Official Title: **A Randomized, Double-Blind, Placebo-controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy**

NCT Number: NCT02527343

Document Dates: Protocol Amendment 4 - 22 August 2017

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IONIS PHARMACEUTICALS, INC.

ISIS 304801-CS17

The BROADEN Study

A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

Protocol Amendment 4 – 22 August 2017

EudraCT No: 2015-000493-35

ISIS 304801-CS17

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Protocol Amendment 4 – 22 August 2017

Protocol History:

Original Protocol:	6 April 2015
Protocol Amendment 1:	7 June 2016
Protocol Amendment 2:	8 August 2016
Protocol Amendment 3:	17 April 2017

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ISIS 304801

Ionis Protocol Number ISIS 304801-CS17

Protocol Amendment 4

EudraCT No: 2015-000493-35

Clinical Phase: 2/3

The BROADEN Study

A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

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Confidentiality Statement

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

Protocol Signature Page

Protocol Number: ISIS 304801-CS17

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

Amendment: Amendment 4

Date: 22 August 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, "A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy" dated 22 August 2017 and agree to conduct the Study as described herein.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 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.

_____
Investigator's Signature

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

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS17

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

Amendment Number: 4

Amendment Date: 22 August 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS17 Amendment 3 dated 17 April 2017:

- To update inclusion criterion, revise secondary and tertiary endpoints, add an option for an additional 52 weeks of open-label dosing, add scoring of disease burden, clarify actions to be taken in regards to events of documented hypoglycemia and hyperglycemia, and add allowance for unblinding of triglyceride values to both Investigator and patient after 13 weeks on the open-label treatment phase of the study.

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

The following table provides a summary list of major changes to the protocol, additions are indicated as bold and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Synopsis Study Design and Treatment Schema	**WAS:** Not applicable **IS:** Following the Week 104 visit of the Open-Label Extension Period, patients will have the option of continued dosing for up to an additional 52 weeks. The schedule of procedures will follow the same schedule as the first year of OLE.	Allowance for additional dosing for patients completing the first year of open-label dosing

Protocol Section	Description of Change	Rationale
Synopsis Inclusion Criterion Section 5.1	**WAS:** 4. Diagnosis of type 2 diabetes mellitus as defined by 2006 WHO criteria (fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) or 2-h post-glucose load plasma glucose ≥ 11.1 mmol/L (200 mg/dL), made at least 6 months prior to the Screening visit, and 2 of the following: • on standard-of-care anti-diabetic therapy, and • HbA1c ≥ 7% to ≤ 10% at Screening **IS:** 4. A diagnosis of type 2 diabetes mellitus, as defined by the International Diabetes Federation guidelines of 2012, made at least 6 months prior to the Screening, and: • A HbA1c ≥ 7% to ≤ 12% at Screening • On anti-diabetic therapy consisting of: a. Metformin ≥ 1500 mg/day, or b. If the dose of metformin is < 1500 mg/day, or metformin is not tolerated, then the patient should be on other oral anti-diabetic drugs (OAD) or an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, or c. Insulin therapy alone or in combination with other anti-diabetic drugs	Revised the diabetic criteria consistent with more current guidelines and an increased HbA1c threshold of 12%. Require that all patients entering the study are on antidiabetic agents, whether oral or injectable.
Synopsis Inclusion Criterion Section 5.1	**WAS:** 5. Hypertriglyceridemia is defined as Fasting TG levels ≥ 500 mg/dL (≥ 5.7 mmol/L) at Screening and Qualification visit. • If the fasting TG value at Screening and/or Qualification visit is < 500 mg/dL (< 5.7 mmol/L) but ≥ 350 mg/dL (≥ 4.0 mmol/L) up to 2 additional tests may be performed in order to qualify **IS:** 5. Hypertriglyceridemia as defined by Fasting TG levels ≥ 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification visits. Patients with the clinical diagnosis of FPL and with Fasting TG levels ≥ 200 (≥ 2.26 mmol/L) to < 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification Visits who meet the genetic or family history criteria for study inclusion may be further screened and enrolled in the study 6. Presence of hepatosteatosis (fatty liver), as evidenced by a Screening MRI indicating a hepatic fat fraction (HFF) ≥ 6.4%	Revised inclusion criteria to allow Group 1 and Group 2 patients with TGs of 200 mg/dL or greater to participate. All groups will now require evidence of fatty liver.
Synopsis Stratification Groups	**WAS:** Not applicable **IS**: 1. Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL 2. Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion 3. Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2	For clarity, added Stratification Groups to Synopsis as stated in Section 4.2 – Randomization

Protocol Section	Description of Change	Rationale
Synopsis Secondary Endpoints Section 1.2.2	**WAS:** Secondary Endpoints: • Change from Baseline in hemoglobin A1c (HbA1c) in patients with diabetes • Change from Baseline in liver volume and hepatic steatosis (as assessed by magnetic resonance imaging [MRI]) • Absolute change from Baseline in fasting TG • Percent of patients who achieve a ≥ 40% reduction in fasting TG • Change from Baseline in fasting plasma glucose (FPG) Endpoints • Reduction in insulin use **IS:** Secondary Endpoints: • Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI]) • Change from Baseline in hemoglobin A1c (HbA1c) • A composite endpoint at Month 6 for percent of patients who achieve a. ≥ 40% reduction in fasting TG, and b. ≥ 30% reduction of hepatic fat fraction percent • Change in patient-reported outcomes (PRO) o Disease burden score o Patient-reported pain o Patient-reported hunger o Quality of life	Revised secondary and tertiary endpoints to move patient reported outcomes to secondary endpoints and to raise hepatic steatosis assessment as the first secondary endpoint
Synopsis Section 1.2.3 [redacted]	**WAS:** Not applicable **IS (added):** [redacted]	[redacted]
Synopsis Study Visit Schedule and Procedures	**WAS:** • A 52-week OLE Period during which ISIS 304801 will be administered as a once-weekly SC injection, with a subsequent 13-week post-treatment evaluation period **IS:** • A 52-week OLE period during which ISIS 304801 will be administered as a once-weekly SC injection, with a subsequent 13-week post-treatment evaluation period, **or an option for continued treatment for 52 weeks**	Allowance for additional dosing for patients completing the first year of open-label dosing

Protocol Section	Description of Change	Rationale
Synopsis Statistical Considerations Section 10.5 Interim Analysis and Early Stopping Guidelines	**WAS:** An interim analysis of TG is planned after approximately the first 20 patients (total ISIS 304801 and placebo treated) have completed the Week 13 visit. The purpose of this analysis is futility as measured by effect on TG levels, so there will be no statistical penalty. **IS:** An interim analysis of the study is not planned.	An interim analysis is no longer planned for futility as the expectation is that based upon the results of the CS6 and CS16 trials there should be significant reduction in triglycerides.
Synopsis Statistical Considerations Section 10.2 Sample Size Considerations	**WAS:** Not applicable **IS:** A sample size of 35 patients (20 active and 15 control) provides 92% power to detect a liver fat treatment difference of 4.7% based on a between patient standard deviation of 4% and a two-sided alpha of 0.05.	Added additional sample size information based on the first secondary endpoint
Section 2.1 Overview of Disease	**WAS:** Not applicable **IS:** Added 3 additional paragraphs describing the metabolic manifestations of familial partial lipodystrophy	Added further information on the metabolic complications of FPL
Section 3.4.3 OLE Period	**WAS:** Not applicable **IS:** After a patient has been in the OLE period for a period of 3 months, an Investigator may consult with the study Medical Monitor and request that triglyceride values become unblinded to the Investigator and patient after Week 13 for the duration of the study. Following the Week 104 of the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks. The schedule of procedures will follow the same schedule as the first year of OLE.	Added that patients and Investigators may become unblinded to triglyceride values after Week 13 of open-label dosing so that patients are aware of potential benefits of continued study participation. Patients may also elect to continue study participation after 1 year of open-label dosing
Section 3.6 Data and Safety Monitoring Board	**WAS:** ~~Additionally, the DSMB will review data during the interim analysis of TG after approximately the first 20 patients have completed the Week 13 visit. More details regarding this interim analysis are presented in Section 10.5.~~ **IS:** Deleted	Removed interim analysis for futility

Protocol Section	Description of Change	Rationale
Section 6	**WAS:** 6.1.2 Randomized Treatment Period 6.1.3 OLE Period 6.1.4 Post-Treatment Period **IS:** 6.1.2 Randomized Treatment Period 6.1.3 Randomized Period Post-Treatment Follow-Up 6.1.4 OLE Period 6.1.5 OLE Post-Treatment Period	Revised Section Headings for clarification in regards to follow-up of patients
Section 6.1.5 OLE Post-Treatment Period	**WAS:** Not applicable **IS:** For patients who continue to receive investigational treatment for the additional 52 weeks, the 13-week post-treatment follow-up period will follow the second year of open-label dosing.	Added an option for patients to continue for an additional 52 weeks in OLE
Section 6.2.9 Quality of Life Assessments	**WAS:** 6.2.9 Quality of Life Assessments All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at the times indicated in Appendix A. **IS:** 6.2.9 Quality of Life Assessments All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at the times indicated in Appendix A. **Patients will complete a survey that will evaluate changes in a disease burden score before and after therapy. The disease burden score will be calculated through analysis of a natural history survey of patients with FPL. In addition, patients will complete the Diabetes Health Profile (DHP18) at the times indicated in Appendix A.**	Added scoring of disease burden, in addition to the standard quality of life assessments (SF-36 and EQ-5D). The scoring will be derived from a natural history survey of FPL patients and included in the study when available. In addition, the Diabetes Health Profile–18 is added as a disease-specific instrument to capture the impact of living with diabetes on the patient's psychological and behavioral functioning.
Section 8.5.7 Safety Monitoring for Hypoglycemia	**WAS:** Not applicable **IS:** In the event of an episode of symptomatic documented hypoglycemia (FPG < 70 mg/dL), if the patient is on insulin, the Investigator shall reduce the total daily dose by 5-15%. If the patient is on oral ant-diabetic drugs, the Investigator should use his or her discretion regarding changes to the drug regimen to help prevent future incidences of hypoglycemic events. In all cases, the adjustments made to medication should be carefully documented via electronic diary (insulin) and/or concomitant medication CRF.	Provided guidance to the Investigator on medication adjustments in the presence of symptomatic documented hypoglycemia

Protocol Section	Description of Change	Rationale
Section 8.5.8 Monitoring Rule for Documented Hyperglycemia	**WAS:** The threshold values are defined as follows, depending on study period: • From Baseline visit to Week 12 (including value at Week 12) of Randomized Treatment period or OLE period: o FPG > 270 mg/dL (15.0 mmol/L) • From Week 12 to Week 24 (including value at Week 24) of Randomized Treatment period or OLE period: o FPG > 240 mg/dL (13.3 mmol/L) or o HbA1c > 9% (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1% from Baseline (for patients with Baseline HbA1c ≥ 8%) • From Week 24 up to Week 52 of Randomized Treatment period or OLE period: o HbA1c > 9% (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1% from Baseline (for patients with Baseline HbA1c ≥ 8%) **IS:** The threshold values are defined as follows, depending on study period: • From Baseline visit to Week 12 (including value at Week 12) of Randomized Treatment period or OLE period: o FPG **> 300 mg/dL (16.6 mmol/L)** • From Week 12 to Week 24 (including value at Week 24) of Randomized Treatment period or OLE period: o FPG **> 270 mg/dL (15.0 mmol/L)** or o HbA1c > **9.5%** (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1.5% from Baseline (for patients with Baseline HbA1c ≥ 8%) • From Week 24 up to Week 52 of Randomized Treatment period or OLE period: o **FPG > 240 mg/dL (13.3 mmol/L)** or o HbA1c > **9.5%** (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1.5% from Baseline (for patients with Baseline HbA1c ≥ 8%)	Threshold values for hyperglycemia are adjusted to reflect the inclusion of patients with an HbA1c of up to 12%.
Section 8.5.8 Monitoring Rule for Documented Hyperglycemia	**WAS:** ~~If none from the above-mentioned reason can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, rescue medication may be introduced at the Investigator discretion and according to local guidelines.~~ **IS:** If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, **an increase in current medication or the addition of new anti-diabetic** rescue medication may be introduced at Investigator discretion and according to local guidelines. **Investigators should minimize changes prior to the primary endpoint, when possible. All adjustments to medication should be captured on the concomitant medication CRF and/or electronic diary.**	Clarified actions to be taken in the instance of documented hyperglycemia

Protocol Section	Description of Change	Rationale
Section 10.6.3 Efficacy Analysis (Primary and Secondary)	Updated to reflect changes in secondary [redacted] endpoints noted above, including: • **Proportion of patients who achieve a ≥ 40% reduction in fasting TG from Baseline and a ≥ 30% reduction of hepatic fat fraction percent from baseline at Month 6 between ISIS 304801 300 mg once-weekly and placebo group will be analyzed using a logistic regression model with the randomization stratification factors, log transformed Baseline TG, and Baseline hepatic fat fraction as covariates.**	Updated statistical analyses
Appendix A Schedule of Procedures	**WAS:** Quality of Life Assessments **IS:** Quality of Life / Disease Burden Assessments / DHP18 Assessment(s)	Added an assessment of disease burden, when available, from a natural history survey of FPL patients

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Partial Lipodystrophy
Study Phase	Phase 2/3
Indication	Familial Partial Lipodystrophy (FPL)
Investigational Drug	ISIS 304801 is a second-generation 2′-*O*-(2-methoxyethyl) chimeric antisense oligonucleotide inhibitor of the apolipoprotein C-III (apoC-III)
Primary Objective	To evaluate the efficacy of ISIS 304801 for reduction in severity of metabolic derangement in patients with FPL with hypertriglyceridemia and uncontrolled diabetes.
Secondary Objectives	To evaluate the safety and tolerability of ISIS 304801 in patients with FPL. To further evaluate the role of serum TGs in modulating insulin resistance in FPL patients and the impact of TG reduction on adipose tissue distribution.
Study Design	This is a multi-center, randomized, double-blind, placebo-controlled study with an open-label extension. The study will comprise the following periods: • **Screening.** An up to 6-week Screening Period, including at least a 4-week diet stabilization phase • **Randomized Treatment Period.** Following stabilization, up to 60 eligible patients will be randomized 1:1 to receive ISIS 304801 300 mg or placebo once-weekly for 52 weeks • **An Open-Label Extension Period** Following the Week 52 visit, patients may enter an Open-Label Extension (OLE) Period for another 52 weeks during which they will all receive ISIS 304801 Following the Week 104 visit of the Open-Label Extension Period, patients will have the option of continued dosing for up to an additional 52 weeks. The schedule of procedures will follow the same schedule as the first year of OLE. • **A 13-week Post-treatment Evaluation Period** Patients who do not enter the OLE period will go straight to a 13-week post-treatment follow-up period. Following the Week 104 OLE period, patients will enter a 13-week post-treatment follow-up period, if they do not option for continued dosing. The primary endpoint for the study will be evaluated after the last patient has completed the Week 52/Early Termination (ET) visit of the randomized treatment period and will be based on the percent change from Baseline in fasting TG at the primary analysis time point (Month 3).
Number of Patients	Up to 60 patients with FPL will be randomized.

PROTOCOL SYNOPSIS *Continued*

Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at the time of informed consent 3. Clinical diagnosis of familial partial lipodystrophy plus diagnosis of type 2 diabetes mellitus and hypertriglyceridemia. Diagnosis of lipodystrophy is based on deficiency of subcutaneous body fat in a partial fashion assessed by physical examination and low skinfold thickness in anterior thigh by caliper measurement: men (≤ 10 mm) and women (≤ 22 mm), and at least 1 of the following: - Genetic diagnosis of familial PL (e.g., mutations in LMNA, PPAR-γ, AKT2, CIDEC, PLIN1 genes) OR - Family history of FPL or family history of abnormal and similar fat distribution plus 1 Minor Criteria OR - 2 Minor Criteria (In the absence of FPL-associated genetic variant or family history) and BMI < 35 kg/m^2 MINOR Criteria a. Requirement for high doses of insulin, e.g., requiring ≥ 200 U/day, ≥ 2 U/kg/day, or currently taking U-500 insulin b. Presence of acanthosis nigricans on physical examination c. Evidence/history of polycystic ovary syndrome (PCOS) or PCOS-like symptoms (hirsutism, oligomenorrhea, and/or polycystic ovaries) d. History of pancreatitis associated with hypertriglyceridemia e. Evidence of non-alcoholic fatty liver disease - Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease or radiographic evidence of hepatic steatosis (e.g., on ultrasound or CT) 4. A diagnosis of type 2 diabetes mellitus, as defined by the International Diabetes Federation guidelines of 2012, made at least 6 months prior to the Screening, and: • A HbA1c ≥ 7% to ≤ 12% at Screening, • On anti-diabetic therapy consisting of: a. Metformin ≥ 1500 mg/day, or b. If the dose of metformin is < 1500 mg/day, or metformin is not tolerated, then the patient should be on other oral anti-diabetic drugs (OAD) or an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, or c. Insulin therapy alone or in combination with other anti-diabetic drugs 5. Hypertriglyceridemia as defined by Fasting TG levels ≥ 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification visits. Patients with the clinical diagnosis of FPL and with Fasting TG levels ≥ 200 (≥ 2.26 mmol/L) to < 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification Visits who meet the genetic or family history criteria for study inclusion may be further screened and enrolled in the study. 6. Presence of hepatosteatosis (fatty liver), as evidenced by a Screening MRI indicating a hepatic fat fraction (HFF) ≥ 6.4% 7. Willing to maintain their customary physical activity level and to follow a diet moderate in carbohydrates and fats with a focus on complex carbohydrates and replacing saturated for unsaturated fats

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Inclusion Criteria: *Continued* 8. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug administration. b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug administration. *Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception. Exclusion Criteria: 1. A diagnosis of generalized lipodystrophy 2. A diagnosis of acquired partial lipodystrophy (APL) 3. Acute pancreatitis within 4 weeks of Screening 4. History within 6 months of Screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive heart failure requiring a change in medication 5. Major surgery within 3 months of Screening 6. History of heart failure with New York Heart Association functional classification (NYHA) greater than Class II or unstable congestive cardiac failure requiring a change in medication 7. Uncontrolled hypertension (blood pressure [BP] > 160 mm Hg systolic and/or 100 mm Hg diastolic) 8. Any of the following laboratory values at Screening: a. Cardiac troponin I > upper limit of normal (ULN) b. LDL-C > 130 mg/dL on maximal tolerated statin therapy c. Hepatic: i. Total bilirubin > ULN ii. Alanine aminotransferase (ALT) > 3.0 x ULN iii. Aspartate aminotransferase (AST) > 3.0 x ULN

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria: *Continued* d. Renal: i. Persistently positive (2 out of 3 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 ii. Two (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 < 1.0 g/24 hrs iii. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min e. Platelet count < lower limit of normal (LLN) f. Clinically-significant (as determined by the Investigator or Sponsor) abnormalities on laboratory examination that will increase risk to the patient or interfere with data integrity 9. Uncontrolled hypothyroidism (abnormal thyroid function tests should be approved by Study medical monitor) 10. History within 6 months of Screening of drug or alcohol abuse 11. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer 16. Unwilling to comply with lifestyle requirements (see Section 6.3) 17. Use of any of the following: a. Metreleptin within the last 3 months prior to Screening b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to screening are also eligible. c. Insulin unless on a stable daily insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	Exclusion Criteria: *Continued* g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant throughout the study i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), liraglutide [rDNA origin] injection (Saxenda) and lorcaserin (Belviq), phentermine, amphetamines, herbal preparations] within 12 weeks prior to screening k. Prior exposure to ISIS 304801 l. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 19. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Groups	Placebo-controlled period: 300 mg ISIS 304801 once per week, or placebo once per week Open-Label Extension period: 300 mg ISIS 304801 once per week
Stratification Groups	1. Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL 2. Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion 3. Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2
Study Drug Dosage and Administration	ISIS 304801 (300 mg) and placebo will be administered as SC injections. Self-administration will be allowed after appropriate training of patient and/or caregiver
Dose Adjustments	Dose adjustments, including dose interruptions, and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor. Dose adjustments should not occur unless absolutely necessary prior to the primary analysis time point (Month 3)
Rationale for Dose and Schedule Selection	Dose of 300 mg once-weekly was chosen based on the pharmacodynamic and safety analysis of the Phase 2 studies in patients with TG levels ≥ 200 mg/dL including patients with type 2 diabetes
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • An up to 6-week Screening Period, including at least a 4-week diet stabilization phase • A 52-week Randomized Treatment Period during which Study Drug will be administered as a once-weekly SC injection followed by either: o A 13-week post-treatment evaluation period (for patients not entering the OLE period) o A 52-week OLE period during which ISIS 304801 will be administered as a once-weekly SC injection, with a subsequent 13-week post-treatment evaluation period, or an option for continued treatment for 52 weeks

PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	Collection and measurement of vital signs, physical examination results, [redacted], electrocardiograms (ECGs), liver MRIs, echocardiograms, clinical laboratory parameters (including hematology; serum chemistry; lipid panel; [redacted], and CRP measured by high sensitivity assay (hsCRP); urinalysis, and other analytes listed in Appendix B), ISIS 304801 plasma trough concentrations, immunogenicity (IM) testing [redacted], collection of SMBG and hunger diary results, adverse events (AEs), concomitant medication/procedure information, and quality of life assessments will be performed according to the schedule of procedures in Appendix A.
Safety and Tolerability Evaluations	Safety and tolerability assessments include: AEs, vital signs and weight, physical examinations, clinical laboratory tests, ECGs, echocardiograms, use of concomitant medications, and independently adjudicated events of pancreatitis and MACE for ISIS 304801 as compared to placebo
Efficacy Evaluations	**Primary Endpoint:** The effect of ISIS 304801 as compared to placebo on the percent change from Baseline in fasting triglycerides (TG) at Month 3 **Secondary Endpoints:** • Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI]) • Change from Baseline in hemoglobin A1c (HbA1c) • A composite endpoint at Month 6 for percent of patients who achieve a. ≥ 40% reduction in fasting TG, and b. ≥ 30% reduction of hepatic fat fraction percent • Change in patient-reported outcomes (PRO): o Disease burden score o Patient-reported pain o Patient-reported hunger Quality of life [redacted]

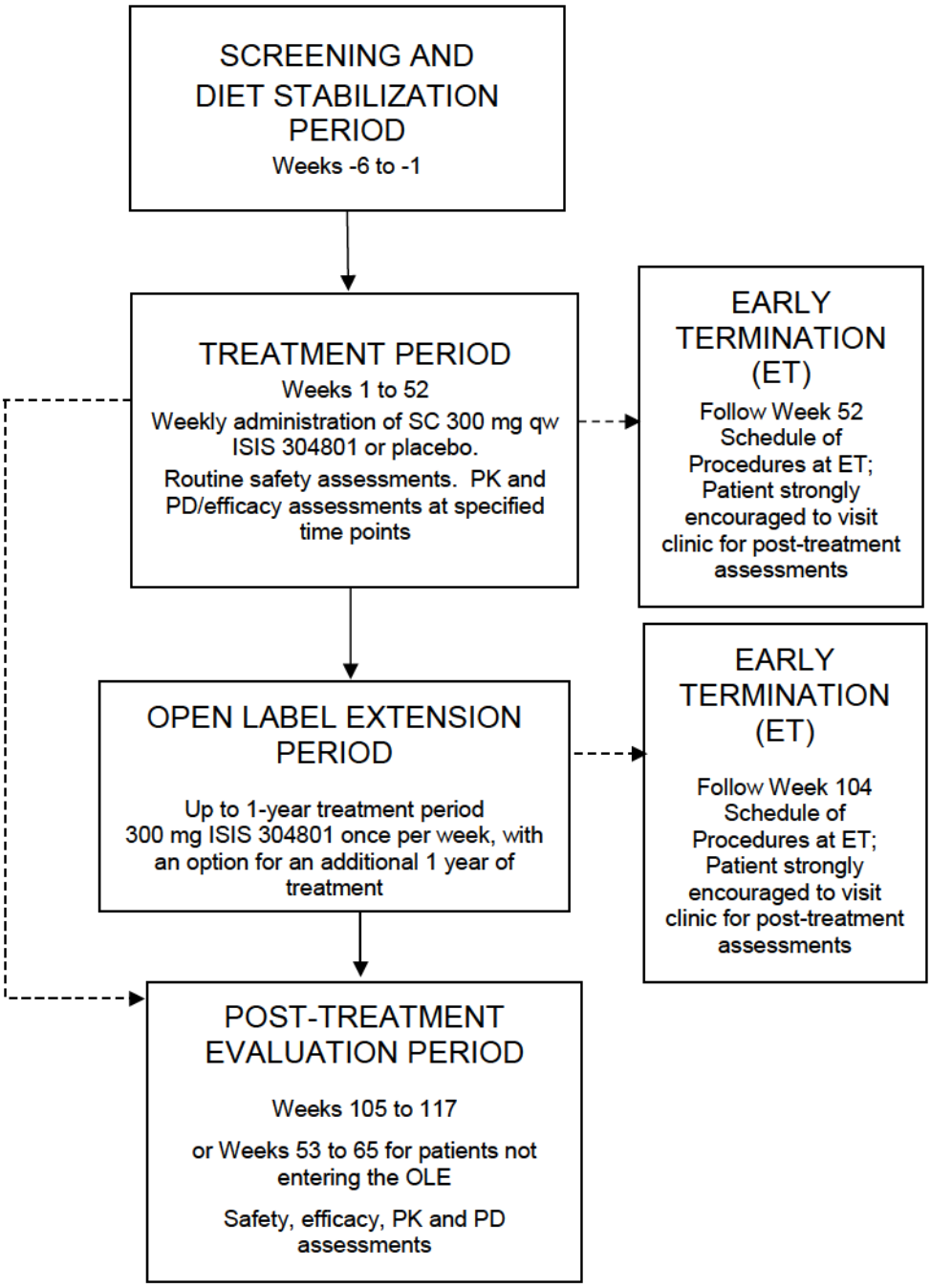
PROTOCOL SYNOPSIS *Continued*

Efficacy Evaluations ***Continued***	[redacted]
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of ISIS 304801 trough and post-treatment levels throughout treatment and during the post-treatment Follow-up period. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	For all lipid parameters the baseline is defined as the average of Day 1 pre-dose assessment and the last fasting measurement prior to Day 1. The primary analysis time point is at the end of Month 3 where the value at primary analysis time point is defined as the average of Week 12 and Week 13 fasting assessments, the value at Month 6 is defined as the average of Week 25 and Week 26 and the value at Month 12 is defined as the average of Week 51 and Week 52 fasting assessments. The primary efficacy analysis will be the comparison of percent changes from Baseline to the primary analysis time point in fasting TG between the ISIS 304801 300 mg qw group and the placebo group in the Full Analysis Set. Analyses will also be performed in which the above primary and secondary endpoints are evaluated at the Month 6, Month 9 and Month 12 analysis time points, where applicable. An interim analysis of the study is not planned. Sample Size Considerations: Based upon prior clinical trial experience with ISIS 304801, it is estimated that the standard deviation (SD) of the percent change in total TG is approximately 40%. With 20 ISIS 304801 300 mg once-weekly patients and 20 placebo patients there would be approximately 80% power to detect a 40% difference in TG levels between treatment groups at an alpha level of 0.05, assuming 50% reduction in the ISIS 304801 treated patients and 10% reduction in the placebo patients.

PROTOCOL SYNOPSIS *Continued*

Statistical Considerations *Continued*	A sample size of 35 patients (20 active and 15 control) provides 92% power to detect a liver fat treatment difference of 4.7% based on a between patient standard deviation of 4% and a two-sided alpha of 0.05. Eligible patients will be randomized 1:1 (ISIS 304801: placebo) and stratified by FPL Group assignment. • Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL • Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion • Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
AGL	acquired generalized lipodystrophy
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
ANCOVA	analysis of covariance
APL	acquired partial lipodystrophy
[redacted]	[redacted]
[redacted]	[redacted]
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CGL	congenital generalized lipodystrophy
CT	computed tomography
[redacted]	[redacted]
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FPG	fasting plasma glucose
FPL	familial partial lipodystrophy
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
HAV	hepatitis A virus

STUDY GLOSSARY *Continued*

Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HbA1C	hemoglobin A1C
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
hERG	human ether-a-go-go
HIV	human immunodeficiency virus
[redacted]	[redacted]
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonisation
IDL	intermediate-density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 304801	antisense inhibitor of apolipoprotein C3
ITT	intent-to-treat
IXRS	interactive voice/internet response system
LCRIS	local cutaneous reactions at the injection site
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCS	not clinically-significant
NOAEL	no observable adverse effect level
NYHA	New York Heart Association
OLE	open-label extension
on study	The patient is 'on study' from signing of the informed consent until their last study visit
PCOS	Polycystic ovary syndrome
PFS	pre-filled syringes
PK	pharmacokinetic(s)
PL	partial lipodystrophy
PT	prothrombin time

STUDY GLOSSARY *Continued*

Abbreviation	Definition
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SC	subcutaneous(ly)
SMBG	self-monitoring blood glucose
SD	standard deviation
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 304801 or placebo
SUSAR	suspected unexpected serious adverse reaction
TChol	total cholesterol
TG	triglyceride(s)
ULN	upper limit of normal
[redacted]	[redacted]
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell
WMA	World Medical Association

1. OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the efficacy of ISIS 304801 for reduction in severity of metabolic derangement in patients with FPL with hypertriglyceridemia and uncontrolled diabetes.

1.1.2 Secondary Objectives

To evaluate the safety and tolerability of ISIS 304801 in patients with FPL.

To further evaluate the role of serum TGs in modulating insulin resistance in FPL patients and the impact of TGs reduction on adipose tissue distribution in FPL patients.

1.2 Endpoints

1.2.1 Primary Endpoint

The primary efficacy analysis will be the comparison of percent changes from Baseline to the primary analysis time point in fasting TG between ISIS 304801 300 mg once-weekly group and placebo group in the Full Analysis Set (FAS).

1.2.2 Secondary Endpoints

- Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using magnetic resonance imaging [MRI])
- Change from Baseline in hemoglobin A1c (HbA1c)
- A composite endpoint at Month 6 for percent of patients who achieve
  a. ≥ 40% reduction in fasting TG, and
  b. ≥ 30% reduction of hepatic fat fraction percent
- Change in patient-reported outcomes (PRO):
  - Disease burden score
  - Patient-reported pain
  - Patient-reported hunger
  - Quality of life

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

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

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

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

As such, in February 2014, the FDA approved Myalept (metreleptin) as replacement therapy to treat the complications of leptin deficiency in addition to diet in patients with congenital or acquired generalized lipodystrophy. The safety and effectiveness of Myalept was evaluated in 2 open-label studies conducted at the NIH, which included 72 patients (48 with generalized lipodystrophy and 24 with partial lipodystrophy [PL]) with diabetes, high TG, and elevated levels of fasting insulin. The best results were achieved in patients with generalized lipodystrophy who had low leptin levels (mean [SD]: 1.3 [1.1] ng/mL), while patients with partial lipodystrophy who had a wider range of baseline leptin values (mean [SD]: 4.9 [3.1] ng/mL) had a more varied and attenuated response. Because of the risks associated with the development of neutralizing antibodies and lymphoma, Myalept is available only through a risk evaluation and mitigation strategy (REMS) program, which requires prescriber and pharmacy certification and special documentation (Chan et al. 2011; Myalept, FDA Briefing Document 2013).

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

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

The diagnosis of FPL is mainly clinical and needs to be considered in patients presenting with the triad of insulin resistance (with or without overt diabetes), significant dyslipidemia in the

form of hypertriglyceridemia, and fatty liver (Huang-Doran et al. 2010). Patients often present with diabetes and severe insulin resistance requiring high doses of insulin. Other evidence of severe insulin resistance is provided by the presence of acanthosis nigricans and polycystic ovary syndrome (PCOS) (with symptoms like hyperandrogenism and oligomenorrhea). Some patients develop severe hypertriglyceridemia resulting in episodes of pancreatitis. In many patients, the TG levels remain persistently elevated despite fully optimized therapy or diet modifications. Radiographic evidence of hepatic steatosis or steatohepatitis with hepatomegaly and/or elevated transaminases is common (Handelsman et al. 2013). Patients with the Dunnigan variety have a higher risk of coronary artery disease (Hegele 2001). Although very rare, patients with a specific mutation in the LMNA gene are at an increased risk of cardiomyopathy and its associated complications, congestive heart failure and conduction defects.

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

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

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

Careful clinical assessment of fat distribution through visual and physical examination can confirm the diagnosis. Patients with FPL have reduced subcutaneous fat in the limbs and truncal regions and may have excess subcutaneous fat deposition in neck, face and intra-abdominal regions. Patients with the Dunnigan variety have normal body fat distribution in childhood and

gradually lose subcutaneous fat from the extremities and trunk around the time of puberty. In women, the loss of fat may be most striking in the buttocks and hips. At the same time these patients accumulate fat on the face ("double chin"), neck and upper back ("Cushingoid appearance with buffalo hump"). The extent of adipose tissue loss usually determines the severity of the metabolic abnormalities. Patients display prominent muscularity and phlebomegaly (enlarged veins) in the extremities and complain of disproportionate hyperphagia. The condition in females is more easily recognized than in men, and so is reported more often. Patients may also have a family history of similar physical appearance and/or fat loss.

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

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

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

- Acute pancreatitis, especially when triglyceride levels are > 1,000 mg/dL
- Accelerated microvascular complications from uncontrolled diabetes
- Accelerated cardiovascular disease from lipid abnormalities and insulin resistance
- Steatohepatitis that can progress to cirrhosis and an increased risk of hepatocellular carcinoma
- Proteinuric nephropathies which can progress to end stage renal disease

In patients with Generalized Lipodystrophy the metabolic complications are partially related to leptin deficiency, and can be ameliorated in part by leptin replacement. However, leptin deficiency alone cannot explain the severity of metabolic disease in patients with PL who have variable leptin levels. A recent study showed that elevated apoC-III plays a role in the hypertriglyceridemia seen in both generalized and partial lipodystrophy and might therefore represent a therapeutic target in these patients (Kassai et al. 2015).

By reducing apoC-III and TG levels, ISIS 304801 may improve the metabolic profile of patients with FPL and reduce their risk of acute pancreatitis. In addition, reductions in TG could improve hepatic steatosis and reduce cirrhosis risk. Furthermore, this mechanism may also improve insulin sensitivity in these patients and potentially lead to a reduction in the complications associated with diabetes.

2.2 Therapeutic Rationale

ApoC-III is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in

regulating plasma TG levels (Chan et al. 2008). It is a component of TG-rich lipoproteins (TRLs) and a potent inhibitor of lipoprotein lipase (LPL; Lemieux et al. 2003). At higher concentrations, apoC-III also inhibits the activity of hepatic lipase (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense VLDL to intermediate-density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apolipoprotein E (apoE)-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of VLDL-TG and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

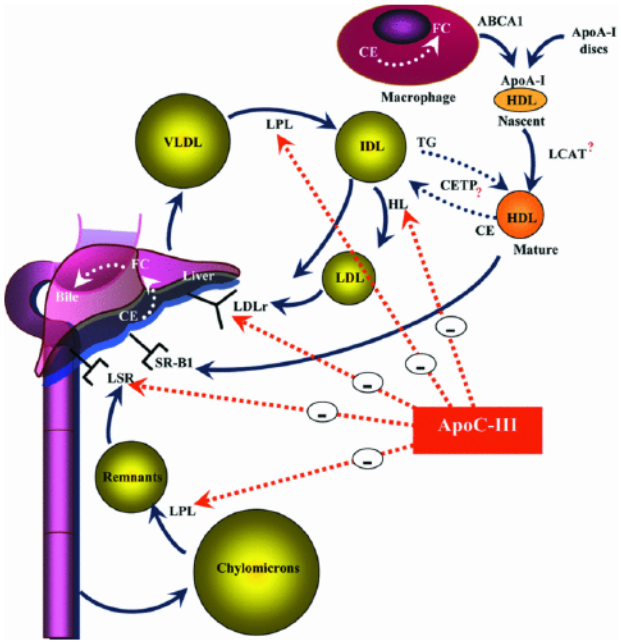


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Although not the primary aim of treatment, a growing body of human genetic data have demonstrated associations with functional mutations affecting apoC-III gene expression and CVD risk (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010; Crosby et al. 2014; Jørgensen et al. 2014). Human genetic data have demonstrated positive phenotypic characteristics with loss of function mutations in apoC-III expression, and no deleterious effects have been reported. A novel null mutation in the apoC-III gene (R19X) was identified in the Heritability and Phenotype Intervention (HAPI) heart study in Old Order Amish individuals who were heterozygous carriers. Mutation carriers in this population had a life-long apoC-III deficiency (~50% of normal) that resulted in lower plasma TG levels (fasting and post-prandial),

a cardioprotective lipid profile (i.e., higher HDL-C and lower LDL-C) and reduced atherosclerosis (as measured by coronary artery calcification) compared with noncarriers (Pollin et al. 2008). Additionally, homozygosity in the apoC-III promoter (*APOC3*-641CC genotype), identified in a group of Ashkenazi Jews of advanced age (near or above 100 years of age), was associated with significantly lower levels of apoC-III, favorable lipoprotein profile (increased HDL, reduced TG/HDL, increased LDL particle size), lower incidence of hypertension, greater insulin sensitivity, cardiovascular health, and longevity compared to controls (heterozygous CA or homozygous AA genotypes) (Atzmon et al. 2006).

Most recently, 2 studies using a Mendelian randomization approach provided compelling evidence that reducing apoC-III expression may reduce coronary heart disease risk (Crosby et al. 2014; Jørgensen et al. 2014). One (1) study identified 4 rare variants in apoC-III that were associated with a 39% reduction in plasma TG levels (Crosby et al. 2014). The variants were then tested for association with CHD in 110,097 individuals from 15 different studies. Mutation carriers had a 40% reduction in CHD compared to non-carriers. The other study, using a similar strategy (Jørgensen et al. 2014) found 3 apoC-III variants that were associated with a 44% reduction in plasma TG levels and in a cohort of 75,725 Danes; carriers of these variants had a 41% reduction in CHD.

In contrast to the above, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear post-prandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating TG and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Potential mechanisms that explain how apoC-III inhibition results in TG reduction in include: (1) by enhancing the activity of LPL, (2) through potentially enhanced activity of other lipases also involved in the metabolism and breakdown of triglycerides, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) it is known that apoC-III interacts with apoE, an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. ISIS 304801-mediated reduction of apoC-III could be contributing to 1 or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel, apoC-III lowering mechanism of action, ISIS 304801 may provide the potential to manage TG levels and associated metabolic derangements in patients with FPL.

2.3 ISIS 304801

2.3.1 Mechanism of Action

ISIS 304801 is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III mRNA and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding)

of ISIS 304801 to the cognate mRNA results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, ISIS 304801 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of ISIS 304801 (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 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) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 304801 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modifications confer increased stability and affinity, they do not support RNase H1 catalysis 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 H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the number of 2′-MOE modifications to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

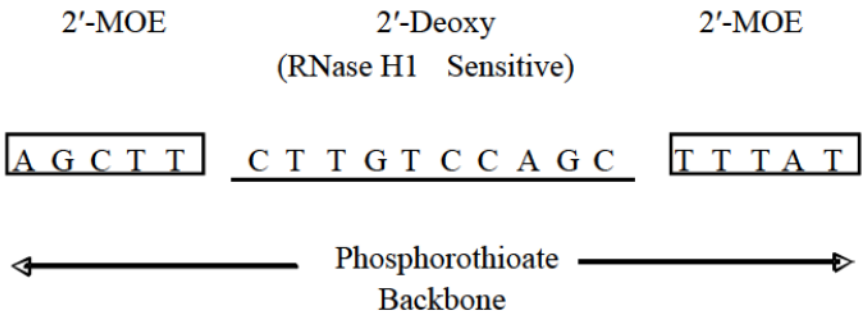


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of ISIS 304801 is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using ISIS 304801 has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with ISIS 304801 also resulted in reduced VLDL and chylomicron TG and reduced post-prandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of ISIS 304801 have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with ISIS 304801 for up to 39 weeks of treatment followed by a 20-week recovery period are complete. The preclinical toxicology program for ISIS 304801 consists of single-dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat-dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

ISIS 304801 treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-*O*-(2-methoxyethyl) (2′-MOE)-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with ISIS 304801 produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects are monitorable by measurement of echocardiograms and cardiac troponin I that will be included in this clinical study.

ISIS 304801 caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). ISIS 304801 had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, ISIS 304801 was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with ISIS 304801 can be found in the ISIS 304801 Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 304801 can be found in the ISIS 304801 Investigator's Brochure. A summary is included below.

ISIS 304801 has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered ISIS 304801 from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of ISIS 304801 have shown very large and clinically meaningful reductions in fasting apoC-III and TG (~80% and 70%, respectively, mean reduction from Baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background of stable fibrate therapy, patients with Familial Chylomicronemia Syndrome (FCS), and patients with hypertriglyceridemia and T2DM. Comparison of the effects of ISIS 304801 at the 300 mg/wk dose across several patient populations is shown in Table 1.

Table 1 Mean Percent Change from Baseline of Lipid Parameters in Hypertriglyceridemia Patients Treated with ISIS 304801 (300 mg/wk for 3 months) in Phase 2 Studies

Mean % (SD) Change from Baseline	Monotherapy in Hypertriglyceridemia and T2DM (N = 7) Mean Baseline TG 259 mg/dL	Monotherapy in Hypertriglyceridemia (N = 11) Mean Baseline TG 559 mg/dL	Add-on to Fibrate in Hypertriglyceridemia (N = 10) Mean Baseline TG 394 mg/dL
ApoC-III	- 88% (6.0)*	- 80% (9.3)***	- 71% (13.0)**
Triglycerides	- 72% (8.3)*	- 71% (14.1)***	- 64% (8.9)**
HDL-C	+ 40% (19.8)*	+ 46% (24.0)***	+ 52% (23.7)**

* $p \leq 0.05$ vs. placebo; **$p \leq 0.01$ vs. placebo; ***$p \leq 0.001$ vs. placebo

In addition to the lipid analysis, the effect of lowering apoC-III on glycemic control and insulin sensitivity was evaluated in the subgroup of patients with hypertriglyceridemia and type 2 diabetes, by measuring fructosamine, glycated albumin, and HbA1c and by performing a hyperinsulinemic euglycemic clamp at Baseline and at the end of the randomized treatment period.

Treatment with ISIS 304801 significantly reduced TG levels (69%, $P = 0.02$) and induced a 57% improvement in whole-body insulin sensitivity ($P < 0.001$). The study also found a strong relationship between enhanced insulin sensitivity and both plasma apoC-III ($r = 20.61$, $P = 0.03$) and TG reduction ($r = 20.68$, $P = 0.01$) (Digenio et al. 2016).

Statistically significant decreases were observed in the mean change from Baseline in % glycated albumin and in fructosamine 1 week after the last dose and in HbA1c and fructosamine at the

end of the Follow-up Period (3 months after the last dose). These significant effects later in the Follow-up Period were likely a result of the long duration of response of ISIS 304801.

In clinical studies conducted to date, ISIS 304801 has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies, there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of volanesorsen, 6 patients out of 182 dosed (approximately 110 receiving volanesorsen and 72 receiving placebo) as of 27 May 2016 have experienced more pronounced falls in platelet count and have had Study Drug interrupted or stopped as a consequence. Of these 6 patients, 2 of them had to be hospitalized with platelet counts less than 25,000/mm^3 for closer monitoring and treatment with corticosteroids. In 1 case the patient was also administered intravenous immunoglobulin (IVIG). No patients had clinically-relevant bleeding, and platelet counts recovered following discontinuation of dosing, with administration of corticosteroids (+/- IVIG) in the 2 cases of patients with platelet counts less than 25,000/mm^3.

The most frequently observed AEs with ISIS 304801 were local reactions at the injection site. Local cutaneous reactions at the injection site (LCRIS) defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, ISIS 304801 treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the no observable adverse effect level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data provide an adequate clinical safety margin. Nonclinical findings were not considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that ISIS 304801 has been well-tolerated at dose levels up to 300 mg in patients with high TG (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks). Analysis of the cohorts in which ISIS 304801 was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of ISIS 304801, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been administered intravenously and SC in multiple clinical studies at doses up to 1200 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study with an open-label extension. Approximately 40 to 70 eligible patients will be randomized 1:1 (ISIS 304801: placebo) and stratified by FPL Group assignment (see Section 4.2 Randomization).

The study will comprise the following periods:

- Screening. An up to 6-week Screening Period, including at least a 4-week diet stabilization phase during which patients will be encouraged to continue on their current diet.
- Randomized Treatment Period. Following stabilization, up to 70 eligible patients will be randomized 1:1 to receive ISIS 304801 300 mg or placebo once-weekly for 52 weeks followed by either:
  - Open-label Extension (OLE) Period when patients will receive ISIS 304801 300 mg once-weekly for 52 weeks. Following the Week 104 visit of the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks.
  - A 13-week Post-Treatment Evaluation Period.

The primary endpoint for the study will be evaluated after the last patient has completed the Week 52/early termination (ET) visit and will be based on the percent change from Baseline in fasting TG at the primary analysis time point (Month 3).

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to 60 patients with FPL will be randomized. Sample size considerations are discussed in Section 10.2.

3.4 Overall Study Duration and Follow-up

The study will consist of an up to 6-week Screening Period and a 52-week Randomized Treatment Period. Following the Week 52 visit, patients may enter a 52-week OLE Period followed by a 13-week Post-treatment Evaluation Period. An option for patients completing the

52-week OLE period will be an additional 1 year of treatment. Patients may participate up to a total of 3 years on study.

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Screening

A period of 6 weeks is given to complete the screening and baseline assessments outlined in the Schedule of Procedures in Appendix A.

3.4.2 Randomized Treatment Period

The randomized treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures in Appendix A. During the randomized treatment period, Study Drug will be administered by SC injection once-weekly.

3.4.3 OLE Period

Following the 52-week randomized treatment period, patients will continue treatment in the OLE treatment period. The OLE period is 52 weeks as detailed in the Schedule of Procedures in Appendix A.

After a patient has been in the OLE period for a period of 3 months, an Investigator may consult with the study Medical Monitor and request that triglyceride values become unblinded to the Investigator and patient after Week 13 for the duration of the study.

Following the Week 104 of the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks. The schedule of procedures will follow the same schedule as the first year of OLE.

3.4.4 Post-Treatment Period

Following the OLE period, patients will enter a 13-week post-treatment follow-up period. Patients who do not enter the OLE period will go straight to the 13-week post-treatment follow-up period.

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 304801 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 304801, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written IEC/IRB approval of the protocol, informed consent form, and all other patient information and/or recruitment material.

Patients or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient 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, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented or re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Randomization

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

Using an Interactive Voice/Web-Response System (IXRS), eligible patients will be randomized 1:1 to receive ISIS 304801 or placebo.

Patients will be stratified by assignment into 1 of 3 groups based on FPL phenotype, genetic variants and family history of PL.

FPL Groups for Stratification

1. Group 1 will consist of patients with the FPL phenotype and genetic variants of FPL
2. Group 2 will consist of patients with the FPL phenotype, but lacking a genetic variant, and having a confirmed family history of FPL or abnormal and similar fat distribution, plus 1 minor criterion
3. Group 3 will consist of those with the FPL phenotype, but without either a genetic variant or family history, plus 2 minor criteria and a BMI < 35 kg/m^2

Genetic analysis reports include characterization of variants into 5 classifications: benign, likely benign, variant of unknown significance, likely pathogenic or pathogenic.

For stratification purposes:

Positive on genetic testing: Documentation of pathogenic or likely pathogenic genes associated with familial partial lipodystrophy will be considered positive for genetic analysis if these

changes are likely to represent the underlying cause of the subject's phenotype. This should be documented in a written report.

Negative on genetic testing: When sequencing analysis of the partial lipodystrophy panel for variants determines that no pathogenic or likely pathogenic variant were identified or is a variant of unknown significance, this will be considered as evidence for negative for genetics. Negative on genetics will also be considered for those subjects for whom the genetic analysis results are unlikely, unknown, or untested.

Positive family history of FPL or family history of abnormal and similar fat distribution includes immediate family / first degree relatives (father, mother, brother, sister, daughter, son), as well as second degree relatives (grandparents, aunts and uncles, nieces and nephews, and grandchildren).

A permuted block schedule will be used. The Sponsor Quality Assurance department or designee will hold a copy of the randomization lists generated by the IXRS vendor.

4.3 Replacement of Patients

Patients who withdraw from the study will not be replaced. The study will continue enrolling until up to 60 patients have been dosed.

4.4 Unblinding of Treatment Assignment

The Sponsor and all patients, monitors, and Study Center personnel will be blinded to treatment assignment throughout the study until all patients have completed the randomized treatment period and the Week 52 assessments and the database has been locked. All patients, monitors and Study Center personnel will maintain blinded to treatment assignment until all patients have completed the Study Week 65 assessments in the OLE period (Week 13 of the OLE). The DSMB may be unblinded upon request as described in the DSMB Charter. In order to ensure maintenance of the study blind, lipid panel results, including apoC-III, will not be available to the Sponsor, monitors, Investigators, Study Center personnel, or the patients until database lock. However, if a patient has suffered a Serious Adverse Event (SAE, as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient using the IXRS. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours but will remain blinded to the patient's treatment allocation. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2). Strict firewalls will be in place between the unblinded Drug Safety and Quality Assurance staff and other Sponsor employees to prevent inadvertent unblinding of individuals involved in study conduct or analysis.

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 6 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

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

   Diagnosis of lipodystrophy is based on deficiency of subcutaneous body fat in a partial fashion assessed by physical examination and low skinfold thickness in anterior thigh by caliper measurement: men (≤ 10 mm) and women (≤ 22 mm), and at least 1 of the following:

   - Genetic diagnosis of familial PL (e.g., mutations in LMNA, PPAR-γ, AKT2, CIDEC, PLIN1 genes)

   OR

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

   OR

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

   MINOR Criteria

   a. Requirement for high doses of insulin, e.g., requiring ≥ 200 U/day, ≥ 2 U/kg/day, or currently taking U-500 insulin
   b. Presence of acanthosis nigricans on physical examination
   c. Evidence/history of polycystic ovary syndrome (PCOS) or PCOS-like symptoms (hirsutism, oligomenorrhea, and/or polycystic ovaries)
   d. History of pancreatitis associated with hypertriglyceridemia
   e. Evidence of non-alcoholic fatty liver disease
      - Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease or radiographic evidence of hepatic steatosis (e.g., on ultrasound or CT)

4. A diagnosis of type 2 diabetes mellitus, as defined by the International Diabetes Federation guidelines of 2012, made at least 6 months prior to the Screening, and:
   - A HbA1c ≥ 7% to ≤ 12% at Screening,

- On anti-diabetic therapy consisting of:
  a. Metformin ≥ 1500 mg/day, or
  b. If the dose of metformin is < 1500 mg/day, or metformin is not tolerated, then the patient should be on other oral anti-diabetic drugs (OAD) or an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, or
  c. Insulin therapy alone or in combination with other anti-diabetic drugs

5. Hypertriglyceridemia as defined by Fasting TG levels ≥ 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification visits. Patients with the clinical diagnosis of FPL and with Fasting TG levels ≥ 200 (≥ 2.26 mmol/L) to < 500 mg/dL (≥ 5.7 mmol/L) at both Screening and Qualification Visits who meet the genetic or family history criteria for study inclusion may be further screened and enrolled in the study
6. Presence of hepatosteatosis (fatty liver), as evidenced by a Screening MRI indicating a hepatic fat fraction (HFF) ≥ 6.4%
7. Willing to maintain their customary physical activity level and to follow a diet moderate in carbohydrates and fats with a focus on complex carbohydrates and replacing saturated for unsaturated fats
8. Satisfy 1 of the following:
   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug administration.
   b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug administration.

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

5.2 Exclusion Criteria

1. A diagnosis of generalized lipodystrophy
2. A diagnosis of acquired partial lipodystrophy (APL)
3. Acute pancreatitis within 4 weeks of Screening

4. History within 6 months of Screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack, or unstable congestive heart failure requiring a change in medication
5. Major surgery within 3 months of Screening
6. History of heart failure with New York Heart Association functional classification (NYHA) greater than Class II or unstable congestive cardiac failure requiring a change in medication
7. Uncontrolled hypertension (blood pressure [BP] > 160 mm Hg systolic and/or 100 mm Hg diastolic)
8. Any of the following laboratory values at Screening:
    a. Cardiac troponin I > ULN
    b. LDL-C > 130 mg/dL on maximal tolerated statin therapy
    c. Hepatic:
        i. Total bilirubin > ULN
        ii. ALT > 3.0 x ULN
        iii. AST > 3.0 x ULN
    d. Renal:
        i. Persistently positive (2 out of 3 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
        ii. Two (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 < 1g/24 hrs
        iii. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60 mL/min
    e. Platelet count < lower limit of normal (LLN)
    f. Clinically-significant (as determined by the Investigator or Sponsor) abnormalities on laboratory examination that will increase risk to the patient or interfere with data integrity
9. Uncontrolled hypothyroidism (abnormal thyroid function tests should be approved by Study medical monitor)
10. History within 6 months of Screening of drug or alcohol abuse
11. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B

14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
15. Treatment with another investigational drug, biological agent, or device within 1-month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Unwilling to comply with lifestyle requirements (see Section 6.3)
17. Use of any of the following:
    a. Metreleptin within the last 3 months prior to screening
    b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to screening. For lipid lowering medications (e.g., omega-3 fatty acids) dose, brand and regimen are expected to remain the same from Day 1 throughout Week 13. Patients not receiving these drugs within 4 weeks prior to screening are also eligible
    c. Insulin unless on a stable daily insulin dose regimen (± 20 %) for at least 4 weeks prior to dosing
    d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis
    e. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant throughout the study
    i. Oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed
    j. Anti-obesity drugs [e.g., the combination of phentermine and extended-release topiramate (Qsymia), orlistat (Xenical), liraglutide [rDNA origin] injection (Saxenda) and lorcaserin (Belviq), phentermine, amphetamines, herbal preparations] within 12 weeks prior to screening
    k. Prior exposure to ISIS 304801
    l. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
18. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
19. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, and C.

6.1.1 Screening and Baseline

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A 6-week period, including a diet stabilization period of at least 4 weeks, is given to perform the screening evaluations. The baseline assessments will be performed at Week -2 to -1, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes.

6.1.2 Randomized Treatment Period

During the randomized treatment period, patients will report to the study center for clinic visits a minimum of 6 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once-weekly (Section 8.1). Collection and measurement of vital signs, physical examination results, [redacted], [redacted], [redacted], electrocardiograms (ECGs), liver MRIs, echocardiograms, clinical laboratory parameters (including hematology; serum chemistry; lipid panel; [redacted], [redacted], [redacted], and CRP measured by high sensitivity assay [hsCRP]; urinalysis, and other analytes listed in Appendix B), ISIS 304801 plasma trough concentrations, immunogenicity (IM) testing, [redacted], collection of SMBG and insulin diary, hunger diary, pain diary, and AEs, concomitant medication/procedure information, and quality of life assessments will be performed according to the schedule of procedures in Appendix A. AEs at the injection site should be collected as AEs. Dietary/alcohol counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the treatment and follow-up period.

Patients must be fasted prior to drawing all lipid samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Blood sampling at Weeks 2,3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51 may be conducted by a home healthcare service. While allowed, it is preferable that visits at Week 8 and 12 are conducted at the clinic if possible. Dosing instructions and training will be provided to the patient where applicable.

All visits have a visit window of at least ± 2 days. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Randomized Period Post-Treatment Follow-Up

Patients who do not enter the OLE period will go straight to the 13-week post-treatment follow-up period. This period consists of 7 visits, as outlined in the Schedule of Procedures in Appendix A.

6.1.4 OLE Period

After completion of the 52-week randomized treatment period patients will enter the OLE period and will receive ISIS 304801 for 52 weeks. Assessments and study visits will be generally similar to the randomized treatment period as outlined in the Schedule of Procedures in Appendix A, with the inclusion of weekly platelet monitoring.

6.1.5 OLE Post-Treatment Period

Following the Week 52 visit of the Open-Label Extension Period, patients will have the option of continuing dosing for up to an additional 52 weeks. Patients who do not enter this option for additional dosing in the OLE period will go straight to the 13-week post-treatment follow-up period after completion of the first 52 weeks or after discontinuing treatment during the first 52 weeks of OLE. This period consists of 7 visits, as outlined in the Schedule of Procedures in Appendix A.

For patients who continue to receive investigational treatment for the additional 52 weeks, the 13-week post-treatment follow-up period will follow the second year of open-label dosing.

6.2 Study Assessments

6.2.1 Physical Exams, Vital Signs, [redacted]

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight (at specific visits), blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at Screening.

[redacted]

6.2.2 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study as indicated in Appendix A. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable or uninterpretable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count $\leq$ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

[redacted]

6.2.4 ECG

ECGs will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at the times indicated in Appendix A.

6.2.5 MRI

MRI of the liver will be conducted at the times indicated in Appendix A for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be evaluated by an independent central reader, blinded to the patient's treatment assignment, to assess liver fat, liver size [redacted].

6.2.6 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at the times indicated in Appendix A. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader, blinded to the patient's treatment assignment. Results will be provided to the DSMB for their review.

6.2.7 Self-monitoring Blood Glucose

A calibrated glucometer will be distributed to patients with diabetes at least 1 week before dosing, for their home-based glucose monitoring (Self-Monitoring Blood Glucose [SMBG]). Fasting SMBG will be self-measured in the morning: daily if the patient is on insulin therapy, and weekly if on oral antidiabetic therapy. Training on the use of the glucometer will be provided before dosing. The SMBG may start at the beginning of the diet run-in period continuing to the end of the post-treatment follow-up period.

[redacted]

Subjects who use a glucometer should bring their glucometer to every clinic visit. The Investigator or delegate will review the glucometer printout at every clinic visit to evaluate if self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring for either Hypoglycemia or Hyperglycemia sections (Sections 8.5.7 and 8.5.8, respectively).

All diabetic patients will note any changes in their insulin dose and/or oral antidiabetic therapy, as well as any hypoglycemic or hyperglycemic episodes they may experience. Diabetic patients on insulin should enter their insulin into their diary daily.

The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic or hyperglycemic episode.

- Patients will be instructed on the monitoring and management of hypoglycemic and hyperglycemic episodes at each visit
- Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L). Should a subject require assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions, this should be recorded as treatment for the adverse event on the AE CRF and documented in the source
- Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF

6.2.8 Hunger and Widespread Pain Diaries

All patients will complete hunger and pain questionnaires once a week starting at the beginning of the diet run-in period and continuing to the end of the post-treatment follow-up period.

6.2.9 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at the times indicated in Appendix A. Patients will complete a survey that will evaluate changes in a disease burden score before and after therapy. The disease burden score will be calculated through analysis of a natural history survey of patients with FPL. [redacted]

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All patients of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 3 months after their 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 that does not meet 1 of the following conditions:

- Post-menopausal: 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 post-menopausal 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 patients:

- 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 patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

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

*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.

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours, but preferably not more than 12 hours, before visits requiring fasted blood sampling.

All patients will be counseled to follow a moderate diet composed of ~50% kcal from carbohydrates (focusing on complex carbohydrates and avoidance of concentrated sugars like juice and candy) and 30% or less kcal from fat (focusing on decreasing intake of trans and saturated fats and increasing intake of mono-unsaturated fats), with an emphasis on mixed meals (combination of protein, carbohydrate and fat). Patients should maintain their customary physical activity level throughout the study.

Alcohol consumption should be limited to not more than 3 drinks/week and not more than 1 drink/day for females and not more than 5 drinks/week and not more than 2 drinks/day for males; 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor). **In addition, patients should refrain from drinking alcohol for at least 48 hours prior to a clinic visit.**

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs, or the patient experiences symptoms of decreased platelets or hypoglycemia/hyperglycemia. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x ULN, imaging, preferably contrast-enhanced computed tomography (CT), should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (defined as ISIS 304801 or placebo) characteristics are listed in Table 2.

The Study Drug is contained in glass pre-filled syringes (PFS). The Study Drug 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 2 Study Drug Characteristics

Study Drug	ISIS 304801	Placebo
Strength	200 mg/mL	Not Applicable
Volume/Formulation	1.5 mL solution per PFS	1.5 mL solution per PFS
Dose	300 mg once-weekly	Not applicable
Route of Administration	SC	SC

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/destruction of Study Drug supplies provided by the Sponsor. The Study Center must return all unused Study Drug to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

For each individual patient, Study Drug will be administered SC as a single 1.5 mL injection once-weekly for Weeks 1-52 of the Randomized Treatment period of the study, and Weeks 53-104 of the OLE period of the study. Self-administration will be allowed after appropriate training of patient and/or caregiver.

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

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

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.

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 Day 1 pre-dose assessment and the last measurement prior to Day 1.

Confirmation Guidance: At any time during the Study (Randomized Treatment, OLE, 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. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients 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 patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below are met below (refer to Sections 8.6.1 to 8.6.3) and are confirmed, the patient will be dose paused or permanently discontinued (as described in the appropriate stopping criterion) from further treatment with Study Drug, and 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 (see Section 8.8).

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft 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.

For patients with Baseline ALT or AST below 2 x ULN

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 (Randomized Treatment, OLE, or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

For patients with Baseline ALT or AST between ≥ 2 and < 3 x ULN

In the event of an ALT or AST measurement that is 2 x the Baseline level any time during the study (Randomized Treatment, OLE, or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Similarly, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels that are continuing to rise should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR] and total bilirubin) retested at least bi-monthly until levels stabilize and begin to recover (ALT and AST levels become ≤ 1.2 x ULN or 1.2 x Baseline value).

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > 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] IgM, hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (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.

8.5.2 Safety Monitoring for Renal Function

Patients with confirmed persistent changes that are observed over 2 consecutive visits, at least 7 days apart, for the criterion below should be retested every 2 weeks with serum creatinine and urine chemistries until creatinine and P/C ratio stabilize:

- P/C ratio change from baseline > 50% and ≥ 1.5 ULN

8.5.3 Safety Monitoring for Platelet Count Results

Monitor every 1 week unless otherwise specified.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.

Actions to be taken in the event of reduced platelet count are shown in Table 4 in Section 8.6.3.

The tests outlined in Table 3 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 3 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (non-consecutive or consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.4 Safety Monitoring for Minor Bleeding Events

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, 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) and platelet count should be performed.

8.5.5 Safety Monitoring for Constitutional Symptoms

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

8.5.6 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has an LDL-C > 160 mg/dL on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy, increase the statin dose for patients who are already on treatment, add ezetimibe if on maximal statin therapy).

8.5.7 Safety Monitoring for Hypoglycemia

Classification of Hypoglycemia

Alert value for hypoglycemia

≤ 70 mg/dL (≤ 3.9 mmol/L) plasma concentration

Severe Hypoglycemia

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

Documented Symptomatic Hypoglycemia

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

Asymptomatic Hypoglycemia

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

Probable Symptomatic Hypoglycemia

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

In the event of an episode of symptomatic documented hypoglycemia (FPG < 70 mg/dL), if the patient is on insulin, the Investigator shall reduce the total daily dose by 5-15%. If the patient is on oral ant-diabetic drugs, the Investigator should use his or her discretion regarding changes to the drug regimen to help prevent future incidences of hypoglycemic events. In all cases, the adjustments made to medication should be carefully documented via electronic diary (insulin) and/or concomitant medication CRF.

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

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

Patients must be instructed on the monitoring and management of hypoglycemic episodes at the Baseline Visit.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

Instructions should be provided to all patients on the appropriate use of a glucose meter.

8.5.8 Monitoring Rule for Documented Hyperglycemia

Routine fasting SMBG and central lab alerts on FPG (and HbA1c after Week 12) are set up to ensure that glycemic parameters remain under predefined thresholds values. If one fasting SMBG value exceeds the specific glycemic limit on 1 day, the patient checks it again during the 2 following days. If all the values in 3 consecutive days exceed the specific limit, the patient should contact the Investigator and a central laboratory FPG measurement (and HbA1c after Week 12) is performed.

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

- From Baseline visit to Week 12 (including value at Week 12) of Randomized Treatment period or OLE period:
  - FPG > 300 mg/dL (16.6 mmol/L)
- From Week 12 to Week 24 (including value at Week 24) of Randomized Treatment period or OLE period:
  - FPG > 270 mg/dL (15.0 mmol/L) or
  - HbA1c > 9.5% (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1.5% from Baseline (for patients with Baseline HbA1c ≥ 8%)
- From Week 24 up to Week 52 of Randomized Treatment period or OLE period:
  - FPG > 240 mg/dL (13.3 mmol/L) or
  - HbA1c > 9.5% (for patients with Baseline HbA1c < 8%) and HbA1c increase of more than 1.5% from Baseline (for patients with Baseline HbA1c ≥ 8%)

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

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

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

- Investigation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the eCRF)
- Stress on the absolute need to be compliant to treatment

- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations
- Schedule a FPG/HbA1c assessment at the next visit

If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, an increase in current medication or the addition of new anti-diabetic rescue medication may be introduced at Investigator discretion and according to local guidelines. Investigators should minimize changes prior to the primary endpoint, when possible. All adjustments to medication should be captured on the concomitant medication CRF and/or electronic diary.

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

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

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to the treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

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

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor**, 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

In the event of persistent changes that are observed over 2 consecutive weeks, for any of the criteria below, dosing of a patient with Study Drug may be stopped temporarily:

1. Quantitative total urine protein measurement of > 3.5 g/24 hours
2. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 4 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with Study Drug will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

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 on dosing at 300 mg every 2 weeks then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 4.

Administration of corticosteroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose corticosteroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 wk for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/day for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral corticosteroids after methylprednisolone). Triglyceride levels will be monitored weekly, and AE monitoring will continue during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/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 will be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. If dosing is reinitiated it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The suitability of the patient for reinitiation of 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 upon holding of dosing.

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

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

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-arterial or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 20.0 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 cm^2
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; epistaxis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 4 Actions in Patients with Low Platelet Count or Drop in Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	Monitor every 1 week unless otherwise specified Obtain additional lab tests (Table 3) if 2 occurrences (consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Weekly 300 mg Study Drug administration	

Table 4 Actions in Patients with Low Platelet Count or Drop in Platelet Count *Continued*

Platelet Count on Rx	Drug Dose	Monitoring
100K/mm^3 - > 75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks	
75K/mm^3 - > 50K/mm^3	If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks only if approved by Sponsor Medical Monitor	Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
≤ 50K/mm^3	• Permanently discontinue Study Drug	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is < 50K/mm^3 if possible

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

8.6.4 Stopping Rule for Documented Severe Hypoglycemia

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

8.7 Adjustment of Dose and/or Treatment Schedule

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 4 above.

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Dose adjustments should not occur unless absolutely necessary prior to the primary analysis time point (Month 3).

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

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

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6
- The patient experiences an AE that necessitates unblinding of the Investigator to the patient's treatment assignment

The reason for discontinuation of study *t*reatment must be recorded in the electronic Case Report Form (eCRF) and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment and OLE Periods

Patients should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26 and 50, 52 of Randomized Treatment period (calculated based on the time elapsed since Day 1) and at Weeks 64, 65, 77, 78 and 102, 104 of OLE period to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A.

Any patient who discontinues early from treatment in the Randomized Treatment Period or OLE with platelet counts < LLN should be followed as per Section 8.5.3 (Safety Monitoring for Platelet Count Results) and Section 8.6.3 (Stopping Rules for Platelet Count Results) 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, an early termination visit (Week 52 or Week 104 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

Patients should be encouraged to undergo a final follow-up visit (Week 117 for OLE for post-treatment follow-up, see Appendix A) prior to leaving the study.

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period with platelet counts < LLN should also be encouraged to follow the platelet monitoring rules as per Section 8.5.3 (Safety Monitoring for Platelet Count Results) and Section 8.6.3 (Stopping Rules for Platelet Count Results) 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 a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

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

Other reasons for withdrawal of patients 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 patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (see procedures and assessments for Early Termination/Week 52/104; see Section 8.8 and Appendix A).

For patients 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 procedures and assessments for Early Termination/Week 52/104; see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. AEs 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 signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over-the-counter omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations], plasma apheresis), GLP-1 agonists or systemic corticosteroids may be started or adjusted after screening (except as described in Section 8.5.6) and 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 (except as described in Sections 8.5.7 and 8.5.8).

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.

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.

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 signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

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 Drug supplies. Patients who are self-administering Study Drug 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 in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

Appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

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

9.3.3 Serious Adverse Event (SAE)

A SAE is any AE 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 patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient 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 patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient 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 patient 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 patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit for patients not continuing with the OLE and going straight to the Post-Treatment Follow-up period or the Week 117 visit for patients who continue with the OLE. 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.

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 patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient'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 patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit for patients not continuing with the OLE and going straight to the Post-Treatment Follow-up period or the Week 117 visit for patients who continue with the OLE. The Investigator will monitor each patient 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 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 patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug 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 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 patient'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 event's severity is characterized by 1 of the following:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient'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 due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug 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
- **Reduced Schedule**: Dosing frequency was reduced

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 AE 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)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major adverse cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter. In addition, this committee will also adjudicate the data for

episodes of MACE over the last 3 years prior to randomization, collected by review of each patient's medical chart.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter.

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.

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 patient 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 patient'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 patient'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 errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of Study Drug that exceeds protocol specifications and the patient 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

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient 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 on Follow-up Pregnancy Forms and reported within 24 hours.

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

Female patients: If a suspected pregnancy occurs while on the study (including Follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient 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 patient 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.

Male patients: The progress of the pregnancy in a male patient'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, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

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

The primary analysis time point is at the end of Month 3 where the value at primary analysis time point is defined as the average of Week 12 and Week 13 fasting assessments. The value at

Month 6 is defined as the average of Week 25 and Week 26 and the value at Month 12 is defined as the average of Week 50 and Week 52 fasting assessments.

10.1.1 Primary Endpoint

The primary efficacy analysis will be the comparison of percent changes from Baseline to the primary analysis time point in fasting TG between ISIS 304801 300 mg once-weekly group and placebo group in the Full Analysis Set (FAS).

10.1.2 Secondary Endpoints

Secondary endpoints include:

- Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction using MRI)
- Change from Baseline in HbA1c
- A composite endpoint at Month 6 for percent of patients who achieve
  a. ≥ 40% reduction in fasting TG, and
  b. ≥ 30% reduction of hepatic fat fraction percent
- Change in patient-reported outcomes (PRO):
  - Disease burden score
  - Patient-reported pain
  - Patient-reported hunger
  - Quality of life

[redacted]

[redacted]

10.1.4 Safety Endpoints

Safety endpoints include the following:

- AEs including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- ECGs
- Use of concomitant medications
- MRIs

10.2 Sample Size Considerations

Based upon prior clinical trial experience with ISIS 304801, it is estimated that the standard deviation (SD) of the percent change in total TG is approximately 40%. With 20 ISIS 304801 300 mg once-weekly patients and 20 placebo patients there would be approximately 80% power

to detect a 40% difference in TG levels between treatment groups at an alpha level of 0.05, assuming 50% reduction in the ISIS 304801 treated patients and 10% reduction in the placebo patients.

A sample size of 35 patients (20 active and 15 control) provides 92% power to detect a liver fat treatment difference of 4.7% based on a between patient standard deviation of 4% and a two-sided alpha of 0.05.

10.3 Populations

Full Analysis Set (FAS): All patients who are randomized and received at least 1 dose of Study Drug and have a Baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of 13 doses and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are randomized and receive at least 1 dose of Study Drug.

PK Population: All patients who are randomized, receive at least 1 dose of active Study Drug (ISIS 304801), and have at least 1 PK sample collected and analyzed.

10.4 Definition of Baseline

The baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1. The baseline for other measurements is defined as the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis and Early Stopping Guidelines

An interim analysis of the study is not planned.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as 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 by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All primary, secondary [redacted] endpoints will be assessed in the FAS and PPS, with the former being the basis for the primary efficacy analysis. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized 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.

Patient incidence rates of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and treatment group. 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.

Injection Site adverse events will be summarized by treatment group, MedDRA preferred term and severity.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, immunogenicity, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug administration, as appropriate.

Vital signs and ECG measures will be tabulated by treatment group.

10.6.3 Efficacy Analysis (Primary and Secondary)

The primary efficacy analysis will be the comparison of percent change from Baseline to the primary analysis time point in fasting TG between ISIS 304801 300 mg once-weekly group and placebo group in the FAS. The data will be analyzed using an analysis of covariance (ANCOVA) model with the randomization stratification factor (diagnosis of disease with or without genetics and family history) and Baseline TG as covariates. In the ANCOVA model, TG will be log-transformed. Patients with a missing primary endpoint will have TG value multiply imputed using an imputation model that contains the following variables: baseline TG, TG values at post-baseline visits and the stratification factor, and the multiple imputation will be stratified by treatment (Schafer 1997; Schafer 1999). Any patient who discontinues early from the Treatment Period will be strongly encouraged to attend applicable landmark visits including Weeks 12 and 13 during which TG values will be collected and used in the primary analysis.

The primary efficacy analysis will take place after the last patient has completed the Week 52/ET visit and the database has been locked, and will be based on the percent change from Baseline in fasting TG at the primary analysis time point (end of Month 3).

A few sensitivity analyses using controlled imputations (pattern mixture models (PMM) with ANCOVA) will be conducted to assess the robustness of the primary analysis results on both the FAS and PPS. With this approach, missing not at random (MNAR) is assumed and the mean

function for the missing data from patients who discontinue the study is pre-specified in ways that assess the robustness of the MAR assumption. The mean function parameterization will be completed using the following approaches:

- Patients treated with volanesorsen who discontinue the study due to lack of efficacy or Adverse Events or other types of treatment failure will have missing post-treatment discontinuation TG values multiply imputed using estimates from the placebo patients. Specifically, the copy increment from reference (CIR) approaches will be used. Otherwise, non-informative missing data will be imputed using MI method as the same as the primary analysis
- All patients treated with volanesorsen who discontinue the study will have missing post-treatment discontinuation TG values multiply imputed using estimates from the placebo patients. Specifically, the copy increment from reference (CIR) approaches will be used
- Patients treated with volanesorsen who discontinue the study will have missing post-discontinuation TG values multiply imputed based on baseline TG and the imputation model for the placebo

The additional sensitivity analyses will be conducted for the primary efficacy analysis, and details of the analyses will be specified in the SAP:

- The primary analysis will be repeated in the PPS
- The primary analysis will be repeated in the subset of FAS who have a non-missing primary endpoint
- The following analyses will be conducted on both the FAS and PPS:
  - The primary analysis will be repeated to compare the percent change from Baseline to average of Weeks 8 (Day 50), 12 (Day 78) and 13 (Day 85) between treatment groups. Missing data will not be imputed
  - The primary efficacy endpoint will be analyzed using Wilcoxon rank-sum test for sensitivity analysis, and the treatment effect will be estimated using Hodges-Lehmann estimator
  - For the responder analysis described above, all patients with a missing primary endpoint will be considered as non-responders
  - The primary efficacy endpoint will also be analyzed using the nonparametric Wei-Johnson method

Secondary [redacted] efficacy analyses will be conducted in both the FAS and PPS, and described fully in the SAP:

- Change from Baseline in hepatic fat fraction (%) as assessed by MRI will be compared between ISIS 304801 300 mg qw and placebo groups using an ANCOVA model with baseline and the stratification factor as covariates

- Change from Baseline in HbA1c will be compared between ISIS 304801 300 mg once-weekly and placebo group using an ANCOVA model with baseline and the stratification factor as covariates
- Proportion of patients who achieve a $\geq$ 40% reduction in fasting TG from Baseline and $\geq$ 30% reduction of hepatic fat fraction percent from baseline at Month 6 between ISIS 304801 300 mg once-weekly and placebo group will be analyzed using a logistic regression model with the randomization stratification factors, log transformed Baseline TG, and Baseline hepatic fat fraction as covariates. Missing data will be considered as informative missing for patients who discontinue the study prior to the primary analysis time point due to lack of efficacy or Adverse Events or other types of treatment failure; otherwise, missing data will be considered as non-informative missing. In the responder analysis, patients with informative missing data will be treated as non-responders. Non-informative missing data will be handled using the same multiple imputation method as the primary analysis. Analyses will also be performed in which the above primary and secondary efficacy endpoints are evaluated at the Month 3, Month 6, and Month 12 analysis time points, where applicable. The efficacy endpoints will also be evaluated at Month 15, Month 18, and Month 24 in the OLE period as appropriate.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

PK analysis will include the following:

- To determine trough (pre-dose) and post-treatment ISIS 304801 plasma concentrations in all patients who receive Study Drug. For all patients who receive ISIS 304801 treatment, trough (pre-dose) and post-treatment ISIS 304801 plasma concentrations will be summarized by treatment period, dose and Study Day, with and without stratification by immunogenicity status, using descriptive statistics

Immunogenicity (IM) analyses will include the following:

- To evaluate IM (confirmed positive/negative and, when applicable, titer of anti-ISIS 304801 antibodies) before, during, and after treatment with Study Drug in all evaluable patients and appropriately summarize by treatment period, treatment and dose over time
- To determine the IM incidence (number) and incidence rate (percent) at each evaluated study time point, and for the overall treatment and post-treatment evaluation period and summarize by treatment period, treatment and dose, as the total number of and percent of evaluated patients with antibody negative, positive, and unknown status
- Study patients with positive anti-ISIS 304801 antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or not determinable
- To evaluate potential relationships of immunogenicity with selected efficacy, safety, and PK measures

Additional details regarding the PK and immunogenicity analysis will be described in the SAP.

Population PK and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

Additional details regarding the PK analysis will be described in the SAP.

[redacted]

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.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient 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 are administered. The patient must be given sufficient time to consider whether to participate in the Study.

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

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated 19 October 2013 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent/assent forms, other written patient 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 before recruitment of patients 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 patients 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

E6 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, 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.

11.4 Patient Confidentiality

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

In compliance with Federal and local regulations, ICH E6 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 patient'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 patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. 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 patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor 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 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.

12.3 Study Documentation and Storage

An 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 patient'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. In this Study, eCRF may not be used as source documents.

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 ICH E6, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient 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
- 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 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.

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 patient confidentiality is respected.

The Sponsor monitor 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 patient 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 E6 and the Sponsor's audit plans, this Study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. 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 E6, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient 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.

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. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients 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. Patients 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

Placebo-Controlled Period

Followed by

Open-Label Extension Period

Appendix A Schedule of Procedures – Placebo-Controlled

Study Period	Screen/ Run In[a]	Qual Visit[k]	Randomized Treatment Period																				
Study Week	-6 to -2	-2 to -1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Primary Endpoint Wk 12	Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6 Wk 25	Month 6 Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12 Wk 50	Month 12 Wk 52 or ET
Study Day	-42 to -15	-14 to -7	1	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	**0**	**0**	**0**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Informed Consent	X																							
Outpatient Visit	X	X	X	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X
Inclusion/Exclusion Criteria	X	X																						
Medical History	X																							
Vital Signs (+ body weight)	X[b]	X	X		X		X			X		X			X		X		X		X			X
Physical Examination	X		X							X					X				X					X
[redacted]																								
12- lead ECG (triplicate)	X									X					X				X					X
Urinalysis (including P/C ratio)	X[c]	X	X[c]		X		X			X		X			X[c]				X[c]					X[c]
MRI liver	----X----													-----X----									-----X----	
Echocardiogram	----------X----------													-----X----									-----X----	
Genetic testing for diagnosis (if not available in medical history)[d]	X																							

Appendix A Schedule of Procedures – Placebo-Controlled *Continued*

Study Period		Screen/ Run In[a]	Qual Visit[k]	Randomized Treatment Period																					
										Primary Endpoint						Month 6									Month 12	
Study Week		-6 to -2	-2 to -1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Wk 25	Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Wk 50	Wk 52 or ET
Study Day		-42 to -15	-14 to -7	1	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Blood Draw (Fasting)[e]	Chemistry Panel	X	X	X		X		X			X		X			X		X		X		X			X
	CBC with Differential[f]	X	X	← X → Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling																					
	Serum Lipid Panel	X	X	X		X		X		X	X		X		X	X		X		X		X		X	X
	Coagulation (aPTT, PT, INR)	X						X			X					X				X					X
	Hepatitis B, C, HIV	X																							
	HbA1c	X		X							X					X				X					X
	[redacted]																								
	hsCRP			X							X					X									X
	[redacted]																								
	Sedimentation Rate			X							X					X									X
	Complement (C5a, Bb)			X							X					X									X
	Troponin I	X		X							X					X									X
	Plasma PK - ISIS 304801			X		X		X			X		X			X		X		X		X			X
	Anti-ISIS 304801 Antibodies			X		X		X			X					X				X					X

Appendix A Schedule of Procedures – Placebo-Controlled *Continued*

Study Period		Screen/ Run In[a]	Qual Visit[k]	Randomized Treatment Period																					
										Primary Endpoint					Month 6									Month 12	
Study Week		-6 to -2	-2 to -1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Wk 25	Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Wk 50	Wk 52 or ET
Study Day		-42 to -15	-14 to -7	1	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Blood Draw (Fasting)[e]	FSH (women only, if applicable)	X																							
	Thyroid Panel	X																							
	Serum Pregnancy Test[g]	X	X			X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[h]			X							X					X									X
	Archived blood sample for potential gene sequencing related to metabolic dyslipidemia[d]	----------X----------																							

Appendix A Schedule of Procedures – Placebo-Controlled *Continued*

Study Period	Screen/ Run In[a]	Qual Visit[k]	Randomized Treatment Period																					
									Primary Endpoint					Month 6										Month 12	
Study Week	-6 to -2	-2 to -1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Wk 25	Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Wk 50	Wk 52 or ET
Study Day	-42 to -15	-14 to -7	1	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
[redacted]																								
Weekly Study Drug: SC Injection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glucometer Dispensation/Training	--------X--------																							
Patient Diary Dispensation/Training[i]	--------X--------																							
Review Daily SMBG and Insulin Dose (patients on insulin therapy)[i]	X	X	X		X		X		X	X		X		X	X		X		X		X		X	X
Review Weekly SMBG (patients not on insulin therapy)[i]			X		X		X		X	X		X		X	X		X		X		X		X	X
Hunger Diary (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Widespread Pain Diary (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life / [redacted] Assessment(s)		X								X					X									X
Diet/Alcohol Counseling[j]	--------X--------		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	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	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Placebo-Controlled *Continued*

Footnotes:

a Screening procedures performed and the patient starts the diet, lifestyle and medication stabilization period. Up to 4 visits may be required during the diet stabilization period in order to schedule and collect MRI [redacted] assessments

b Height only required at Screening. Body weight is to be measured at Screening, Week 1, Week 13, Week 26, Week 52, and Week 65

c Expanded urinalysis (see Appendix B)

d To be collected during screening/run in before Week -2, if needed for eligibility, otherwise to be collected before Week 12. Genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing. If the patient does not consent to the blood sample and genetic testing, but has documentation of previous genetic testing for partial lipodystrophy, and is willing, and has consented, to provide that documentation to the site, this should ideally be provided by the time of the qualification visit. Results from previous genetic testing should be documented prior to randomization/stratification

e Blood samples to be collected after an overnight fast of at least 10 hours, and preferably no longer than 12 hours. During treatment period, urine and blood samples will be collected prior to Study Drug administration

f Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable or uninterpretable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

g Females of childbearing potential only

h 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.) in this or subsequent clinical studies of ISIS 304801

i Patients on insulin will enter SMBG values preferably daily and insulin dose at least once a week. Patients not on insulin will enter SMBG values preferably at least once a week. Subjects who use a glucometer should bring their glucometer to every clinic visit

j To reinforce compliance to the lifestyle recommendations

k Qualification requires a fasting TG ≥ 200 mg/dL at Screening and after at least 4 weeks of diet stabilization

l Assessments and procedures to be conducted by either a home healthcare service, or the Study Center as arranged by the Study Center personnel

Appendix A Schedule of Procedures – Open-Label

Study Period	Open Label Treatment Period																					Post-Treatment Follow-up		
OLE Study Week	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Primary Endpoint		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
							Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Week	Wk 53	Wk 54	Wk 56	Wk 58	Wk 60	Wk 62	Primary Endpoint		Wk 67 & 69	Wk 71	Wk 73 & 75	Month 6		Wk 80 & 82	Wk 84	Wk 86 & 88	Wk 90	Wk 92 & 94	Wk 96	Wk 98 & 100	Month 12		Wk 106 & 108	Wk 110	Wk 117
							Wk 64	Wk 65				Wk 77	Wk 78								Wk 102	Wk 104 or ET			
Study Day	365	372	386	400	414	428	442	449	463 & 477	498	505 & 519	533	540	554 & 568	582	596 & 610	624	638 & 652	666	680 & 694	708	722	736 & 750	764	813
Visit Window+/- Days	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Outpatient Visit	X	X[h]	X	X[h]	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X[h]	X	X[h]	X[h]	X
Vital Signs (+ body weight)			X		X			X		X			X		X		X		X			X		X	X
Physical Examination								X					X				X					X			X
[redacted]																									
12- lead ECG (triplicate)								X					X				X					X			X
Urinalysis (including P/C ratio)			X		X			X[a]		X			X[a]				X[a]					X[a]		X	X[a]
MRI liver												-----X----									-----X----				
Echocardiogram												-----X----									-----X----				

Appendix A Schedule of Procedures – Open-Label *Continued*

Study Period	Open Label Treatment Period																					Post-Treatment Follow-up		
OLE Study Week	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Primary Endpoint Wk 12	Primary Endpoint Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6 Wk 25	Month 6 Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12 Wk 50	Month 12 Wk 52 or ET	Wk 54 & 56	Wk 58	Wk 65
Study Week	Wk 53	Wk 54	Wk 56	Wk 58	Wk 60	Wk 62	Primary Endpoint Wk 64	Primary Endpoint Wk 65	Wk 67 & 69	Wk 71	Wk 73 & 75	Month 6 Wk 77	Month 6 Wk 78	Wk 80 & 82	Wk 84	Wk 86 & 88	Wk 90	Wk 92 & 94	Wk 96	Wk 98 & 100	Month 12 Wk 102	Month 12 Wk 104 or ET	Wk 106 & 108	Wk 110	Wk 117
Study Day	365	372	386	400	414	428	442	449	463 & 477	498	505 & 519	533	540	554 & 568	582	596 & 610	624	638 & 652	666	680 & 694	708	722	736 & 750	764	813
Visit Window+/- Days	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Blood Draw (Fasting)[b] Chemistry Panel			X		X			X		X			X		X		X		X			X		X	X
CBC with Differential[c]	← X → Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling																								
Serum Lipid Panel			X		X		X	X		X		X	X		X		X		X		X	X		X	X
Coagulation (aPTT, PT, INR)					X			X					X				X					X			
HbA1c								X					X				X					X			X
[redacted]																									
hsCRP								X					X									X			X
[redacted]																									
Sedimentation Rate								X					X									X			X
Complement (C5a, Bb)								X					X									X			X
Troponin I								X					X									X			X
Plasma PK - ISIS 304801			X		X			X		X			X		X		X		X			X		X	X
Anti-ISIS 304801 Antibodies			X		X			X					X				X					X			X
[redacted]																									
Serum Pregnancy Test[d]			X		X			X		X			X		X		X		X			X		X	X
[redacted]																									

Appendix A Schedule of Procedures – Open-Label *Continued*

Study Period	Open Label Treatment Period																						Post-Treatment Follow-up		
OLE Study Week	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Primary Endpoint		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
							Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Week	Wk 53	Wk 54	Wk 56	Wk 58	Wk 60	Wk 62	Primary Endpoint		Wk 67 & 69	Wk 71	Wk 73 & 75	Month 6		Wk 80 & 82	Wk 84	Wk 86 & 88	Wk 90	Wk 92 & 94	Wk 96	Wk 98 & 100	Month 12		Wk 106 & 108	Wk 110	Wk 117
							Wk 64	Wk 65				Wk 77	Wk 78								Wk 102	Wk 104 or ET			
Study Day	365	372	386	400	414	428	442	449	463 & 477	498	505 & 519	533	540	554 & 568	582	596 & 610	624	638 & 652	666	680 & 694	708	722	736 & 750	764	813
Visit Window+/- Days	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
[redacted]																									
Blood Draw (Fasting)[b] Archived Serum & Plasma Samples[e]								X					X									X			X
[redacted]																									
Weekly Study Drug: SC Injection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Review Daily SMBG and Insulin Dose (patients on insulin therapy)[f]			X		X		X	X		X		X	X		X		X		X		X	X			
Review Weekly SMBG and Insulin Dose (patients on OADs)[f]			X		X		X	X		X		X	X		X		X		X		X	X			
Hunger Diary (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Widespread Pain Diary (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life / Disease Burden / [redacted] Assessment(s) [i]								X					X									X			
Diet/Alcohol Counseling[g]	X		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	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	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Open-Label *Continued*

Footnotes:

a Expanded urinalysis (see Appendix B)

b Blood samples to be collected after an overnight fast of at least 10 hours, and preferably no longer than 12 hours. During treatment period, urine and blood samples will be collected prior to Study Drug administration

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable or uninterpretable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

d Females of childbearing potential only

e 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.) in this or subsequent clinical studies of ISIS 304801

f Patients on insulin will enter SMBG values preferably daily and insulin dose at least once-weekly. Patients not on insulin will enter SMBG values at least weekly. Subjects who use a glucometer should bring their glucometer to every clinic visit

g To reinforce compliance to the lifestyle recommendations

h Assessments and procedures to be conducted by either a home healthcare service, or the Study Center as arranged by the Study Center personnel

i Disease burden survey to be conducted after having completed at least 6 months of the open-label period

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 ISIS 304801 or other similar oligonucleotides.

Clinical Chemistry Panel

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

Screening Tests

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)
- TSH, T3, T4

Coagulation

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

Lipid Panel

- Triglycerides

Hematology

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

Pharmacokinetics[1] & Immunogenicity

- ISIS 304801 levels in plasma
- Anti-ISIS 304801 antibodies in plasma

Additional measures for expanded urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Other assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- HbA1c
- Glucose
- Insulin
- Troponin I

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation), or to assess other actions of ISIS 304801 with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C PK Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma ISIS 304801 concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below. Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability and metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation), or to assess other actions of ISIS 304801 with plasma constituents.

Plasma Trough Sampling Schedule for all Patients during Randomized Treatment Period

Week	Wk1	Wk4	Wk8	Wk13	Wk19	Wk26	Wk32	Wk38	Wk44	Wk52
Study Day	D1	D22	D50	D85	D127	D176	D218	D260	D302	D358
Visit Window +/- Days	0	2	2	2	3	2	3	3	3	2
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose

Plasma Trough and Post-Treatment Sampling Schedule for all Patients during Open-Label and Post-Treatment Periods

Week	Wk53	Wk56	Wk60	Wk65	Wk71	Wk78	Wk84	Wk90	Wk96	Wk104	Wk110	Wk117
Study Day	D365	D386	D414	D449	D491	D540	D582	D624	D666	D722	D764	D813
Visit Window +/- Days	0	2	2	2	3	2	3	3	3	2	7	7
	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime