
- Total Triglycerides
- CM triglycerides
- VLDL cholesterol
- VLDL triglycerides
- Non-HDL cholesterol

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG
- Drug screen

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

Complement
- C5a
- Bb

PD Panel
- ANGPTL3
- ANGPTL4
- ANGPTL8
- ApoA-I
- ApoB
- ApoC-III

Specialized Lipoprotein and post-prandial Analyses[1]
- Lipoprotein particle analysis
- Oxidized chylomicrons and VLDLs
- Isoprostanes
- HDL function
- Lipoprotein subclass analysis
- Newly formed CM kinetics
- Post-prandial lipid panel
- Post-prandial platelet count
- Post-prandial glucose

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

Thyroid Panel
- TSH
- Free T4
- Free T3

Pharmacokinetics and Immunogenicity[2]
- AKCEA-ANGPTL3-L_{RX} levels in plasma
- Anti- AKCEA-ANGPTL3-L_{RX} antibodies in plasma

Genetic Testing
- Molecular confirmation of FCS
- Genetic sequencing of FCS causing genes[3]

Post-Heparin Panel[4]
- Post-heparin lipoprotein lipase mass
- Post-heparin lipoprotein lipase activity
- Post-heparin triglycerides

Inflammatory
- Hs-CRP
- IL-1b, IL-6, IL-8
- Cytokines panel

Urinalysis
- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[5]
- P/C Ratio[6]

1 Scope of specialized lipoprotein analyses will be determined based on results from fasting lipid panel

2 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation, stability assessments, metabolite assessments, testing of additional exploratory pharmacodynamics markers, immunogenicity testing (or possibly for immunogenicity assay development and/or validation), or to assess other actions of AKCEA-ANGPTL3-L_{RX} with plasma constituents

3 If the genotype is not already available, blood will be collected to assess genetic evidence of null loss-of-function for LPL. May not be collected if adequate genetic data are available in medical history or if patient does not consent to genetic testing

4 Will be performed on samples per schedule in Appendix D. Samples may be used to assay other analytes
5 Will be performed on abnormal findings unless otherwise specified
6 Will be performed at Screening only

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

D1	D29	D43	D57	D71	D92	D120	D148	D176
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 Post-prandial Meal, Sampling Schedule, and Assessment

Appendix E Post-prandial Meal, Sampling Schedule, and Assessment

Post-prandial assessment for lipoproteins metabolism will be performed using a radiolabelled meal supplemented with a labeled tracer, ^{3}H-palmitate (300µCi, [redacted] Canada), sonicated into the liquid meal. Palmitate is a fatty acid that is a common constituent of any diet. The ^{3}H-palmitate tracer emits weak radioactivity, equivalent to an X-ray. Since dietary palmitate is incorporated into chylomicrons as they are formed in the enterocytes of the gut, this enables monitoring the appearance and clearance of newly-formed chylomicrons from circulation. The methodology to be applied for studying post-prandial kinetics of chylomicrons appearance and clearance is well-established (Mittendorfer et al. 2003; Bickerton et al. 2007; Normand-Lauziere et al. 2010).

A liquid meal (similar to a milkshake) containing a small amount (300µCi) of radiolabelled fatty acids (^{3}H-palmitate) will be provided. The liquid meal will provide about a third of the daily caloric requirements. From 1 hr prior to 9 hrs after the ingestion of the meal, a constant infusion of [U-^{13}C]-K palmitate (0.01µmol/kg/min in 100 ml 25% human serum albumin; [redacted]) and a primed (1.6 µmol/kg) continuous (0.05 µmol/kg/min) infusion of [1,1,2,3,3-^{2}H]-glycerol [redacted] will be administered as previously described (Normand-Lauziere et al. 2010). Plasma palmitate and glycerol appearance rates will be calculated using Steele's non-steady state equation assuming a volume of distribution of 90ml/kg and 230ml/kg, respectively (Gastaldelli et al. 1999).

Blood samples will be drawn at intervals before and after the ingestion of the radiolabelled meal on days prior to and after the Treatment phase as noted in the table below. A standardized meal will be given to the participants after the 9 hr blood draw. Blood will be collected in tubes containing Na_2EDTA and Orlistat (30 µg/ml, [redacted] Canada) to prevent *in vitro* triacylglycerol lipolysis and separate samples will be collected in NaF tubes for plasma glucose determination.

Post-prandial Sampling (Blood) Schedule

Study Day	D -1	D1	D103	D104
Visit Window +/- Days	0	0	2	0
	-1 hr pre-prandial, and 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hrs post prandial	24 hrs post-prandial /pre SC injection	-1 hr pre-prandial, and 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hrs post-prandial	24 hrs post-prandial

The following will be measured:

- Plasma and CM fraction levels for ^{3}H-tracer
- Plasma [U-^{13}C]-K palmitate and [1,1,2,3,3-^{2}H]-glycerol appearance rates

- Plasma and CM fraction levels for TG, TC, and apoB
- Plasma, CM, and VLDL fraction levels for apo CIII, apo CII, and apo E
- Plasma levels for glucose and insulin

Plasma samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, or to assess other actions of AKCEA-ANGPTL3-L_{RX} with plasma constituents.

Sponsor:
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Collaborator:
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IONIS PHARMACEUTICALS, INC.

ISIS 703802-CS3

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 1 – 26 OCTOBER 2017

ISIS 703802-CS3

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 1– 26 OCTOBER 2017

Protocol History

Original Protocol: 20 JULY 2017

Protocol Amendment 1: 26 OCTOBER 2017

Approved by:

[redacted]

[redacted] MD, FACP

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ISIS 703802-CS3

Ionis Protocol Number ISIS 703802-CS3

Protocol Amendment 1

Clinical Phase: 2

A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 26 OCTOBER 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 703802-CS3
Protocol Title:	**A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)**
Amendment:	Protocol Amendment 1
Date:	26 OCTOBER 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 2 Open-Label Study of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)" dated 26 OCTOBER 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.

[redacted]
Investigator's Signature

[redacted]
Investigator's Name *(please print)*

2017 Nov 29
Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 703802-CS3

Protocol Title: **A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)**

Amendment Number: Protocol Amendment 1

Amendment Date: 26 OCTOBER 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 703802-CS3 Original Protocol dated 20 July 2017:

- Change in language for Exclusion Criteria on how to confirm urine laboratory tests
- Further clarify in the Synopsis that subjects who are on a stable diet do not need to have a six week diet stabilization period during screening period
- Include language requested by Health Authority
- Include a measure of abdominal pain assessment (this change is not included in the table below, it has resulted in one additional line in the Schedule of Procedures, Appendix A).
- Appendix E was modified to remove the stable isotope tracer [U-^{13}C]-K palmitate and replace it by L-[5,5,5-D3] leucine, allowing to document kinetics of all apolipoprotein B containing lipoproteins. Section 6.1.2 has also been updated to align with these changes.
- An objective has been added in order to align with the update to the post-prandial assessment: To evaluate postprandial lipoprotein kinetics: of CM, VLDL, IDL, LDL and HDL
- Clarify various inconsistencies:
  - Screening period duration
  - Fibrates have been deleted from disallowed concomitant therapy
  - Change to contact for SAE reporting
  - Plasma TG is being updated to serum TG for efficacy analysis
  - Urine samples will not be archived
  - Appendix A has updates, including deletion of FSH at week 1, deletion of FPG since this parameter is being measured with the chemistry panel, platelet aggregation has been deleted from screening visit, footnote (a, g, l and m) in SOP have changed.
  - Appendix B has updates, including deletion of Post Heparin Panel, as that assessment will not be done, deletion of Free T3 under the Thyroid Panel, deletion of drug screen under Screening Tests, inclusion of cystatin-C under Clinical Chemistry Panel, inclusion of the category Cytokine Panel under Inflammatory and A/C Ratio (UACR) under Urinalysis, Specialized Lipoprotein and post-prandial Analyses section has been updated and 24 Hour Urine Test has been added (these changes do not appear in the table below, they appear updated in Appendix B).
  - Appendix E has been updated to have the pre-dose post-prandial assessment done over a period prior to first dose and the post-dose post-prandial assessment is now aligned with

week 14 in Appendix A (this change does not appear in the table below, it only appears updated in Appendix E).

- Two new references have been included as a result to the changes to Appendix E.

Protocol Section	Description of Change	Rationale
Synopsis Section 5.2 Subject Eligibility Exclusion Criteria	WAS: • ~~Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs~~ • ~~Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field~~ • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (~~MDRD or~~ CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) IS: • **Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field** • **Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr** • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)	Central laboratory will be used for this trial. Language revised to align with safety monitoring process at central laboratory.
Synopsis Study Visit Schedule and Procedures	WAS: • An up to 8-week screening period, including a diet stabilization period of at least 6 weeks IS: • An up to 8-week screening period, including a diet stabilization period of at least 6 weeks **for subjects who are not already on a stable diet**	The additional language further clarifies that subjects already on a stable diet can forgo the diet stabilization period and aligns with other sections of the protocol.
Synopsis and Section 1.2	WAS: To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on postprandial TG IS: To evaluate the effect of AKCEA-ANGPTL3-LRX on postprandial TG **and lipoprotein kinetics: of CM, VLDL, IDL, LDL and HDL**	An objective was added in order to align with the change made to the post-prandial assessment.
Section 6.1.1	WAS: A **4** week period…	The inconsistency of this section was corrected to align

	IS: **An up to 8** week period… **Subjects on stable diet known to the investigator and followed at the site may skip the 4-week diet run-in.**	with all other sections and further instruction is provided for subject on a stable diet.
Section 6.1.2	WAS: … On each of the post-prandial evaluation days, following the blood draws, patients will consume a standardized liquid meal (which represents about a third of the daily caloric requirements) ~~with a stable~~ radioisotope tracer, followed by an 8 hour ~~radioisotope~~ infusion and serial IS: On each of the post-prandial evaluation days, following the **first** blood draw, patients will consume a standardized liquid meal (which represents about a third of the daily caloric requirements) **containing a** radioisotope tracer, followed by an **9** hour infusion **of two stable isotope tracers** and serial	
Section 6.1.4	WAS: A ± **1**-day excursion from the scheduled visit date is permitted for this time period. IS: A ± **3**-day excursion from the scheduled visit date is permitted for this time period.	Correction made to align with Appendix A.
Section 6.2	WAS: Blood chemistry and urine samples (excluding 24-hour urine collection) should be taken ~~be taken~~ after fasting… IS: Blood chemistry and urine samples (excluding 24-hour urine collection) should be taken after fasting…	Error corrected
Section 8.5.1	WAS: All patients will have liver chemistry tests monitored every 2 weeks during **and** treatment and follow-up Period. IS: All patients will have liver chemistry tests monitored every 2 weeks during **the** treatment and follow-up Period.	Error corrected.
Section 8.10.1	WAS: ~~Fibrates within 8 weeks of screening~~ IS: Not applicable	The inconsistency of this section was corrected to align with all other sections.
Section 9.4.1	WAS: **Attention:** [redacted] **Email:** [redacted] **Fax:** [redacted]	The safety reporting vendor was changed.

	IS: [redacted] [redacted] – USA: Telephone: [redacted] **or** [redacted] Facsimile: [redacted] **or** [redacted] e-mail: [redacted]	
Section 10.6.3	WAS: Response rate of patients with fasting **plasma** TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3 will be summarized. Response analysis will also be conducted using a range of fasting **plasma** TG thresholds for determination of responder status. IS: Response rate of patients with fasting **serum** TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3 will be summarized. Response analysis will also be conducted using a range of fasting **serum** TG thresholds for determination of responder status.	The matrix in which TG are measured in serum.
Section 11.1	WAS: Not applicable IS: **The sponsor shall maintain all records referred to in the applicable Regulations for a period of 25 years.**	Requested by Health Authority
Appendix A footnote	WAS: ~~Urine~~, 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. IS: 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.	There is no plan to archive urine from subjects in this trial.
Appendix E footnote	WAS: Not applicable IS: **a There is a range for this visit, it should happen prior to and as close as possible to Day 1.**	Clarification
Appendix E	WAS: Post-prandial assessment for lipoproteins metabolism will be performed ~~using a~~ radiolabelled meal supplemented with a	This change will allow documentation of kinetics for all apolipoprotein B containing

	labeled tracer, ^{3}H-palmitate (300µCi, [redacted] Canada), sonicated… A liquid meal (similar to a milkshake) containing a small amount (300µCi) of radiolabelled fatty acids (^{3}H-palmitate) will be provided. The liquid meal will provide about a third of the daily caloric requirements. From 1 hr prior to 9 hrs after the ingestion of the meal, ~~a constant infusion of [U-^{13}C] K palmitate (0.01 µmol/kg/min in 100 mL 25% human albumin;~~ [redacted] ~~) and a~~ primed (1.6 mmol/kg) continuous (0.05 mmol/kg/min) infusion of [1,1,2,3,3-^{2}H]-glycerol [redacted] will be administered as previously described (Normand-Lauziere et al. 2010). ~~Plasma palmitate and~~ glycerol appearance rates will be calculated using Steele's non-steady state equation assuming a volume of distribution of 90mL/kg and 230ml/kg, respectively (Gastaldelli et al. 1999). … ~~The following will be measured:~~ ~~Plasma and CM fraction levels for ^{3}H tracer~~ ~~Plasma [U-^{13}C] K palmitate and [1,1,2,3,3-^{2}H] glycerol appearance rates~~ ~~Plasma and CM fraction levels for TG, TC, and apoB~~ ~~Plasma, CM, and VLDL fraction levels for apo CIII, apo CII, and apo E~~ ~~Plasma levels for glucose and insulin~~ IS: Post-prandial assessment for lipoproteins metabolism **(lipoprotein kinetics: newly formed CM, VLDL, IDL, LDL and HDL)** will be performed as follow. A radiolabelled meal supplemented with a labeled tracer, ^{3}H-palmitate (300µCi, [redacted] Canada), **will be** sonicated A liquid meal (similar to a milkshake) containing a small amount (300µCi) of radiolabelled fatty acids (^{3}H-palmitate) will be provided. The liquid meal will provide about a third of the daily caloric requirements. From 1 hr prior to 9 hrs after the ingestion of the meal, **two stable isotope tracers will be continuously infused.** A primed (1.6 mmol/kg) continuous (0.05 mmol/kg/min) infusion of [1,1,2,3,3-^{2}H]-glycerol [redacted] will be administered as previously described (Normand-Lauziere et al. 2010). **To document VLDL, IDL, LDL and HDL kinetics, L-[5,5,5-D3] leucine (10 mmol/kg) will be injected as a bolus intravenously and then by continuous infusion (10 mmol·kg body weight^{-1}·h^{-1}) (**Tremblay et al. 2006**).** Glycerol appearance rates will be calculated using Steele's non-steady state equation assuming a volume of distribution of 230ml/kg, respectively (Gastaldelli et al. 1999). **The isotopic enrichment of leucine in the apolipoproteins will be expressed as tracer/tracee ratio (%) using standardized formulas (**Cobelli et al. 1987**).**	lipoproteins.

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2 Open-Label Study to Assess the Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of AKCEA-ANGPTL3-L_{RX} (ISIS 703802) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	2
Indication	Familial Chylomicronemia Syndrome
Objectives	The primary objective is to evaluate the efficacy of AKCEA-ANGPTL3-L_{RX} for reduction of triglyceride (TG) levels in patients with FCS Secondary objectives are: To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on plasma angiopoietin-like 3 (ANGPTL3) and other lipid parameters. To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on postprandial TG and lipoprotein kinetics: of CM, VLDL, IDL, LDL and HDL To evaluate the pharmacokinetics of AKCEA-ANGPTL3-L_{RX} To evaluate safety and tolerability of AKCEA-ANGPTL3-L_{RX}
Study Design	This is an, open-label study in 3 FCS patients. After confirming eligibility for the study during the screening period, patients will enter a 13-week treatment period. Study drug (AKCEA-ANGPTL3-L_{RX}) will be administered every week for 13 weeks during the treatment period. The patients will then enter a 13 week post-treatment evaluation follow-up period.
Number of Subjects	3
Study Population	*Inclusion:* 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements. 2. Males or females aged ≥ 18 years old at the time of informed consent 3. Genetically confirmed homozygote or compound heterozygote for known null loss-of-function mutations in the LPL gene. 4. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening. If the fasting TG < 750 mg/dL up to 2 additional tests may be performed in order to qualify. 5. Willing to follow a diet comprising ≤ 20g fat per day during the study 6. Females: must be non-pregnant and non-lactating and either; i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved); iii. Abstinent* or, iv. If engaged in sexual relations of child-bearing potential, agree to

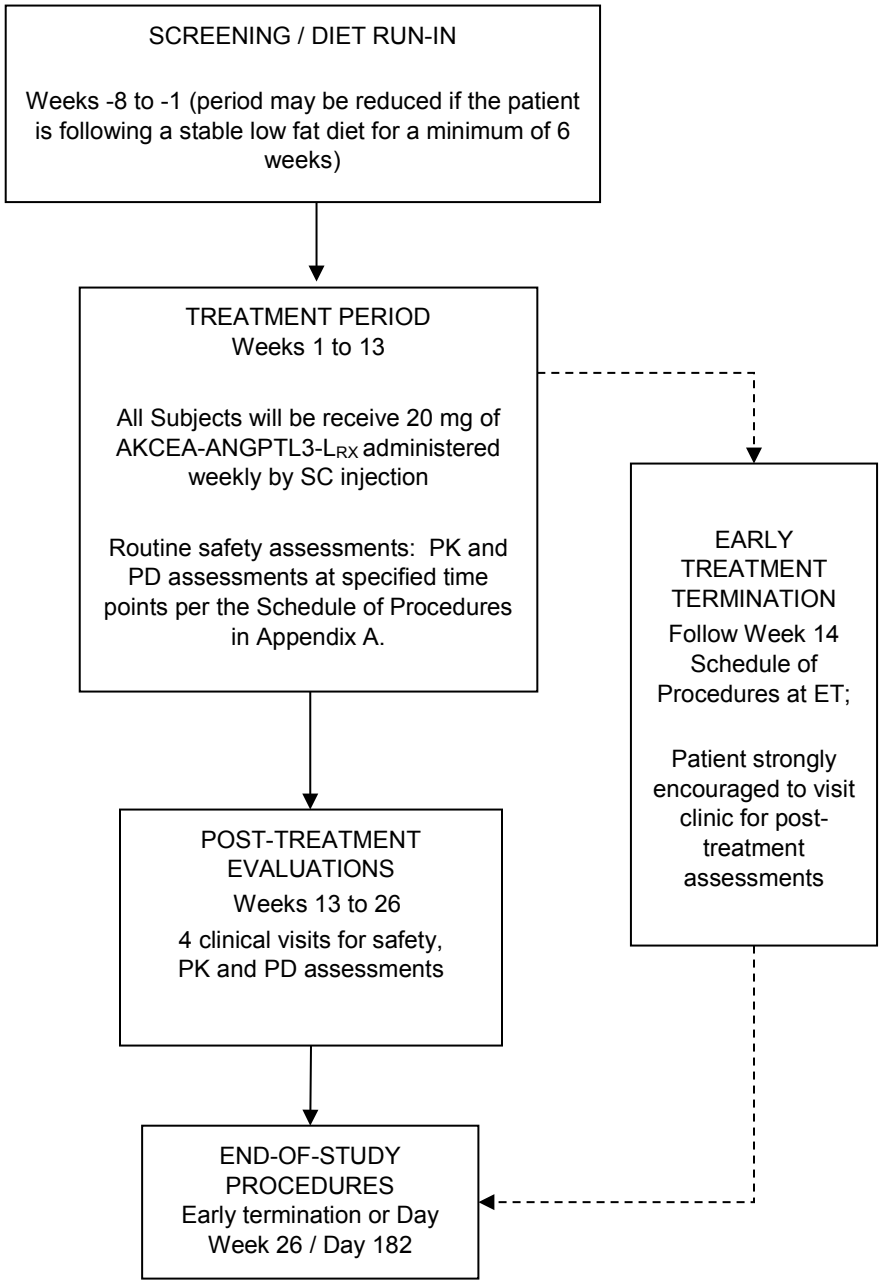
	use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L_{RX}) a. Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject 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 (AKCEA-ANGPTL3-L_{RX}) * 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:* 1. Diabetes mellitus with any of the following: b. Newly diagnosed within 12 weeks of screening c. HbA1c ≥ 9.0% at Screening d. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) e. Current use of GLP-1 agonists 2. Active pancreatitis within 2 weeks prior to screening 3. 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 cardiac failure requiring a change in medication) or major surgery within 3 months of screening 4. Any of the following laboratory values at Screening f. Hepatic: g. Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL h. ALT > 2.0 x ULN i. AST > 2.0 x ULN j. Renal: • Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr k. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (CKD-EPI

	formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) l. Platelet count < 140,000 mm^3 m. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg) 6. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 7. History of heart failure with NYHA greater than Class II 8. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 9. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 10. 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 11. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer 12. Unwilling to comply with lifestyle requirements 13. Use of any of the following: a. Statins, omega-3 fatty acids (prescription or OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study. b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed 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 during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to AKCEA-ANGPTL3-L_{RX} k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 14. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 15. Known hypersensitivity to any of the excipients of the Study Drug 16. 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 AKCEA-ANGPTL3-L_{RX} by subcutaneous injection at 20 mg weekly
Study Drug Dosage and Administration	The Sponsor will provide AKCEA-ANGPTL3-L_{RX} in a single use vial with a concentration of 100 mg/mL. The study dose of 20 mg (0.2 mL) of AKCEA-ANGPTL3-L_{RX} will be administered every week during the treatment period. All doses will be given by SC injection. Self-administration will be allowed after appropriate training of patient and/or caregiver.
Rationale for Dose and Schedule Selection	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 AKCEA-ANGPTL3-L_{RX} observed in healthy volunteers with elevated TGs.
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 consist of the following periods: An up to 8-week screening period, including a diet stabilization period of at least 6 weeks for subjects who are not already on a stable diet A 13 week treatment period during which Study Drug will be administered open label by SC injection A 13-week post-treatment follow-up period Patients will receive up to 13 SC doses of AKCEA-ANGPTL3-L_{RX} weekly. Patients will return regularly for outpatient visits throughout the treatment and post-treatment follow-up periods according to the Schedule of Procedures (Appendix A). Blood and urine samples will be collected regularly throughout the study for safety, efficacy, and PK analysis. Appendix B shows a list of analytes required for the study and Appendix C details the PK sample schedules.
Pharmacodynamic and postprandial Evaluations	Fasting TGs, plasma angiopoietin-like 3 (ANGPTL3), ANGPTL4, ANGPTL8, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C). total apoC-III, apolipoprotein B-100 (apoB-100), apolipoprotein B-48 (apoB-

	48), apolipoprotein A-1 (apoA-1), apolipoprotein A-2 (apoA-2), apolipoprotein E (apoE), very-low-density lipoprotein-triglyceride (VLDL-TG), chylomicron-cholesterol (CM-C), chylomicron triglyceride (CM-TG), free fatty acids (FFA), and free glycerol levels Postprandial TGs and lipoprotein kinetics: of CM, VLDL, IDL, LDL and HDL prior and post dose by postprandial assessment
Pharmacokinetic Evaluations	The plasma PK of AKCEA-ANGPTL3-L_{RX} (as total full length oligonucleotides, including, fully conjugated, partially conjugated, and unconjugated AKCEA-ANGPTL3-L_{RX}) will be assessed following multiple-dose SC administration. The plasma trough levels of AKCEA-ANGPTL3-L_{RX} during treatment period and those during post-treatment follow up period will be descriptively summarized with stratification by subject immunogenicity status if applicable.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: adverse events, vital signs and weight, physical examinations, clinical laboratory tests, ECGs and use of concomitant medications.
Statistical Considerations	There is no statistical rationale for the selected sample size. The sample size is based on prior experience with second generation and N-acetyl galactosamine (GalNAc)-modified antisense oligonucleotides (ASOs) in healthy volunteers and to ensure that the safety, tolerability, pharmacokinetics, and preliminary pharmacodynamics of AKCEA-ANGPTL3-L_{RX} will be adequately assessed while minimizing unnecessary subject exposure.
Sponsor / Collaborator	Ionis Pharmaceuticals/Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
apoA-I	Apolipoprotein A-I
apoB	Apolipoprotein B
apoC-III	Apolipoprotein C-III
aPTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC_t	Area under the plasma concentration-time curve from zero time (pre-dose) to selected time (t) after Study Drug administration
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CK	Creatine kinase
C_{max}	Maximum observed drug concentration
Day 1	Defined as the first day Study Drug product is administered to the subject
ECG	Electrocardiogram
eCRF	Electronic case report form
FCS	Familial Chylomicronemia Syndrome
FH	Familial hypercholesterolemia
FHBL	Familial hypobetalipoproteinemia
FHBL2	Familial combined hypolipidemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation/Acronym	Definition
HbA1c	Glycated hemoglobin
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HoFH	Homozygous familial hypercholesterolemia
HR	Heart rate
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional review board
LDL-C	Low density lipoprotein cholesterol
LDLR	LDL receptor
LLN	Lower limit of normal
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
MedDRA™	Medical Dictionary for Regulatory Activities
MOE	2′-*O*-(2-methoxyethyl)
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid (RNA)
MTP	Microsomal triglyceride transfer protein
NCS	Not clinically-significant
NEFA	Non-esterified fatty acids
Non-HDL-C	Non-high density lipoprotein cholesterol
OTC	Over-the-counter
P/C	Urine protein/creatinine
PCSK9	Proprotein convertase subtilisin kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time

Abbreviation/Acronym	**Definition**
RBC	Red blood cell
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SC	Subcutaneous
siRNA	Small interfering RNA
Study Drug	AKCEA-ANGPTL3-L_{RX} (ISIS 703802)
SUSAR	Suspected unexpected serious adverse reactions
t	Times
$t_{1/2\lambda z}$	Plasma terminal elimination half-life
TC	Total cholesterol
TG	Triglyceride
T_{max}	Time to reach C_{max}
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol

1. OBJECTIVES

1.1 Primary Objective(s)

- The primary objective is to evaluate the efficacy of AKCEA-ANGPTL3-L_{RX} (also known as ISIS 703802 in this document) for reduction of triglyceride (TG) levels in patients with FCS

1.2 Secondary Objective(s)

- To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on plasma angiopoietin-like 3 (ANGPTL3) and other lipid parameters.
- To evaluate the effect of AKCEA-ANGPTL3-L_{RX} on postprandial TG and lipoprotein kinetics: of CM, VLDL, IDL, LDL and HDL
- To evaluate the pharmacokinetics of AKCEA-ANGPTL3-L_{RX}
- To evaluate safety and tolerance of AKCEA-ANGPTL3-L_{RX}

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

FCS is characterized by frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and in children, can result in a failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011). Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011).

Patients with FCS often present in infancy or childhood with recurrent episodes of abdominal pain or pancreatitis, eruptive xanthomas or hepatomegaly. The diagnosis of FCS is then established by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, one hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze

triglycerides in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

The preclinical and human genetic studies strongly support a potential role for an ASO approach to lower plasma ANGPTL3 in humans to decrease elevated TG and LDL-C levels in patients that cannot be adequately managed by existing therapies.

Numerous genome-wide association studies have been published in recent years confirming the association of mutations in human ANGPTL3 with reductions in serum lipids in human subjects (Minicocci et al. 2013). The mechanism(s) by which ANGPTL3 affects lipoprotein metabolism appears to be complex, as loss of ANGPTL3 leads to a decrease in multiple atherogenic lipoprotein levels that is hard to ascribe to any 1 single mode of action. ANGPTL3 deficiency in animals accelerates the clearance of VLDL particles from plasma because of increase in lipoprotein lipase (LPL) activity, whereas overexpression or intravenous injection of recombinant ANGPTL3 has opposite effects. These and other observations support a possible role of the LPL enzyme. However, a direct demonstration of this mechanism has not been provided. Understanding the mechanism of action of ANGPTL3 is a present area of active research (Gusarova et al. 2015; Haridas et al 2015; Wang X et al. 2015; Wang Y et al. 2015a; Wang Y et al. 2015b).

The goal of the present protocol is to explore the effects of lowering ANGPTL3 in FCS patients using AKCEA-ANGPTL3-L_{RX} (also known ISIS 703802), using a dose selected on the basis of results in healthy volunteers, to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of AKCEA-ANGPTL3-L_{RX} in these patients.

The known potential risks to study participants associated with AKCEA-ANGPTL3-L_{RX} are further discussed in the Guidance to Investigator section of the Investigator's Brochure.

2.3 AKCEA-ANGPTL3-L_{RX} (ISIS 703802)

2.3.1 Mechanism of Action

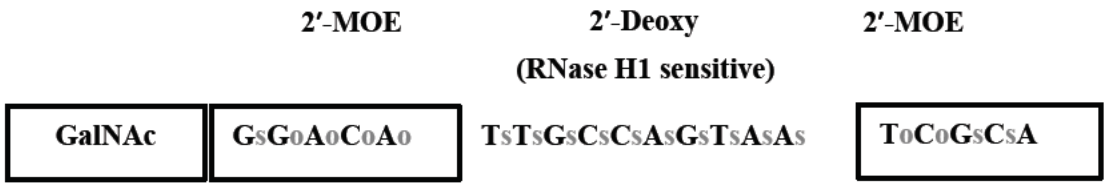
AKCEA-ANGPTL3-L_{RX} is a second-generation ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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, AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} (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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX}, at doses higher than planned for AKCEA-ANGPTL3-L_{RX}.

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 AKCEA-ANGPTL3-L_{RX}, a human specific 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 AKCEA-ANGPTL3-L_{RX} consisted of sub-chronic (16-week) and chronic (26- or 39-week) toxicity studies CD-1 in mice and cynomolgus monkeys. Since AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX}.

Pharmacokinetic data confirmed continuous and dose-dependent exposure to AKCEA-ANGPTL3-L_{RX}. An estimated liver and plasma 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 AKCEA-ANGPTL3-L_{RX} 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 pre-study 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 AKCEA-ANGPTL3-L_{RX} in humans.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with AKCEA-ANGPTL3-L_{RX} can be found in the Investigator's Brochure. A summary is included below.

The study drug, AKCEA-ANGPTL3-L_{RX}, 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 AKCEA-ANGPTL3-L_{RX}, was also evaluated in a blinded, placebo-controlled Phase 1 study.

AKCEA-ANGPTL3-L_{RX} Phase 1 SAD/MAD interim analysis of 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 AKCEA-ANGPTL3-L_{RX} 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 ANGPTL3-L_{Rx}) and three reported dizziness (two who received placebo and one who received ANGPTL3-L_{Rx}). There was no clinical evidence of prothrombotic effects, bleeding episodes, significant decreases in platelet count or thrombocytopenia, or significant changes in liver or renal function. 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).

The pharmacokinetics of AKCEA-ANGPTL3-L_{RX} 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 AKCEA-ANGPTL3-L_{RX} declined in a multi-phasic fashion with a rapid disposition phase, followed by a slower elimination phase with terminal elimination half-life of 3 to 5 weeks. The peak (C_{max}) and total exposure (AUC) after a single SC dose increased approximately dose proportionally from 20 to 40 mg, and greater than dose proportionally from 40 to 80 mg, suggesting more efficient tissue uptake at lower doses. After single and multiple SC doses in the range of 10 to 60 mg, the

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

2.3.4.1 ISIS 563580-CS1 Phase 1 SAD/MAD

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

2.4 Rationale for Dose and Schedule of Administration

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 AKCEA-ANGPTL3-L_{RX} in chronic monkey study was determined to be 12 mg/kg/wk.

Preclinical pharmacology experiments in Tg-mice and in non-human primates demonstrated that AKCEA-ANGPTL3-L_{RX} achieved an equivalent reduction in ANGPTL3 plasma concentration to that of the unconjugated form, at $1/10^{th}$ of the unconjugated ASO (ISIS 563580) dose. The dose level planned for this study for AKCEA-ANGPTL3-L_{RX} is 20 mg, which is the lowest dose that provided maximum TG lowering of approximately 60% in Study ISIS 703802-CS1 and is approximately 200-fold lower than NOAEL dose in monkey at 12 mg/kg/wk in the 39-week chronic monkey study up to terminal necropsy.

An interim analysis of the phase 1 study completed for all but the 120 mg single dose cohort showed approximately 60% reduction of TG at 20 mg dose. However, at 40 mg and 60 mg dose the TG reduction did not differ significantly from 20 mg dose. Thus, the lower dose was selected for this study for optimal risk to benefit.

2.5 Benefit-Risk Assessment

2.5.1 Benefit Assessment

The current study is designed to evaluate the safety and tolerance of AKCEA-ANGPTL3-L_{RX} in FCS subjects. The dose selected is expected to reduce ANGPTL3 and result in a reduction of the severe hypertriglyceridemia and chylomicronemia that afflicts FCS subjects. Importantly, although we do not know if subjects participating in this study would necessarily benefit from the treatment, the increased understanding of AKCEA-ANGPTL3-L_{RX} in this population is expected to result in improved treatment options that would ultimately benefit all FCS patients, including participants in the study. 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 AKCEA-ANGPTL3-L_{RX} are elaborated on in the Guidance to Investigator section of the Investigator's Brochure.

- In preclinical mouse studies, there were increases in ALT and AST and were correlated with increased incidence and/or severity of necrosis of individual hepatocytes (minimal to mild in severity). Those changes were most prominent in the high dose groups and showed no clear progression over time. No increases in liver enzymes were observed in monkeys from the 39-week toxicity study up to 12 mg/kg/week (~200-fold of the 20 mg clinical dose by plasma AUC). In the 16-week monkey study, increase in ALT was only evident in 1 early-sacrifice animal at 35 mg/kg/week, no meaningful increase in ALT was observed in the schedule sacrificed animals.
- There were no observed significant changes in ALT and liver function in an ongoing Phase 1 human study (Graham et al. 2017). The risk of observing significant ALT/AST changes in this clinical human study is expected to be relatively low with the proposed 20 mg dose. 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 patient to tolerate dosing. Injection site adverse events are the most common side effects observed following SC administration of 2′-MOE ASOs and are dose and concentration dependent. Erythema is the most prevalent characteristic. Generally, these events are mild and reversible, resolve spontaneously and do not worsen with time. The histologic findings are consistent with a local inflammatory response. While planned doses of AKCEA-ANGPTL3-L_{RX} for clinical evaluation are generally below the doses that are historically associated with these effects, patients 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.

While the long term consequences 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 despite a reported decrease in VLDL production, there is no apparent difference in hepatic fat content compared to controls. 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

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Given the unmet medical need for FCS patients, AKCEA-ANGPTL3-L_{RX} has demonstrated the ability to reduce TGs by 60% in the Phase 1/2 study in healthy volunteers. The objective of this study is to assess the effect of TG lowering in FCS patients. Although the FCS patients enrolled in this study will not derive long term benefits due to the short duration of the

study, the information obtained in the course of this study is critical to further development of AKCEA-ANGPTL3-L_{RX} for this disease with an extremely high unmet need. Taking into account the measures taken to minimize risk to subjects participating in this study, the fact that potential risks identified in association with AKCEA-ANGPTL3-L_{RX} are minimal and are manageable by routine monitoring exposure of FCS patients in this study is justified by the anticipated benefits that may be afforded to the wider population of FCS subjects by continued development of AKCEA-ANGPTL3-L_{RX}.

3. EXPERIMENTAL PLAN

3.1 Study Design

This will be a Phase 2 open-label multiple-dose study of approximately 3 subjects with FCS and will be treated with AKCEA-ANGPTL3-L_{RX}.

Subject will receive 20 mg of AKCEA-ANGPTL3-L_{RX} SC weekly.

3.2 Number of Study Centers

This study will be conducted at a single center but could be expanded to more than one center.

3.3 Number of Subjects

Approximately 3 subjects will be treated in this study.

3.4 Overall Study Duration and Follow-up

The study will consist of a screen/ run-in period, study treatment, post-treatment and long term follow-up. Please refer to the Schedule of Procedures in Appendix A.

Subjects may be required to attend additional visits for monitoring of adverse events or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

The length of subjects' participation in the study may be up to 34 weeks, including an up to 8-week screening period, that includes a 6-week diet stabilization / run-in period, a 13-week treatment period, and a 13-week post-treatment evaluation period. Subjects will perform the first dosing at the site, with subsequent dosing occurring at home following training on how to dose. The diet stabilization period may be reduced if the patient is following a stable low fat diet for optimal disease control and disease management prior to screening.

3.4.1 Screening

Subject eligibility for the study will be determined within 56 days/8 weeks prior to study entry.

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 13-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 every four weeks (refer to the Schedule of Procedures in Appendix A). The final study visit will be Study Week 26.

3.5 End-of-Study

The End-of-Study is defined as the last subject's last visit.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the Study, the Sponsor or designee requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

Subjects must sign the informed consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled into the Study and will be assigned a unique screening number before any Study procedures, including screening procedures, are performed. At the time of randomization or registration, subjects will be assigned a unique subject identification number. 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 screening number and subject identification number must remain constant throughout the entire trial. Screening numbers and subject identification numbers, once assigned, will not be reused.

4.2 Registration

Patients 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 56 days of treatment day 1 or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements.
2. Males or females aged $\geq$ 18 years old at the time of informed consent.
3. Genetically confirmed homozygote or compound heterozygote for known null loss-of-function mutations in the LPL gene.
4. Fasting TG $\geq$ 750 mg/dL (8.4 mmol/L) at Screening. If the fasting TG < 750 mg/dL up to 2 additional tests may be performed in order to qualify.

5. Willing to follow a diet comprising ≤ 20g fat per day during the study.
6. Females: must be non-pregnant and non-lactating and either;
   i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);
   ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);
   iii. Abstinent* or,
   iv. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (AKCEA-ANGPTL3-L_{RX}).
7. Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject 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 (AKCEA-ANGPTL3-L_{RX}).

* 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. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c ≥ 9.0% at Screening
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])
   d. Current use of GLP-1 agonists
2. Active pancreatitis within 2 weeks prior to screening
3. 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 cardiac failure requiring a change in medication) or major surgery within 3 months of screening
4. Any of the following laboratory values at Screening
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN
   b. Renal:

- Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
- Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. In the event of a UPCR above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min (CKD-EPI formula can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Platelet count < 140,000 mm^3

d. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

5. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
6. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
7. History of heart failure with NYHA greater than Class II
8. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
9. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
10. 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
11. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
12. Unwilling to comply with lifestyle requirements (Section 6.3)
13. Use of any of the following:

    a. Statins, omega-3 fatty acids (prescription or OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening

    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor

    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study

    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period

f. Glybera gene therapy within 2 years prior to screening

g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed

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 during the treatment period

i. Plasma apheresis within 4 weeks prior to screening or planned during the study

j. Prior exposure to AKCEA-ANGPTL3-L_{RX}

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

14. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
15. Known hypersensitivity to any of the excipients of the Study Drug
16. 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 period. These periods are described below.

All required study procedures are outlined in Appendix A.

6.1.1 Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. An up to 8-week period is provided for completing screening assessments and determining subject eligibility for the study. Subjects on stable diet known to the investigator and followed at the site may skip the 6-week diet run-in. Safety labs may be re-tested for determination of subject eligibility after consultation with the Sponsor Medical Monitor.

During the screening period, 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.

Eligible subjects will be on a stable low-fat diet (according to local clinical guidelines) beginning at least 6 weeks prior to the first dose of Study Drug. The diet stabilization period may be reduced if the patient is following a stable low fat diet for optimal disease control and disease management prior to screening.

Subjects meeting eligibility criteria at Screening will receive standardized meals in preparation for the pre-dose postprandial analysis to be performed on Day -1.

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.

Postprandial Assessment (Appendix E): Postprandial assessments will be performed at Day -1 and at Week 14. Subjects will consume standardized pre-cooked meals (lunches and dinners (provided) and instructions for breakfasts and snacks) for the 2 days prior to the post-prandial evaluations. Patients will remain fasted after consuming the standardized pre-cooked meal for the dinner on the evening prior to their visit. Alcohol consumption is not allowed for the 2 days prior to the post-prandial evaluations. On each of the post-prandial evaluation days, following the first blood draw, patients will consume a standardized liquid meal (which represents about a third of the daily caloric requirements) containing a radioisotope tracer, followed by an 9 hour infusion of two stable isotope tracers and serial blood sampling. Patients will receive a standardized pre-cooked meal 9 hrs after consuming the liquid meal, after which they will fast until the 24 hour blood draw the following day.

6.1.4 Post-Treatment Period

Each subject will be followed for safety assessments for up to 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 on Days 119, 147 and 182 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 approximately 10 hours. During this time subjects can drink water and should ensure that they consume sufficient water to not become dehydrated.

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

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

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

6.3.2 Other Requirements

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

7. STUDY DRUG

7.1 Study Drug Description

7.1.1 AKCEA-ANGPTL3-L$_{RX}$ (ISIS 703802)

Study Drug characteristics are listed in Table 1.

A solution of Study Drug contained in stoppered glass vials will be provided. The Study Drug and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug must be stored securely at 2° to 8° Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	AKCEA-ANGPTL3-LRX (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 supplies provided by the Sponsor. The Study Center must return all used and unused Study Drug to the Sponsor or designee.

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.

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 stable lipid-lowering therapy 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. The medical monitor should be informed.

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described in Section 8.6 are met, the subject will be permanently discontinued from further treatment with Study Drug, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study.

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

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the FDA guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

All patients will have liver chemistry tests monitored every 2 weeks during the treatment and follow-up Period.

- In the event of appearance of symptoms or signs of hepatic injury (jaundice, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, abnormal bleeding or bruising, or eosinophilia > ULN) liver enzymes and bilirubin should be tested as soon as possible. Testing at a lab that is local to the patient is permissible for this purpose.
- In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (treatment or post-treatment period), the initial measurement(s) should be confirmed as described in Section 8.5.
- Patients with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR] and total bilirubin) retested at least once weekly until ALT and AST levels become ≤ 1.2 x ULN.

- All results of liver function tests must be reviewed promptly (within 48 hours of receipt) by the Investigator or the designee to ensure that the result has not met the stopping rules per Section 8.6.1. Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN, the following evaluations should be performed:

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

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

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

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

Lab alerts for abnormal liver chemistry tests will be issued for:

1. ALT or AST > 3 x ULN;
2. ALT or AST > 2 x baseline;
3. total bilirubin > ULN;
4. ALP > ULN.

These alert levels are set to anticipate the risk of a combined elevation of aminotransferases and bilirubin as per the FDA Guidance referenced in Section 8.5.1. A more frequent liver function test monitoring may be recommended by the Investigator if warranted. The Investigator should inform the Medical Monitor.

All clinically significant lab alerts for monitoring/ stopping rules as described above are reviewed promptly by the Medical Monitor and communicated with the Investigator and/or the study personnel within 24 hours of receiving an actionable lab alert.

8.5.2 Safety Monitoring for Renal Function

All patients will have renal function tests monitored every 4 weeks throughout the study.

In the event of appearance of symptoms or signs consistent with renal dysfunction such as hematuria, polyuria, anuria, flank pain, new-onset hypertension, nausea and/or anorexia, renal function should be tested as soon as possible.

During the course of the study, urinary surveillance will include urinalysis to include urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR) and urinary red blood cells (RBCs), as well as serum creatinine and cystatin-C to estimate glomerular filtration rate (eGFR), which will be monitored every 4 weeks.

All renal function test results will be reviewed on an ongoing basis at the safety review by the Medical Monitor.

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

Lab alerts for abnormal renal tests will be issued for:

- Creatinine clearance (by CKD-EPI formula) decrease from baseline > 25%,
- Urine albumin/creatinine ratio (UACR) > 250 mg/g, urine protein/creatinine ratio (UPCR) > 0.5 mg/mg, or
- An increase in serum creatinine from baseline > 0.3 mg/dL).

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

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

In addition, the following supplemental renal tests should be immediately obtained:

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

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

8.5.3 Safety Monitoring Rules for Platelet Count Results

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

In addition, platelet function may be evaluated by aggregometry, using an approved point-of-care diagnostic device, in all patients at each study site visit.

All platelet count results 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 rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm^3 as specified in Section 8.6.3.

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

Lab alerts related to platelet monitoring/stopping rules are issued when:

1. Platelet counts are < 140,000 mm^3;
2. When platelet count is ≥ 30% decreased from baseline, or
3. When the hematology sample is unreportable.

Actions to be taken in the event of reduced platelet count are shown in Table 3 below. In the event of a platelet count < 100,000/mm^3 the laboratory tests outlined 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.

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).

All clinically significant lab alerts for monitoring/stopping rules as described above are reviewed promptly by the Medical Monitor and communicated with the Investigator and/or the study personnel within 24 hours of receiving an actionable lab alert as described in Section 6.2.

8.5.4 Safety Monitoring for Minor Bleeding Events

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

8.6 Stopping Rules

For the purposes of the stopping rules, Baseline is defined as the average of the pre-dose test closest to Day 1 and Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

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

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

8.6.2 Stopping Rules for Renal Function Test Results / 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 (AKCEA-ANGPTL3-L_{RX}) 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.

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.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is already on reduced dose, dosing of the patient with Study Drug will be stopped permanently (Table 3).

Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

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

In the event of a platelet count < 75,000/mm^3 and > 50,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with Study Drug should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued it must be at a reduced dose as shown in Table 3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count after interruption of dosing. This will be documented in the patient by the investigator and filed in the TMF.rec.

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

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

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

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

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

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

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

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.

Patients 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

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

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

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

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

Any patient who discontinues early from the treatment period or from post-treatment follow-up period should be followed as per the platelet monitoring rules shown in Table 3, Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

If the patient declines or is unable to participate in the above, the early termination visit procedures should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.9 Withdrawal of Subjects from the Study

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

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

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).

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 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.

Disallowed concomitant therapy are identified in exclusion criteria, Section 5.2, and include the following as specified*:

- Anti-obesity medications (e.g., orlistat, sibutramine), or has discontinued treatment < 12 weeks prior to screening
- Systemic corticosteroids or anabolic agents within 6 weeks of screening*
- Treatment with another investigational drug, biological agent, or device within 4 weeks of screening or 5 half-lives of study agent, whichever is longer
- Prior treatment with gene therapy
- No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification.
- Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted.
- Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.
- Other experimental agents during the study including investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. This includes marketed agents at experimental dosages
- Treatment with any non-Ionis oligonucleotide (including siRNA) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of screening. Patients that have previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may be included as long as ≥ 4 months has elapsed since dosing

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

Note: 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.

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 (See Section 9.5.2)
- 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:

[redacted]
[redacted] – USA:
Telephone: [redacted] **or** [redacted]
Facsimile: [redacted] **or** [redacted]
e-mail: [redacted]

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

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

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

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

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug (e.g., confirmation by positive re-challenge test)
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D).
Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities
- **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (AKCEA-ANGPTL3-L_{RX} or placebo) administration and dose
- **Permanently Discontinued:** Study drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Temporarily Interrupted, Restarted Reduced Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the next lower dose

9.4.3.4 Treatment Given for Adverse Event

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

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

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

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

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious eCRF (the SAE resolution date should be entered as the date of onset of that AE)

- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment (e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia). Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. 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 (AKCEA-ANGPTL3-L_{RX}) 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

For fasting lipid measurements, the values for the Month 3 analysis time point are defined as the average of Week 13 (Day 85) and Week 14 (Day 92) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Percent change and absolute change from baseline in fasting ANGPTL3
- Fasting lipid measurements, including: non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Postprandial TG change from baseline
- Frequency and severity of patient reported abdominal pain during the treatment period

10.1.2 Safety Endpoints

- Adverse events
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Electrocardiograms (ECGs)
- Use of concomitant medications

10.2 Sample Size Considerations

There is no formal statistical justification for the selected sample size. The sample size is selected based upon prior experience with AKCEA-ANGPTL3-L_{RX} to ensure that the safety, tolerability and efficacy of AKCEA-ANGPTL3-L_{RX} can be explored while minimizing unnecessary subject exposure. In 6 healthy volunteers, AKCEA-ANGPTL3-L_{RX} reported a 63% TG reduction after 6 weeks of administration.

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

Definitions of baseline are given below for the purposes of the final analysis.

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 patients 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 tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3 in fasting TG will be summarized. Response rate of patients with fasting serum TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3 will be summarized. Response analysis will also be conducted using a range of fasting serum TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3 will also be summarized by treatment group for other fasting lipid measures including ANGPTL3, non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

10.6.4 Pharmacokinetic Analysis

The plasma PK of AKCEA-ANGPTL3-L_{RX} (as total full length oligonucleotides, including, fully conjugated, partially conjugated, and unconjugated AKCEA-ANGPTL3-L_{RX}) will be assessed following multiple-dose SC administration. The plasma trough levels of AKCEA-ANGPTL3-L_{RX} during treatment period and those during post-treatment follow up period will be descriptively summarized with stratification by subject immunogenicity status if applicable.

10.6.5 Pharmacodynamic Analysis

The following parameters will be measured throughout the trial: Fasting TGs, plasma angiopoietin-like 3 (ANGPTL3), ANGPTL4, ANGPTL8, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), total apoC-III, apolipoprotein B-100 (apoB-100), apolipoprotein B-48 (apoB-48), apolipoprotein A-1 (apoA-1), apolipoprotein A-2 (apoA-2), apolipoprotein E (apoE), very-low-density lipoprotein-triglyceride (VLDL-TG), chylomicron-cholesterol (CM-C), chylomicron triglyceride (CM-TG), free fatty acids (FFA), and free glycerol levels.

10.6.6 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-AKCEA-ANGPTL3-L_{RX} antibodies) before, during, and after treatment with AKCEA-ANGPTL3-L_{RX} 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.

10.6.7 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 AKCEA-ANGPTL3-L_{RX} are administered. The subject or

legally acceptable representative must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the subject's agreement or refusal to notify his/her primary care physician should be documented in the subject's medical records and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

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

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

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002, the applicable regulations and guidelines of current Good Clinical Practice (GCP), as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed. The more recent Declaration of Helsinki version from 2013 is not being 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

Study Period		Screen/ Run-in [a]	Treatment Period										Post-treatment Follow-up		
Study Week		**-8 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**14/ET**			**18**	**22**	**26**
Study Day		**-56 To -1**	**1 [b]**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**94**	**95**	**120**	**148**	**176**
Visit and Testing Window +/- Days		**0**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**0**	**0**	**3**	**3**	**3**
Informed Consent		X													
Inclusion/Exclusion Criteria		X	X												
Medical History		X													
Height & Weight [c]		X	X		X		X			X					X
Vital Signs		X	X		X		X			X			X	X	X
Physical Examination [d]		X	X		X		X			X					X
12- lead ECG (triplicate)		X	X		X		X			X					X
24-hour urine creatinine clearance and protein		X													
Abdominal Pain Assessment		X	X		X		X			X					X
Urinalysis		X	X		X		X			X			X	X	X
Blood Draw [e]	Chemistry Panel (+ CPK) [f g]	X	X	X	X	X	X	X	X				X		X
	CBC with Differential [f g]	X	X	X	X	X	X	X	X	X			X [h]	X	X
	Serum Lipid Panel	X	X		X		X		X	X			X	X	X
	PD Panel		X		X		X		X	X			X	X	X
	Coagulation (aPTT, PT, INR)	X	X		X		X			X			X	X	X
	Complement Markers C5A, Bb	X	X							X					
	hsCRP	X	X		X		X			X					X
	Hepatitis B, C, HIV, TSH, Free T_4	X													
	Plasma PK [i]		X[1]		X [1]	X [1]	X [1]	X [1]		X			X	X	X
	Genetic Testing [j]	X													
	Anti-ANGPTL3-L_{RX} Antibodies		X[1]		X[1]		X[1]			X			X		X
	FSH (women only, if applicable) [k]	X													
	Serum Pregnancy Test [k]	X	X		X		X		X	X			X	X	X

Appendix A Schedule of Procedures *Continued*

Study Period		Screen/ Run-in [a]	Treatment Period										Post-treatment Follow-up		
Study Week		**-8 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**14/ET**			**18**	**22**	**26**
Study Day		**-56 To -1**	**1 [b]**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**94**	**95**	**120**	**148**	**176**
Visit and Testing Window +/- Days		**0**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**0**	**0**	**3**	**3**	**3**
	HbA1C and delipidated free glycerol	X													
	Archived Serum & Plasma [m]		X							X					X
	Post-Prandial Assessment	X[l]								X[l]	X[l]	X[l]			
	Platelet aggregation		X		X		X			X					X
Study Drug Administration			WEEKLY SUBCUTANEOUS ADMINISTRATION OF STUDY DRUG (Week 1 through Week 13)												
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													

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

a Subject starts the tightly controlled diet, if needed.

b After 6 weeks on the controlled diet, patients will have baseline measurements and be assessed for qualification of enrollment.

c Height is only required on Day 1.

d Full physical exam to be given at Screening and abbreviated physical exam to be given during treatment and follow-up period as indicated to assess changes from screening.

e 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.

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

g If not done as part of a Study Center visit, 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.

h During follow-up period, hematology sampling for platelet values are taken every 14 days for 6 weeks after last dose of Study Drug, then at Week 22 and Week 26 Follow-up visits.

i Refer to Appendix C for PK Sampling schedule.

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

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

Appendix A Schedule of Procedures *Continued*

l The postprandial assessment for Screening will only be performed after other eligibility criteria are met. Subjects will be provided a standardized meal during Screening visit with instructions on when and how to consume and will return to the study center on Day -1 (2 days after consumption) for pre-dose postprandial assessments. Subjects will again be provided standardized meal at the Week 14 visit (Day 92) and will return to the site 2 days later (Day 94) plus one more day (Day 95) for post-dose postprandial assessments.

m 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

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of AKCEA-ANGPTL3-L_{RX} or other similar oligonucleotides.

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

Fasting Lipid Panel
- Total cholesterol
- Total ApoB
- ApoB-100
- ApoB-48
- LDL cholesterol
- HDL cholesterol
- Total Triglycerides
- CM triglycerides
- VLDL cholesterol
- VLDL triglycerides
- Non-HDL cholesterol

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

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

Complement
- C5a
- Bb

PD Panel
- ANGPTL3
- ANGPTL4
- ANGPTL8
- ApoA-I
- ApoB
- ApoC-III

Specialized Lipoprotein and post-prandial Analyses[1]
- Lipoprotein particle analysis
- Oxidized chylomicrons and VLDLs
- Isoprostanes
- HDL function and characterization
- Lipoprotein subclass analysis
- Newly formed CM and LDL, IDL, HDL kinetics
- Post-prandial lipid panel
- Post-prandial platelet count and function
- Post-prandial glucose

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

Thyroid Panel
- TSH
- Free T4

Pharmacokinetics and Immunogenicity[2]
- AKCEA-ANGPTL3-L_{RX} levels in plasma
- Anti- AKCEA-ANGPTL3-L_{RX} antibodies in plasma

Genetic Testing
- Molecular confirmation of FCS
- Genetic sequencing of FCS causing genes[3]

Inflammatory
- Hs-CRP
- Cytokine panel
  - IL-1b,
  - IL-6,
  - IL-8

Urinalysis
- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[5]
- P/C Ratio (UPCR)
- A/C Ratio (UACR)

24 Hour Urine Test
- Creatinine clearance
- Protein
- Albumin

1 Scope of specialized lipoprotein analyses will be determined based on results from fasting lipid panel

2 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation, stability assessments, metabolite assessments, testing of additional exploratory pharmacodynamics markers, immunogenicity testing (or possibly for immunogenicity assay development and/or validation), or to assess other actions of AKCEA-ANGPTL3-L_{RX} with plasma constituents

Appendix B List of Laboratory Analytes *Continued*

3 If the genotype is not already available, blood will be collected to assess genetic evidence of null loss-of-function for LPL. May not be collected if adequate genetic data are available in medical history or if patient does not consent to genetic testing

4 Will be performed on abnormal findings unless otherwise specified

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

D1	D29	D43	D57	D71	D92	D120	D148	D176
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[t]
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 Post-prandial Meal, Sampling Schedule, and Assessment

Appendix E Post-prandial Meal, Sampling Schedule, and Assessment

Post-prandial assessment for lipoproteins metabolism (lipoprotein kinetics: newly formed CM, VLDL, IDL, LDL and HDL) will be performed as follows. A radiolabelled meal supplemented with a labeled tracer, ^{3}H-palmitate (300µCi, [redacted] Canada), will be sonicated into the liquid meal. Palmitate is a fatty acid that is a common constituent of any diet. The ^{3}H-palmitate tracer emits weak radioactivity, equivalent to an X-ray. Since dietary palmitate is incorporated into chylomicrons as they are formed in the enterocytes of the gut, this enables monitoring the appearance and clearance of newly-formed chylomicrons from circulation. The methodology to be applied for studying post-prandial kinetics of chylomicrons appearance and clearance is well-established (Mittendorfer et al. 2003; Bickerton et al. 2007; Normand-Lauziere et al. 2010).

A liquid meal (similar to a milkshake) containing a small amount (300µCi) of radiolabelled fatty acids (^{3}H-palmitate) will be provided. The liquid meal will provide about a third of the daily caloric requirements. From 1 hr prior to 9 hrs after the ingestion of the meal, two stable isotope tracers will be continuously infused. A primed (1.6 mmol/kg) continuous (0.05 mmol/kg/min) infusion of [1,1,2,3,3-^{2}H]-glycerol [redacted] will be administered as previously described (Normand-Lauziere et al. 2010). To document VLDL, IDL, LDL and HDL kinetics, L-[5,5,5-D_3] leucine (10 mmol/kg) will be injected as a bolus intravenously and then by continuous infusion (10 mmol·kg body weight^{-1}·h^{-1}) (Tremblay et al. 2006). Glycerol appearance rates will be calculated using Steele's non-steady state equation assuming a volume of distribution of 230ml/kg (Gastaldelli et al. 1999). The isotopic enrichment of leucine in the apolipoproteins will be expressed as tracer/tracee ratio (%) using standardized formulas (Cobelli et al. 1987).

Blood samples will be drawn at intervals before and after the ingestion of the radiolabelled meal on days prior to and after the Treatment phase as noted in the table below. A standardized meal will be given to the participants after the 9 hr blood draw. Blood will be collected in tubes containing Na_2EDTA and Orlistat (30 mg/ml, [redacted] Canada) to prevent *in vitro* triacylglycerol lipolysis and separate samples will be collected in NaF tubes for plasma glucose determination.

Post-prandial Sampling (Blood) Schedule

Study Day	D -1[a]	D1	D94	D95
Visit Window +/- Days	0	0	0	0
	-1 hr pre-prandial, and 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hrs post prandial	24 hrs post-prandial /pre SC injection	-1 hr pre-prandial, and 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hrs post-prandial	24 hrs post-prandial

a There is a range for this visit, it should happen prior to and as close as possible to Day 1.

Plasma samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, or to assess other actions of AKCEA-ANGPTL3-L_{RX} with plasma constituents.