This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

IONIS PHARMACEUTICALS, INC.

ISIS 484137-CS2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

Original Protocol - 1 August 2017

EudraCT No: 2017-003197-13

Sponsor:

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

ISIS 484137-CS 2

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2855 Gazelle Court
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PPD

Chief Medical Officer
Chair Drug Safety Oversight Committee
Franchise Head - CardioMetabolics

ISIS 484137

Ionis Protocol Number ISIS 484137-CS 2

Original Protocol – 1 August 2017

EudraCT No: 2017-003197-13

Clinical Phase: 2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

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Date: 1 August 2017

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Protocol Number:	ISIS 484137-CS2
Protocol Title:	A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes
Amendment:	Original Protocol
Date:	1 August 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes," dated 1 August 2017, and agree to conduct the study as described herein.

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

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

_____
Investigator's Signature

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

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PROTOCOL SYNOPSIS

Protocol Title	A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{Rx}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes
Study Phase	2
Indication	Hepatic Steatosis in type 2 diabetes (T2DM)
Primary Objective(s)	To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with T2DM. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM.
Secondary Objective(s)	To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver fat (percent relative reduction and percent of subjects with ≥ 30% relative reduction) assessed by MRI-PDFF. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver volume assessed by MRI-PDFF. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on plasma lipoprotein profile (triglycerides [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], very low density lipoproteins [VLDL], high density lipoprotein [HDL] and Non-HDL). To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on insulin resistance (IR) and glucose control (insulin, glucose, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c]).
Exploratory Objective(s)	To evaluate the pharmacodynamic effects of ISIS 484137 on potential biomarkers of DGAT2 activity, (e.g., stearoyl-CoA desaturase-1 [SCD-1]) and biomarkers of hepatic inflammation (e.g., cytokeratin 18 (CK 18), haptoglobin)
Study Design	Randomized, double-blind, placebo controlled, multi-center
Number of Subjects	Approximately 45 patients are planned to be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 or placebo
Study Population	**Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Males or females. Aged 18 to 75, inclusive, at the time of informed consent 3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 484137 or placebo)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Inclusion Criteria** *Continued* * 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 4. Body Mass Index (BMI) ≥ 27.0 - ≤ 39.0 kg/m^2 5. Diagnosis of T2DM with an HbA1c ≥ 7.3% and ≤ 9.5% at Screening 6. Subjects must have been on a stable dose of the following oral antidiabetic therapy: metformin, sulfonylurea (SU), dipeptidyl peptidase-IV (DPPIV inhibitor) or sodium glucose like transport protein 2 (SGLT2) inhibitor for a minimum of 3 months prior to screening evaluation and will be required to continue their stable dose of oral antidiabetic therapy throughout the study. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, glucagon-like peptide [GLP1 analogs]) 7. ≥ 10% liver fat as assessed by MRI-PDFF prior to randomization 8. Stable body weight (BW) (i.e., not varying by > 5% for at least 3 months) before Screening 9. Agree to maintain current diet and exercise regimen 10. Agree to abstain from alcoholic beverages for at least 48 hours prior to clinic visits and not increase alcohol consumption during the study **Exclusion Criteria** 1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination 2. Central laboratory results prior to randomization (Screening and/or Run-In) as follows, or any other clinically-significant abnormalities in Screening laboratory values that would render a subject unsuitable for inclusion: a. Urine protein/creatinine (P/C) ratio > 0.2 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr b. Persistently positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing < 5 red blood cells (RBC) per high power field (Persistently positive defined as 2 out of 3) c. Serum creatinine > upper limit of normal (ULN) d. Estimated glomerular filtration rate (GFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance) e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 ULN f. Total bilirubin > ULN g. Have a current or previous diagnosis of Gilbert's disease h. Platelet count < 170,000/mm^3 (< 170 X 10^9/L)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria** *Continued*
	3. Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening. Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to Screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that subject is euthyroid 4. History of solid organ transplantation or renal dialysis 5. Clinically-significant complications of diabetes (e.g., history of painful neuropathy, nephropathy, proliferative retinopathy and/or foot ulcers) 6. Subjects on lipid lowering medications must be on a stable dose and regimen for ≥ 3 months prior to Screening. Subjects receiving treatment with statins should be within the dose levels listed below. Other statin regimens should be discussed and approved with the Sponsor Medical Monitor or designee • Simvastatin, pravastatin, atorvastatin and fluvastatin at ≤ 40 mg/day • Lovastatin or rosuvastatin at ≤ 20 mg/day • Pitavastatin up to 4 mg/day 7. Known history of or evidence of liver disease with a positive test for human immunodeficiency virus (HIV), hepatitis C (HCV) or chronic hepatitis B (HBV) or chronic liver disease other than NASH including alcoholic liver disease, Wilson's disease, hemochromatosis, or iron overload, Alpha-1-antitrypsin (A1AT) deficiency, prior known drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC), current placement on a liver transplant list, or MELD score > 12, established fibrosis ≥ Stage 3 fibrosis (Scale 0-4) or any cirrhosis 8. 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. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor 9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 10. Treatment with any non- ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Subjects who have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration of ≥ 4 months has elapsed since dosing 11. Recent history of, or current drug or alcohol abuse. Regular and excessive use of alcohol within 6 months prior to Screening (> 7 drinks/week for females, > 14 drinks/week 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), or use of soft drugs (such as marijuana) within 3 months prior to Screening, or hard drugs (such as cocaine and phencyclidine [PCP]) within 1-year prior to Screening, or positive urine drug screen at Screening

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria** *Continued* 12. Concomitant medication restrictions: a. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact BW within 3 months prior (e.g., sibutramine, phenetamine and orlistat) b. chronic use of systemic corticosteroids c. other antidiabetic medications not outlined in Inclusion Criteria #6 d. other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or steatosis (e.g., amiodarone, methotrexate, tamoxifen, carbamazepine) e. Use of anticoagulant/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed, use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours) f. obeticholic acid or ursodeoxycholic acid 13. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 14. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 15. Subjects with known intolerance to MRI or with conditions contraindicated for MRI Procedures: • Subjects who have any metal implant (including a heart pacemaker, rods, screws, aneurysm clip) • Subjects with claustrophobia 16. Confirmed reduction in fasting plasma glucose (FPG) of > 40 mg/dL (> 2.2 mmol/L) at the Run-In Visit (Week -1) compared to a FPG value taken at Screening 17. Confirmed reduction in BW ± 2 kg (4.4 lbs) at the Run-In Visit (Week -1) compared to BW taken at Screening 18. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study, including unwillingness to continue with SC injections after the SC Tolerability assessment
Treatment Groups	Placebo and ISIS 484137 250 mg per week

PROTOCOL SYNOPSIS *Continued*

Study Drug Dosage and Administration	The SC tolerability assessments using 0.9% sterile saline will be administered as a 1.25 mL injection on Study Day Week -1 (may also be delivered as 2 non-contiguous injection volumes of 0.75 mL and 0.50 mL). ISIS 484137 (200 mg/mL) and placebo will be supplied as 1.0 mL of solution in a 2 mL stoppered glass vial. Study Drug (ISIS 484137 or placebo) SC injection volume will be 1.25 mL (may also be delivered as two non-contiguous injection volumes of 0.75 mL and 0.50 mL). Subjects will be administered 13 weekly SC injections during the 13-week treatment period.
Rationale for Dose and Schedule Selection	The dose of 250 mg of ISIS 484137 was selected for this study based on the results of the Phase 1 trial ISIS 484137-CS1 which demonstrated an acceptable safety and tolerability profile for doses up to 300 mg after 6 weeks (8 total doses) of treatment. Additionally, several ASOs of this class have demonstrated significant efficacy and acceptable safety profiles at a similar dose level for 13 weeks and longer (Ackermann et al. 2016; Duell et al. 2016; Digenio et al. 2016). The 13-week treatment duration is supported by the ISIS 484137 nonclinical 13-week toxicology study (see Investigators Brochure) and by previous long-term weekly clinical dosing studies with several other 2'-MOE-modified ASOs. Thirteen (13) weeks of study treatment is a sufficient treatment duration to observe changes in liver fat content and improvements in IR in this patient population.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in Section 6 and Appendices A-C. The duration of subject participation in the study includes up to a 2-week Screening Period, up to a 4-week Run-In evaluation period, and a 13-week Treatment Period. Subjects will be required to complete a Post-Treatment Period for 13 weeks following the last dose of study medication (or early termination). The Ionis Medical Monitor or Designee will perform routine reviews of the safety results throughout the conduct of the study. **Screening Period: Week -6 – Week -5 (up to 2 weeks)** Laboratory and other study procedures will be performed to assess eligibility during the Screening Period. **Run-In Period: Week -4 – Week -1 (4 weeks)** Subjects will maintain his/her diet and exercise routine. In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will confirm tolerance of SC administration prior to randomization during the Run-In-Period. This injection will follow the same procedures as injections of the Study Drug (ISIS 484137 or placebo) during the treatment period. During Weeks -4 and -3, subjects will have an MRI to assess liver fat content and liver volume. MRIs will be conducted using standardized procedures and settings. MRIs will be evaluated by an independent central reader, blinded to the subject's treatment assignment, to assess liver fat and liver size.

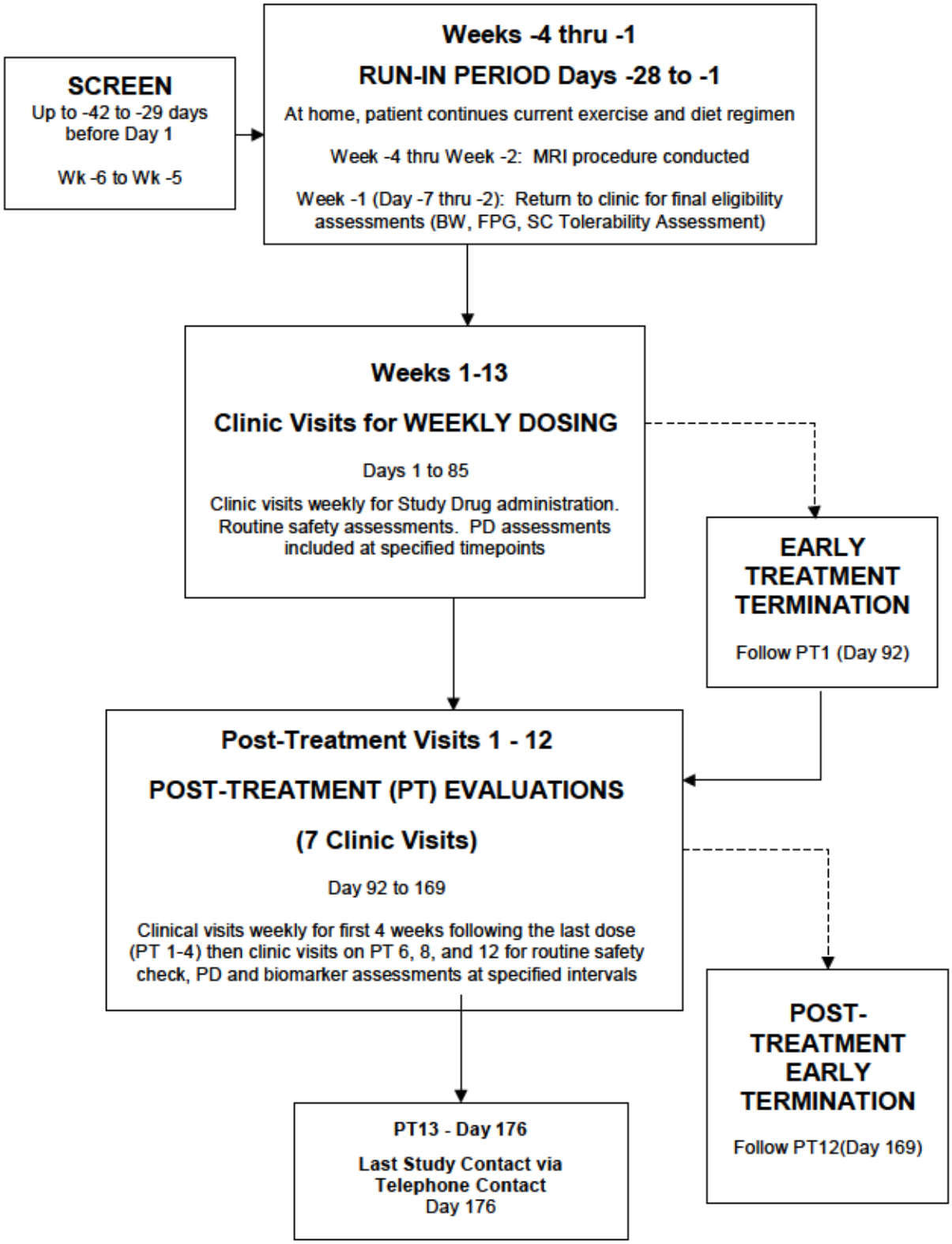
PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	**Run-In Period: Week -4 – Week -1 (4 weeks)** *Continued* Subjects with a qualifying MRI (at least 10% liver fat assessed by MRI-PDFF via central reviewer) return to clinic for Study Visit Week -1. At this visit, final qualification assessments will be conducted including BW and FPG assessments as well as a SC Tolerability Assessment with 0.9% sterile saline injection to determine tolerability to SC injections. If it is not possible for MRI results to be available by the clinic Week -1 visit, the MRI results must be available for final qualification prior to randomization. Eligible subjects will be stratified based on MRI liver fat levels (< 20% vs. ≥ 20%) and then subjects will be randomized prior to the first dose in a 2:1 ratio to receive either ISIS 484137 or placebo. Eligible/qualified subjects will be randomized and return to clinic for the Treatment Period. **Treatment Period: Week 1 – Week 13** STUDY DRUG ADMINISTRATION: Weekly injections will be administered at the study center. SAFETY ASSESSMENTS: Weekly laboratory assessments will be obtained including chemistry, hematology, urinalysis, adverse events and concomitant medication usage. Blood samples for pharmacokinetic analysis will be drawn weekly. Additional blood tests for exploratory purposes will be collected at less frequent intervals including lipids, inflammatory markers and exploratory biomarkers. Subjects who discontinue treatment early will enter the Post-Treatment Period unless consent is withdrawn. If a subject's glycemic control deteriorates after Week 8 according to the Monitoring Rule, the oral anti-diabetic (OAD) regimen can be adjusted. **Post-Treatment Period: Week 14 – Week 26** SAFETY ASSESSMENTS: Laboratory assessments will be obtained at regular intervals throughout the 13-week Post-Treatment Period. MRI: Liver fat content and volume will be measured in the Post-Treatment Period in all subjects who complete at least 5 doses during the Treatment Period.
Safety and Tolerability Evaluations	The safety and tolerability of ISIS 484137 will be assessed by determining the incidence, severity, dose-relationship of adverse effects and changes in laboratory evaluations. Safety results in subjects dosed with ISIS 484137 will be compared with those from subjects dosed with placebo. The safety and tolerability profile of the Study Drug will be monitored weekly during the Treatment Period and at each scheduled visit in the Post-Treatment Period.
Pharmacokinetic Evaluations	Selected plasma trough and post-treatment concentrations of ISIS 484137 will be assessed in evaluable subjects receiving ISIS 484137 treatment.

PROTOCOL SYNOPSIS *Continued*

Pharmacodynamic Evaluations	The effect of ISIS 484137on the following will be assessed • hepatic fat and liver weight content will be evaluated over time using magnetic resonance imaging that is conducted at Baseline and Post-Treatment. A central reader will calculate the percent liver fat by PDFF. MRI results in subjects dosed with ISIS 484137 will be compared with those subjects dosed with placebo • plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, ApoB, VLDL, HDL and Non-HDL) • hepatic IR and glucose control (insulin, glucose, HOMA-IR, HbA1c)
Statistical Considerations	Approximately 45 subjects will be randomized (2:1 allocation ratio) to ensure at least 33 subjects will have data on the primary study endpoint. This will result in > 90% power to detect a of 5% difference in mean absolute change in liver fat as measured by MRI-PDFF between the active and placebo groups with a 2-sided alpha of 0.05, assuming a common standard deviation of 4%.
Sponsor	Ionis Pharmaceuticals, Inc

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
apoB	apolipoprotein B
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BW	body weight
BP	blood pressure
BUN	blood urea nitrogen
C5a	complement factor C5a (activated complement split product)
CBC	complete blood count
CK18	cytokeratin 18
CMV	Cytomegalovirus
CRF	case report form
CRNMB	clinically-relevant non-major bleeding
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAG	*sn*-1,2-diacylglycerol
DGAT	Diacylglycerol Acyltransferase
DGAT1	diacylglycerol *O*-acyltransferase 1
DGAT2	diacylglycerol *O*-acyltransferase 2
DNA	phosphorothioate modified oligodeoxynucleotides
DPPIV inhibitor	dipeptidyl peptidase-IV
EBV	Epstein-Barr virus
ECG	electrocardiogram

eCRF	electronic Case Report Form
EDC	electronic data capture
FPG	fasting plasma glucose
ET PT	Early Termination patients from the Post-Treatment Period
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP1	glucagon-like peptide 1
HAV	hepatitis A virus
HbA1C	Hemoglobin A1C
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	Homeostatic model assessment- insulin resistance
HR	heart rate
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgM	immunoglobulin M
INR	international normalized ratio
IL6	Interleukin-6
IR	insulin resistance
IRB	Institutional Review Board
ISIS 484137	antisense inhibitor of DGAT2
IV	Intravenous(ly)
IXRS	Interactive voice/internet response system
LDH	lactate dehydrogenase

LDL-C	Low density lipoprotein cholesterol
MAG	monoacylglycerol
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
MRI	magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-estimated proton density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCS	not clinically-significant
Non-HDL	Non- high density lipoprotein
NSAID	non-steroidal anti-inflammatory drug
OAD	oral anti-diabetic agent
P/C	urine protein/creatinine
PD	pharmacodynamic(s)
PDFF	proton density fat fraction
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
pRBC	packed red blood cells
PT	prothrombin time
RBC	red blood cells
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan

siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
SCD-1	Stearyl CoA desaturase-1
SGLT2	Sodium glucose like transport protein 2
Study Day 1	defined as the first day Study Drug product is administered to the subject
Study Drug	ISIS 484137 or placebo
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VLDL	Very low density lipoproteins
WAT	white adipose tissue
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective(s)

The primary objectives are:

1. To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with type 2 diabetes mellitus (T2DM)
2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM

1.2 Secondary Objective(s)

The secondary objectives are:

1. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver fat (percent relative reduction and percent of subjects with ≥ 30% relative reduction) assessed by MRI-PDFF
2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver volume assessed by MRI-PDFF
3. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on plasma lipoprotein profile (triglycerides [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], very low density lipoproteins [VLDL], high density lipoprotein [HDL] and Non-HDL)
4. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on insulin resistance (IR) and glucose control (insulin, glucose, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c])

1.3 Exploratory Objectives

The exploratory objectives are to evaluate the pharmacodynamic (PD) effects of ISIS 484137 on potential biomarkers of DGAT2 activity (e.g., stearoyl-CoA desaturase-1 [SCD-1] and biomarker of hepatic inflammation (e.g., cytokeratin 18 [CK18], haptoglobin).

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of the metabolic syndrome (Marchesini et al. 2003) and is characterized by the accumulation of triglycerides in the liver of subjects without a history of excessive alcohol consumption. NAFLD is classified into simple steatosis, in which only hepatic steatosis is observed, and non-alcoholic steatohepatitis (NASH), in which intralobular inflammation and ballooning degeneration of hepatocytes is observed along with hepatic steatosis. The majority of patients with NAFLD are obese or morbidly obese and have accompanying IR (Byrne and Targher 2015) and type 2 diabetes mellitus. NASH is a progressive disease and may lead to liver cirrhosis and hepatocellular carcinoma (HCC) (Farrell and Larter 2006; Cohen et al. 2011). Twenty (20) percent of NASH patients are reported to develop cirrhosis, and 30-40% of patients with NASH

cirrhosis experience liver-related death (McCullough 2006). The incidence of NAFLD and NASH have been rapidly increasing worldwide consistent with the increased prevalence of obesity, and is currently the most common chronic liver disease. Recently, the incidence of NAFLD and NASH was reported to be 46% and 12%, respectively, in a largely middle-aged population (Williams et al. 2011). NASH has become the third most common indication for liver transplantation in the United States (Charlton et al. 2011).

Hepatic steatosis results from an imbalance between triglyceride accumulation and elimination in the liver. Insulin resistance, which is frequently seen in obese individuals, is closely linked to this process because it alters nutrient distribution among tissues and nutrient metabolism (Tomeno et al. 2013). Peripheral IR leads to an influx of free fatty acids into the liver by decreased suppression of lipolysis and increased *de novo* lipogenesis (Ibrahim et al. 2013). Although the pathogenesis of NAFLD/NASH has not been completely elucidated, the "two-hit" (Day and James 1998) and "multiple parallel hit" (Tilg and Moschen 2010) hypotheses have been proposed. In the two-hit hypothesis, hepatic steatosis occurs first through an initial metabolic disturbance and progresses to NASH by subsequent second hits derived from the gut and/or the adipose tissue such as increased levels of inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6 [IL6]), decreased levels of anti-inflammatory cytokines (e.g., adiponectin), oxidative stress, and endotoxins originating from intestinal bacterial flora. Therefore, a compound such as an antisense oligonucleotide (ASO) against Diacylglycerol Acyltransferase 2 (DGAT2) that reduces hepatic steatosis could result in prevention or attenuation of the secondary inflammation and oxidative stress thereby benefiting NAFLD and NASH patients.

2.2 Therapeutic Rationale

2.2.1 Overview of Target

Diacylglycerol acyltransferase (DGAT) catalyzes the final step in TG synthesis by facilitating the linkage of *sn*-1,2-diacylglycerols (DAG) with an acyl-CoA. DGAT has 2 isoforms, diacylglycerol *O*-acyltransferase 1 (DGAT1) and diacylglycerol *O*-acyltransferase 2 (DGAT2), and studies indicate that both DGAT1 and DGAT2 play important roles in TG synthesis. DGAT1 is most highly expressed in small intestine and white adipose tissue (WAT), whereas DGAT2 is primarily expressed in liver and WAT (Cases et al. 1998; Cases et al. 2001). The existence of DGAT2 was predicted from the finding that mice lacking DGAT1 have abundant TG in their tissues. The hDGAT2 gene is composed of 8 exons, and spans 42.03 kb on Chromosome 11. It is located ~37.5 kb from the monoacylglycerol acyltransferase 2 (MGAT2) gene (Yen et al. 2008). In most species, the gene encodes a protein of 350-400 residues, and the calculated molecular mass for DGAT2 enzymes is in the range of 40-44 kD (Yen et al. 2008).

Although both DGAT1 and DGAT2 catalyze the same reactions in TG synthesis with DAG or monoacylglycerols (MAG) and acyl-CoA as substrates, they are functionally distinguished by their differences in catalytic properties (Cao et al. 2007; Cheng et al. 2008), subcellular localization (Stone et al. 2009), physiological regulation (Meegalla et al. 2002), and phenotypic consequences when rendered deficient (Smith et al. 2000) or overexpressed in preclinical models (Naik et al. 2014). DGAT1 null mice were found to be resistant to high-fat-diet-induced obesity because of an increased metabolic rate (partly due to increased physical activity), modestly decreased levels of tissue TGs, and increased insulin and leptin sensitivity (Smith et al. 2000).

DGAT2 null mice are lipopenic and die soon after birth as a result of profound reductions in substrates for energy metabolism and impaired skin permeability (Stone et al. 2004), while DGAT2 heterozygous mice are viable, healthy, and physically indistinguishable from non-deficient mice (Yu et al. 2005). The effects of specific pharmacologic antagonism of hepatic DGAT2 expression were not known until studies conducted with DGAT2 ASOs.

DGAT2 ASOs were developed to reduce the rate of TG synthesis by specifically reducing hepatic DGAT2 expression. Suppression of DGAT2, but not of DGAT1, by ASO treatment improved hepatic steatosis and blood lipid levels independent of adiposity in rodent models of obesity and data indicated that these effects were related to decreased hepatic lipid synthesis (Yu et al. 2005). In rats with diet-induced hepatic steatosis (model of human NAFLD), treatment with both DGAT1 and DGAT2 ASOs selectively reduced DGAT1 and DGAT2 ribonucleic acid (RNA) levels in liver and fat. However, only DGAT2 ASO treatment significantly reduced hepatic lipids (DAG and TG but not long chain acyl-CoAs) and reversed diet-induced hepatic IR in this rat model of diet-induced NAFLD (Choi et al. 2007). Pharmacologic effects correlated with the level of antisense inhibition of DGAT2 liver expression and > 80% decrease of DGAT2 in liver and adipose tissue did not cause any target related toxicity. These pharmacologic data indicate different functions of the two DGAT enzymes during TG biosynthesis and are consistent with those from overexpression studies. In overexpression studies in mice, DGAT2 has been identified as being more active than DGAT1, yielding a higher increase in intracellular TG that accumulates as large, centrally located cytosolic droplets (Stone et al. 2004). Furthermore, in rat hepatoma cells, DGAT1 overexpression resulted in considerably less TG accumulation than was shown by DGAT2 overexpression.

These results suggest that DGAT2 plays an important role in hepatic lipid metabolism, hepatic steatosis, hepatic insulin signaling, and hepatic insulin sensitivity and that therapeutic interventions aimed at reducing DGAT2 function in lipogenic tissues may provide clinical benefit for fatty liver disease, metabolic syndrome and cardiovascular diseases.

2.2.2 Therapeutic Rationale

ISIS 484137 is being investigated as a possible treatment for NAFLDs including NASH. Currently, the principal treatment for NAFLD/NASH is lifestyle modification by diet and exercise. There are no approved medications for these conditions. However, pharmacological therapy is indispensable because obese patients with NAFLD often have difficulty maintaining improved lifestyles. Selective inhibition of DGAT2 has been suggested as a new target for the treatment of these obesity-related metabolic diseases. Important advances have been made regarding potential applications for DGAT inhibitors, including several reports of DGAT inhibitors with improved solubility, cell-based activity, and pharmacokinetic (PK) properties. Despite strong interest and efforts of pharmaceutical companies and many academic research groups, very few compounds have reached clinical trials. Hence, the need for the development of safe and effective DGAT inhibitors remains high.

There are currently no known strategies for a small molecule approach to lower DGAT2 expression specifically in liver and/or adipose tissue. In contrast, ISIS 484137 has been shown to specifically lower hepatic DGAT2 expression and, may therefore, have the potential to reduce liver steatosis and development of NASH.

This short-term study will assess changes in hepatic steatosis over a 13-week treatment period in a patient population with higher risk for development of NAFLD and NASH, obese T2DM with elevated HbA1c. Changes in the PDFF in the liver will be estimated by MRI, referred to as MRI-PDFF. It is the fraction of the MRI visible protons bound to fat divided by all protons in the liver (bound to fat and water). The liver MRI-PDFF has been utilized as a noninvasive biomarker of hepatic steatosis as it has been strongly correlated with histologic grade of hepatic steatosis (Dulai et al. 2016; Patel et al. 2016) and has been used in trials as an objective, quantitative, precise and reproducible noninvasive imaging biomarker of liver fat content (Le et al. 2012; Kang et al. 2011). The primary endpoint is to assess absolute changes in the liver MRI-PDFF after therapy with ISIS 484137 or placebo, as longitudinal changes in PDFF have identified subjects with reduced steatosis grade with reduction of PDFF (Middleton et al. 2017).

2.3 ISIS 484137

2.3.1 Mechanism of Action

ISIS 484137 is a second-generation 2′-*O*-(2-methoxyethyl) (2′-MOE) chimeric ASO inhibitor of the molecular target DGAT2. It is complementary to a region within the non-coding region of the DGAT2 RNA and binds to the RNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 484137 to the cognate RNA results in the RNase H1-mediated degradation of the DGAT2 RNA, thus preventing production of the DGAT2 protein. Maximal antisense-mediated reduction of target RNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target RNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

ISIS 484137 is a second generation 2′-MOE chimeric antisense drug. Chemically, ISIS 484137 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of ISIS 484137 (Figure 1) is fully complementary to a 20-nucleotide stretch within the second intronic region of the DGAT2 gene at position 6–15. 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 484137 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 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 enzyme (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE

modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

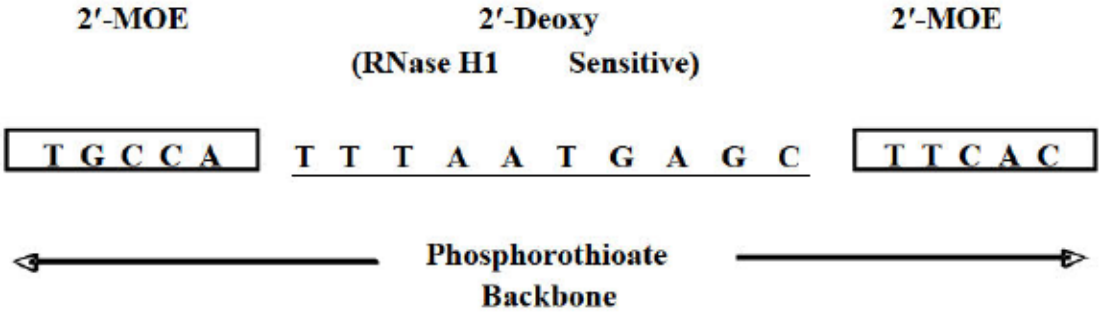


Figure 1 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence of ISIS 484137 is shown.

2.3.3 Preclinical Experience

Detailed information concerning the preclinical studies conducted with ISIS 484137 can be found in the Investigator's Brochure. A summary is included below.

Nonclinical Pharmacology

DGAT2 ASOs were developed to reduce the rate of TG synthesis by reducing liver and adipose DGAT2 expression. Treatment with DGAT2 ASOs in rodent models of obesity improved hepatic steatosis and hyperlipidemia (Yu et al. 2005) in addition to improving insulin sensitivity in a rat model of diet-induced NAFLD (Choi et al. 2007). Pharmacologic effects correlated with the level of antisense reduction of DGAT2 RNA expression. The robust and sustained improvements in hepatic TG levels and the improved plasma lipid profile were accompanied by secondary reductions in several key hepatic enzymes involved in lipid synthesis. The benefits associated with inhibiting the hepatic lipogenic pathway with DGAT2 treatment also included increased hepatic fat oxidation, improvements in hepatic insulin signaling and hepatic insulin sensitivity. More than 80% decrease of DGAT2 in liver and adipose tissue did not cause any target related toxicity. Specifically, the tissue-related skin abnormalities and dehydration associated with systemic DGAT2 deficiency was not observed.

Thus, reduction of DGAT2 expression with ISIS 484137 in animal models provided a mechanism to reduce hepatic steatosis, thereby potentially attenuating subsequent inflammation and fibrosis. This mechanism of action could offer an attractive treatment option especially for patients who have significant hepatic steatosis associated with NAFLD and NASH.

Pharmacokinetics and Product Metabolism in Animals

Dose-dependent exposures to ISIS 484137 in plasma and liver and kidney tissues were established in the 13-week mouse and monkey toxicity studies at doses between 4 and 100 mg/kg/wk and between 4 and 40 mg/kg/wk, respectively. A half-life of approximately 2 to 3 weeks was observed in monkeys. Pharmacokinetics observed in monkeys for this class of compounds typically predict the observed plasma exposure levels in humans on the basis of mg/kg equivalent doses (Geary et al. 2003; Yu et al. 2007).

ISIS 484137 was highly bound to plasma proteins, greater than 96% in mouse, monkey, and human plasma studies. The high protein binding prevents glomerular filtration and limits urinary excretion. The binding sites for these types of hydrophilic drugs differ from the binding sites of low molecular weight hydrophobic drugs; thus, few DDIs on the level of plasma protein binding are expected at clinically-relevant concentrations.

Toxicology and Safety Pharmacology

General toxicology studies were conducted with ISIS 484137 in the mouse and monkey for 13 weeks of treatment. Dose administration was by SC injection at weekly doses of 4, 12, 40, and 100 mg/kg/wk ISIS 484137 in mice or 4, 8, 12, and 40 mg/kg/wk ISIS 484137 in monkeys.

The most noteworthy findings observed in mice and monkey toxicology studies following 13-weeks of ISIS 484137 treatment were, in general, non-specific class effects that are typical for 2′-MOE ASOs (Henry et al. 2008). There was no drug-related mortality or changes in clinical signs up to the highest doses tested (100 mg/kg in mice and 40 mg/kg in monkeys). Reduction in platelet count (33,000/mm^3) was observed in a single monkey (1 of 10) in the 12 mg/kg/wk dose group on Day 93, with no clinical signs in this animal, and no microscopic evidence of hemorrhage. Since platelet reduction below 200,000/mm^3 was not observed in any other animals in the study, including the high dose of 40 mg/kg/wk, the relationship to the test article is unclear.

In vivo safety pharmacology studies conducted to date indicate that ISIS 484137 had no effects on cardiovascular parameters (blood pressure [BP], heart rate [HR] and electrocardiogram [ECG]) or pulmonary function or neurobehavior in monkeys. Genetic toxicity studies (the Ames assay and *in vitro* chromosomal aberrations in Chinese hamster lungs [CHL cells]) were negative.

There were no toxicologically significant findings at doses up to 12 mg/kg/wk for 13 weeks in the mouse and monkey studies, and therefore there is sufficient therapeutic margin to support the safe clinical use of ISIS 484137 at the proposed clinical doses and regimen.

2.3.4 Clinical Experience

The safety and tolerability of ISIS 484137 was evaluated in a total of 40 healthy overweight subjects in a double-blinded, placebo-controlled, dose-escalation Phase 1 study ISIS 484137-CS1. Of these 40 subjects, 30 received ISIS 484137 (12 in the single-dose cohorts and 18 in the multiple-dose cohorts), and 10 received placebo. ISIS 484137 was well-tolerated at doses up to 300 mg/wk for 6 weeks. There were no SAEs and all reported AEs were mild in severity. There were no dose-dependent clinically meaningful trends in laboratory assessments.

2.4 Rationale for Dose and Schedule of Administration

The safety data obtained in the Phase 1 study (ISIS 484137-CS1) as well as the clinical experience with several other 2′-MOE-modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006), supports the dosing regimen planned for this Phase 2 study. The planned regimen has been employed safely in previous clinical studies with a number of other ASOs. This class of ASOs has been safely administered intravenously (IV) and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008; Crooke et al. 2016) and treatment durations that exceed 24 months.

The currently proposed 250 mg ISIS 484137 dose level was selected based on results from the previous ISIS 484137-CS1 Phase 1 clinical study (doses 50 to 400 mg) that showed a satisfactory safety profile with these dose levels after 6 weeks (8 total doses) of treatment. Additionally, several ASOs of this class have demonstrated significant efficacy and acceptable safety profiles at a similar dose level for 13 weeks and longer (Ackermann et al. 2016; Duell et al. 2016; Digenio et al. 2016)

Weekly administration for 13-weeks is also supported by the ISIS 484137 nonclinical 13-week toxicology study (see Investigators Brochure). Kidney, liver, and adipose tissue concentrations of ISIS 484137 collected after 13 weeks of dosing during a monkey toxicology study indicate that tissue distribution for this compound is consistent with previously administered antisense oligonucleotides. Post-distribution plasma concentrations (i.e., terminal elimination phase) of ISIS 484137 are expected to be in equilibrium with tissue concentrations in humans, as was observed in monkeys, mice, and rats for similar 2′-MOE gapmers. With an estimated tissue half-life of approximately 2-3 weeks for ISIS 484137 predicted for humans based on previous experience with other second generation ASOs (Yu et al. 2009), achieving steady-state concentrations in the liver (the target organ) will be a prolonged process (e.g., time to approximately 90% of steady-state in tissues is estimated to take about 8 weeks with once-weekly dosing regimen). Thirteen (13) weeks of study treatment is a sufficient treatment duration to observe changes in liver fat content and improvements in IR in this patient population.

2.5 Risk Assessment

The known potential risks to study participants associated with ISIS 484137 are elaborated on in the Guidance to Investigator section of the ISIS 484137 Investigator's Brochure. Risks associated with DGAT2 reduction are not anticipated in this short-term trial.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study in subjects with type 2 diabetes and evidence of hepatic steatosis seen on MRI scan. Subjects will be stratified based on the liver content by MRI-PDFF during the Run-In-Period (< 20% vs. ≥ 20%). Subjects will be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 250 mg or placebo (See Study Design and Treatment Schema).

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Subjects

Approximately 45 subjects are planned to be enrolled in this study, randomized 2:1 to ISIS 484137 or placebo.

3.4 Overall Study Duration and Follow-up

The study will consist of Screening and Run-in, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in Appendix A. The expected duration of the study will be up to 6 weeks of Screening with the Run-In-Period, 13 weeks of Study Drug dosing, and 13 weeks of post-treatment evaluations, for a total of up to 32 weeks of participation.

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

3.4.1 Screening and Run-In

Subject eligibility for the study will be determined within 6 weeks prior to study entry, consisting of up to 2-week Screening (Week -6 to Week -5) and a 4-week Run-In-Period (Week -4 to Week -1).

During the beginning of the Run-In-Period (approximately Week -4 to Week -3), subjects will have a baseline hepatic MRI to assess eligibility with liver fat content. MRIs will be conducted using standardized procedures and settings. MRIs will be evaluated by a central reader, blinded to the subject's treatment assignment, to assess liver fat and liver size.

3.4.2 Treatment

Eligible subjects will be randomized will report to the Study Center for study treatment every week for 13 weeks (Week 1- Week 13).

3.4.3 Post-Treatment

Subjects are to return to the Study Center for follow-up visits at the following time points after the last dose: 1 week (PT1), 2 weeks (PT2), 3 weeks (PT3), 4 weeks (PT4), 6 weeks (PT6), 8 weeks (PT8), 12 weeks (PT12). The final study visit will occur 13 weeks after the last dose and via telephone.

Completed subjects will have a Post-Treatment hepatic MRI to assess liver fat content and volume 2 weeks after the last dose. The timing of the Post-Treatment MRI for subjects who terminate early from the Treatment Period is outlined in Section 6.1.4 and Appendix A.

3.5 End-of-Study

The End-of-Study is defined as when the last subject has had their last visit.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the Study, the Sponsor and designated contract research organization (CRO) requires a copy of the Study Center's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

Subjects or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled into the Study and will be assigned a unique screening number before any Study procedures, including screening procedures, are performed. In the event the subject is re-consented or re-screened the patient must be given a new screening number. Screening numbers, once assigned, will not be re-used.

4.2 Randomization

Subjects will be randomized after all Screening and Run-In assessments through Week -1 have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

All subjects will be randomized using an automated system (IXRS). Subjects will be stratified based on liver fat content results from the MRI conducted in the Run-In Period ($< 20\%$ or $\geq 20\%$), and then subjects will be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 250 mg or placebo. The Sponsor or designee will prepare the randomization list.

4.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all subjects, monitors, and Study Center personnel related to the study will be blinded throughout the study. However, if a subject 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 subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the automated IXRS. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. An unblinded randomization schema will be maintained securely by the Sponsor's designated vendor. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for the purpose of regulatory reporting (see Section 9.2).

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

In addition, the safety team assigned to review relevant Study Drug safety and tolerability data during the study in a blinded fashion will also have the ability to request the Ionis Drug Safety

Oversight Committee, chaired by the Chief Medical Officer, for unblinding the treatment assignment if needed for safety and data interpretation.

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria at Screening and through randomization or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females. Aged 18 to 75, inclusive, at the time of informed consent
3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved

   Males must be surgically sterile, abstinent*or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 484137 or placebo)

   * 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.
4. Body Mass Index (BMI) ≥ 27.0 - ≤ 39.0 kg/m^2
5. Diagnosis of T2DM with an HbA1c $\geq 7.3\%$ and $\leq 9.5\%$ at Screening
6. Subjects must have been on a stable dose of the following oral antidiabetic therapy: metformin, sulfonylurea (SU), dipeptidyl peptidase-IV (DPPIV inhibitor) or sodium glucose like transport protein 2 (SGLT2) inhibitor for a minimum of 3 months prior to screening evaluation and will be required to continue their stable dose of oral antidiabetic therapy throughout the study. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, glucagon-like peptide [GLP1 analogs])
7. $\geq 10\%$ liver fat as assessed by MRI-PDFF prior to randomization
8. Stable body weight (BW) (i.e., not varying by $> 5\%$ for at least 3 months) before Screening
9. Agree to maintain current diet and exercise regimen
10. Agree to abstain from alcoholic beverages for at least 48 hours prior to clinic visits and not increase alcohol consumption during the study

5.2 Exclusion Criteria

1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Central Laboratory results prior to randomization (Screening and/or Run-In) as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion:
   a. Urine protein/creatinine (P/C) ratio > 0.2 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr
   b. Persistently positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing < 5 red blood cells (RBC) per high power field (Persistently positive defined as 2 out of 3)
   c. Serum creatinine > upper limit of normal (ULN)
   d. Estimated glomerular filtration rate (GFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance)
   e. Alanine aminotransferase (ALT) ALT or aspartate aminotransferase (AST) > 1.5 ULN
   f. Total bilirubin > ULN
   g. Have a current or previous diagnosis of Gilbert's disease
   h. Platelet count < 170,000/mm^3 (< 170 x 10^9/L)
3. Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening. Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to Screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that subject is euthyroid
4. History of solid organ transplantation or renal dialysis
5. Clinically-significant complications of diabetes (e.g., history of painful neuropathy, nephropathy, proliferative retinopathy and/or foot ulcers)
6. Subjects on lipid lowering medications must be on a stable dose and regimen for ≥ 3 months prior to Screening. Subjects receiving treatment with statins should be within the dose levels listed below. Other statin regimens should be discussed and approved with the Sponsor Medical Monitor or designee:
   - Simvastatin, pravastatin, atorvastatin and fluvastatin at ≤ 40 mg/day
   - Lovastatin or rosuvastatin at ≤ 20 mg/day
   - Pitavastatin up to 4 mg/day
7. Known history of or evidence of liver disease with a positive test for human immunodeficiency virus (HIV), hepatitis C (HCV) or chronic hepatitis B (HBV) or chronic liver disease other than NASH including alcoholic liver disease, Wilson's

disease, hemochromatosis, or iron overload, Alpha-1-antitrypsin (A1AT) deficiency, prior known drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC), current placement on a liver transplant list, or MELD score > 12, established fibrosis ≥ Stage 3 fibrosis (Scale 0-4) or any cirrhosis

8. 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. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor
9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
10. Treatment with any non- ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Subjects who have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration of ≥ 4 months has elapsed since dosing
11. Recent history of, or current drug or alcohol abuse. Regular and excessive use of alcohol within 6 months prior to Screening (> 7 drinks/week for females, > 14 drinks/week 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), or use of soft drugs (such as marijuana) within 3 months prior to Screening, or hard drugs (such as cocaine and phencyclidine [PCP]) within 1-year prior to screening, or positive urine drug screen at Screening
12. Concomitant medication restrictions:
    a. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact BW within 3 months prior (e.g., sibutramine, phenetamine and orlistat)
    b. chronic use of systemic corticosteroids
    c. other antidiabetic medications not outlined in Inclusion Criteria #6,
    d. other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or steatosis (e.g., amiodarone, methotrexate, tamoxifen, carbamazepine)
    e. Use of anticoagulant/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed, use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours)
    f. obeticholic acid or ursodeoxycholic acid
13. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening

14. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
15. Subjects with known intolerance to MRI or with conditions contraindicated for MRI Procedures:
    - Subjects who have any metal implant (including a heart pacemaker, rods, screws, aneurysm clip)
    - Subjects with claustrophobia
16. Confirmed reduction in fasting plasma glucose (FPG) of > 40 mg/dL (> 2.2 mmol/L) at the Run-In Visit (Week -1) compared to a FPG value taken at Screening
17. Confirmed reduction in BW ± 2 kg (4.4 lbs) at the Run-In Visit (Week -1) compared to BW taken at Screening
18. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study, including unwillingness to continue with SC injections after the SC Tolerability assessment

6. STUDY PROCEDURES

6.1 Study Schedule

The study period for an individual subject consists of a ≤ 6-week Screening and Run-in Period followed by a 13-week Treatment Period, and a 13-week Post-Treatment Period. Additional visits may be scheduled if required for further evaluation of an abnormal laboratory value or reported AE.

Any AEs, concomitant medications, and other safety and tolerability profiling data will be promptly reported and reviewed by Sponsor's Medical Monitor (or designee).

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

6.1.1 Screening Period (Week -6 to Week -5)

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including Screening and Run-In procedures. A ≤ 6-week period is provided to complete Screening assessments and to determine subject eligibility for the study, with Screening at Week -6 to Week -5, and the Run-In Period from Week -4 to Week -1. Subjects will be questioned for medical history, and undergo physical examination, confirmation of their diabetes status and exclude other causes of liver disease and fibrosis, 12-lead electrocardiogram (ECG) conducted in triplicate, vital signs, BW, and height. Subjects will also be screened for infections of HIV, Hepatitis B and C, and for blood coagulation abnormalities including prolonged activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), and thyroid function tests (TSH, free T4 and free T3) levels. Follicle-stimulating hormone (FSH) will be measured to confirm menopause in women who have not undergone surgical sterilization. Additional blood samples will be taken for routine clinical laboratory testing (Appendix A).

Individuals may be disqualified if the result of any laboratory test is outside of the range specified in the eligibility criteria (Sections 5.1 and 5.2) or, if no range is specified, is abnormal and clinically-significant as judged by the Investigator or Sponsor Medical Monitor or Designee.

During the Screening Period, screening results may be retested for assessment by the Sponsor Medical Monitor or Designee for eligibility purposes.

6.1.2 Run-In Period (Week -4 thru Week -1)

Upon completion of the Screening period, eligible patients enter the 4-week Run-In Period for subjects to maintain their routine diet and exercise stabilization during this period and for a baseline liver MRI Assessment. Subjects will maintain their routine diet and exercise routine and continue to take their oral anti-diabetic agent (OAD) daily during this 4-week period. Substantial changes in diet and exercise activities could have an impact on liver fat content and should be avoided during study participation.

6.1.2.1 Liver MRI Assessment (Week -4 to Week -3)

An MRI of the liver will be conducted 2 times during study participation, once before treatment and once after treatment. The Baseline MRI will be conducted during the Run-In Period (Week -4 to Week -3) and the Post-Treatment MRI Assessment will be conducted during the Post-Treatment Period (Week of PT2 Visit).

These MRIs will be conducted using standardized procedures and settings and will be evaluated by a central reader, blinded to the subject's treatment assignment, to assess liver fat and liver volume.

All subjects may be required to fast for at least 4 hours before the MRI assessment.

Subjects with a qualifying Baseline MRI (at least 10% liver fat assessed by MRI-PDFF via central reviewer) will return to clinic for Run-In Week -1 Visit. If it is not possible for MRI results to be available by this visit or if it needs to be repeated, the MRI results must be available for final qualification prior to randomization. Failure to reach eligibility criteria of liver fat content by MRI is considered a screen failure and will not be repeated.

6.1.2.2 Run-In Week -1

At this visit, final qualification assessments will be conducted according to Appendix A including BW and FPG assessments as well as a SC Tolerability Assessment. Subjects will maintain their routine diet and exercise routine and continue to take their OAD daily during this period. Substantial changes in either one of these activities could have an impact on liver fat content and should be avoided during study participation.

6.1.2.2.1 FPG and BW Eligibility Assessments (Week -1)

Patients will be required to visit the clinic for FPG and BW measurements in both the Screening Period (Wk-6 - Wk-4) and Run-In Period (Week -1). The FPG central lab results and BW clinic assessment from these 2 visits (at least 3 weeks apart) will be compared to assess the patient's eligibility for randomization.

- If a > 40 mg/dL (2.2 mmol/L) FPG reduction is observed (and confirmed with a retest) from the screening result to the Run-In Week-1, the patient cannot be randomized (Exclusion Criteria #15). If a patient is not randomized due to an observed > 40 mg/dL (2.2 mmol/L) drop in fasting glucose, the patient may be eligible for rescreening after 6 weeks have elapsed
- If a reduction in BW ± 2 kg (4.4 lbs) (and confirmed with a retest) from the screening result to the Run-In Week -1, the patient cannot be randomized (Exclusion Criteria #16)

6.1.2.2.2 SC Tolerance Assessment

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will confirm tolerance of SC administration prior to randomization. This injection will follow the same procedures as the injection of the Study Drug (ISIS 484137 or placebo) during the treatment period. Specifically, during the Run-In-Period during Week -1, subjects will receive 1 SC injection of 1.25 mL saline (may also be delivered as 2 non-contiguous injection volumes of 0.75 mL and 0.50 mL).

When the Screening and Run-In results are available thru Week -1, individuals will be notified of their eligibility. Qualified patients will be randomized and will proceed to the Treatment Period with Week 1, Day 1 Assessments.

6.1.3 Treatment Period (Weeks 1-13)

Enrolled subjects will be administered ISIS 484137 or placebo once each week for a total of 13 weeks of treatment. Once-weekly SC administration will occur during the visits. At each visit, subjects will be reminded to retain the same diet and exercise regimen as was followed during the Screening and Run-In Period. Substantial changes in either one of these activities could have an impact on liver fat content and should be avoided during study participation. Subjects will continue to take their OAD daily during this period.

Safety and clinical laboratory evaluations will be performed on a weekly basis. Vital signs, BP assessments, AEs and concomitant usage will be assessed during clinic visits. Other assessments will be conducted during the Treatment Period in less frequent intervals as indicated in Appendices A, B, and C include ECG, drug/alcohol screening, HbA1c, FPG, lipid panel, insulin, hsCRP, TSH, exploratory markers and PK. Any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or designee. Any questions on study procedures and visit windows may be directed to the Sponsor (or designee).

Early termination patients from the Treatment Period will be required to complete their study termination evaluations following the PT1 study procedures (see Appendix A). The timing of the Post-Treatment MRI for early termination patients from the Treatment Period is outlined in Section 6.1.4. All patients receiving at least 1 dose of study medication are required to enter the Post-Treatment Period for continuing safety evaluations.

6.1.4 Post-Treatment Period (PT 1-13)

After completing the 13 weeks of the Treatment Period, including subjects who discontinue early from the Treatment Period, subjects will return for post-treatment follow-up evaluation visits as

indicated in Appendix A. All subjects will be followed for 13 weeks until the PT13 visit. During the Post-Treatment Period from PT 1- 4 (weekly visits), a visit window of ± 3 days is permitted, whereas for visits PT 6-13 a visit window of ± 7 days is permitted. Safety and clinical laboratory evaluations as well as PD markers, including those for PK analysis, will be performed as indicated in Appendices A, B, and C. Any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or designee. At each visit, subjects will be reminded to retain the same diet and exercise regimen as was followed during the Screening and Run-In Period. Subjects will continue to take their OAD daily during this period.

A Post-Treatment MRI (See Section 6.1.2.1) to assess liver fat content and volume will occur during PT2 Visit (2 weeks after last dose) for all subjects completing 13 doses. For subjects who terminate from the treatment period early, the timing and conduct of the MRI in the Post-Treatment Period will be adjusted as follows (+/- 7-day window)

i. Subject received 4 or less doses, the Post-Treatment MRI Assessment will not be required

ii. Subject received 5-9 doses, the Post-Treatment MRI Assessment will occur 2 weeks after last dose at the PT2 Visit

iii. Subject received 10-12 doses, the Post-Treatment MRI Assessment will be scheduled as follows:

- If subject received 10 doses, subject moves into Post-Treatment Period, the MRI will be conducted 5 weeks after the last dose (during Study Week PT5)
- If subject received 11 doses, subject moves into Post-Treatment Period, the MRI will be conducted 4 weeks after the last dose (during Study Week PT4)
- If subject received 12 doses, subject moves into Post-Treatment Period, the MRI will be conducted 3 weeks after the last dose (during Study Week PT3)

Early termination patients from the Post-Treatment Period (ET PT) will be required to complete their End-Of-Study evaluations following the ET PT 12 Visit study procedures (see Appendix A).

6.2 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. Blood chemistry and urine samples should be taken be taken after fasting for at least 8 hours. During the fasting period, the subject can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

If during the treatment period, a platelet, creatinine, or ALT result is uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) the test must be repeated and a result not meeting stopping rule must be obtained prior to next dose.

6.3 Restriction on the Lifestyle of Subjects

6.3.1 Contraception Requirements

Male subjects must refrain from sperm donation and either be abstinent† or, if engaged in sexual relations with a female of child-bearing potential, they must use effective barrier contraception with their partner from the time of signing the informed consent form until at least 13 weeks after their last dose of Study Drug. Effective contraception includes a vasectomy with negative semen analysis at Follow-up, or the use of condoms together with spermicidal foam/gel/film/cream/suppository. Male subjects engaged in sexual relations with a female of child-bearing potential must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment. Effective contraception 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 subjects with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

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

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

6.3.2 Fasting Requirements

All subjects will be required to fast for at least 8 hours before each study visit.

6.3.3 Lifestyle restrictions

Subjects are instructed to refrain from alcohol containing beverages at least 48 hours prior to a clinic visit and should not increase alcohol consumption during the study. Additionally, subjects are requested to maintain a stable diet and exercise regimen throughout the study.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 484137 or Placebo) characteristics are listed in Table 1.

The Study Drug (ISIS 484137 or Placebo) is contained in 2 mL stoppered glass vials. The Study Drug (ISIS 484137 or Placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 484137 or placebo) must be stored securely at 2-8 °Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	ISIS 484137	Placebo
Strength	200 mg/ mL	Not Applicable
Volume/Formulation	1 mL solution per vial	1 mL solution per vial
Route of Administration	SC	SC

* SC = subcutaneous

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 484137 or placebo) labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 484137 or placebo) supplies provided by the Sponsor.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

Study Drug administration will occur at weekly study visits from Week 1 through Week 13 by the trained personnel at the study site. ISIS 484137 or placebo will be administered subcutaneously. Study Drug (ISIS 484137 or placebo) SC injection volume will be 1.25 mL at each weekly visit (may also be delivered as 2 non-contiguous injection volumes of 0.75 mL and 0.50 mL). Vials are for single use only.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug (ISIS 484137 or placebo) preparation and administration.

8.2 Other Protocol-Required Drugs

0.9% sterile saline will be used for a SC tolerability injection. During the Run-In Period Week -1, subjects will receive a 1.25 mL SC injection (may also be delivered as 2 non-contiguous injection volumes of 0.75 mL and 0.50 mL).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4 Treatment Precautions

There are no specific treatment precautions required.

8.5 Safety Monitoring Rules

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

Baseline is defined as the average of week -1 visit (Day -7) and Day 1 pre-dose values.

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.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. 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 (ISIS 484137 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described in Appendix E are met, the subject will be permanently discontinued from further treatment with Study Drug (ISIS 484137 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the Protocol.

8.5.1 Safety Monitoring Rules 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.

In the event of an ALT or AST measurement that is > 3 x ULN: (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Subjects 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) should have their liver chemistry tests (ALT, AST, alkaline phosphatase [ALP], INR, and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For subjects 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] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], HCV antibody, cytomegalovirus [CMV] IgM, and Epstein-Barr virus [EBV antibody panel])
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

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

8.5.2 Safety Monitoring Rules for Platelet Count Results

If a subject's platelet count falls by 30% or greater from Baseline or the absolute platelet count is 100,000/mm^3 or less, then the subject's platelet counts should be monitored at least weekly. In the event of a platelet count < 75,000/mm^3, additional laboratory investigations will be conducted (Table 2). The frequency of monitoring and additional lab tests will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee.

Table 2 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

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) Complete blood count (CBC) with reticulocytes and mean platelet volume (MPV)
Fibrinogen
von Willebrand factor
Total globulins, total immunoglobulin A (IgA), IgG and IgM
Complement: total C3, total C4, Bb, C5a
CRP measured by high sensitivity assay (hsCRP)
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)

Table 2 Additional Labs to be Performed in the Event of a Platelet Count $< 75{,}000/mm^3$ *Continued*

To Be Performed at Central Lab
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 (if available)

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

8.5.3 Monitoring Rules for Deteriorating Glycemic Control

If after 8 weeks of treatment with Study Drug (ISIS 484137 or placebo), FPG levels > 270 mg/dL (or > 15 mmol/L) confirmed on 2 consecutive weekly study visits with no other explanation(s) for the elevation, additional oral glucose-lowering therapy may be started or previous therapies may be titrated up by the Investigator in consultation with the Sponsor Medical Monitor or designee. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy (e.g., insulin, GLP1 analogs) is not permitted. See Dose Adjustment Guidance in Section 8.7.

8.6 Stopping Rules

For the purposes of the stopping rules baseline is defined as the average of Day -7 and Day 1 values.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor**, dosing of a subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently; values that are not confirmed due failure to retest or missing lab values will be presumed confirmed:

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) with 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, and/or concomitant eosinophilia (> ULN)

8.6.2 Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a subject with Study Drug (ISIS 484137 or placebo) may be stopped temporarily:

1. Serum creatinine increase that fulfills all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) increase and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)

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 Rule for Platelet Count Results

In the event of a confirmed platelet count less than 75,000/mm^3, and in the presence of major bleeding (MB) or clinically-relevant non-major bleeding (CRNMB) (defined below; Schulman et al. 2005), dosing of a subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently. Furthermore, additional laboratory investigations will be conducted as outlined in Table 2. 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 a confirmed platelet count less than 50,000/mm^3, dosing of a subject with Study Drug (ISIS 484137 or placebo) 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 or designee.

Definitions:

Major bleeding (MB) is defined as one of the following:

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

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

8.6.4 Stopping Rules for Documented Severe Hypoglycemia

In the event of a documented severe hypoglycemic event as defined below, dosing of the subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently. Also, if the Investigator considers a hypoglycemic event as clinically-significant, he/she may stop dosing at any time. Any subject with a clinically-significant event of hypoglycemia should be discussed with the Sponsor Medical Monitor or Designee.

A documented severe hypoglycemic event is defined as one in which the subject requires assistance of another person to obtain treatment for the event and has a plasma glucose level < 60 mg/dL (3.3 mmol/L). This may include treatment with IV glucose or buccal or intramuscular glucagon.

All subjects participating in the trial must be instructed to recognize the characteristic symptoms of hypoglycemia and receive detailed instructions from the Investigator on the treatment and reporting of hypoglycemic events.

The symptoms of hypoglycemia can be divided into 2 categories, neuroglycopenic and neurogenic (or autonomic) responses.

- Neuroglycopenic symptoms are the direct result of central nervous system neuronal glucose deprivation and include behavioral changes (dizziness, headaches, cloudy vision, confusion, abnormal behavior, loss of consciousness, and seizures)
- Hypoglycemia-induced neurogenic (autonomic) responses are those related to increased adrenergic activity (sweating, tremor, tachycardia, anxiety, and hunger)

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

8.7 Adjustment of oral antidiabetic regimen for subjects with persistent hyperglycemic

If after 8 weeks of treatment with Study Drug (ISIS 484137 or placebo), FPG levels > 270 mg/dL (or > 15 mmol/L) confirmed on 2 consecutive weekly study visits with no other explanation(s) for the elevation, additional oral glucose-lowering therapy may be started or existing therapies may be titrated in dose by the Investigator in consultation with the Sponsor Medical Monitor or designee. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, GLP1 analogs).

8.8 Discontinuation of Study Drug

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an AE that necessitates permanent discontinuation of Study Drug

- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.4
- The subject experiences an AE that necessitates unblinding of the Investigator or Sponsor to the subject's treatment assignment
- Initiation of chronic disallowed therapies which include the use of thiazolidinediones (e.g., piogitazone, rosiglitazone) and injectable antidiabetic therapy (e.g., insulin, GLP1 analogs), use of agents (including herbal or over-the counter weight loss preparations) and medications known to significantly impact BW (e.g., sibutramine, phenetamine and orlistat)

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

Subjects who discontinue Study Drug should be encouraged to remain in the study and complete the Post-Treatment Evaluation Period and continue protocol required tests and assessments. Every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

8.9 Withdrawal of Subjects from the Study

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

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

Other reasons for withdrawal of subjects from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF as appropriate.

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

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF as appropriate.

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 the signing of the informed consent and the last protocol specified Post-Treatment Evaluation Period (Appendix A).

Allowed Concomitant Therapy

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

Disallowed Concomitant Therapy

The use of thiazolidinediones (e.g., piogitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, GLP1 analogs) while on Study Drug. In case a short-term insulin therapy is given when a patient is hospitalized during the study, the Investigator needs to consult with the Sponsor Medical Monitor or designee to evaluate whether the patient will be allowed to continue the study. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact BW within 3 months prior (e.g., sibutramine, phenetamine and orlistat) is not permitted while on Study Drug.

High-dose statin therapy is not permitted, nor is initiating a new statin or increasing therapy above the thresholds listed. Simvastatin, atorvastatin, fluvastatin, pravastatin must be maintained $\leq$ 40 mg/day. Rosuvastatin and lovastatin doses should be $\leq$ 20 mg/day, and pitavastatin must be $\leq$ 4 mg/day. Fish oils or prescription lipid-regulating drugs (e.g., bile acid analogues [e.g., obeticholic acid or ursodeoxycholic acid], bile-acid sequestering resins, fibrates and derivatives) are not permitted. If statin therapy is necessary above these noted dose levels or other lipid lowering therapies are required, the Investigator should discuss with the Medical Monitor whether the subject must discontinue Study Drug.

Chronic use of systemic corticosteroids and other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or cause steatosis (e.g., amiodarone, methotrexate) are not permitted while on Study Drug.

Use of anticoagulants/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours) are not permitted while on Study Drug.

Antineoplastic agents are not permitted while on Study Drug.

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 the informed consent and the last protocol-specified Post-Treatment Evaluation visit (Appendix A)

8.11 Treatment Compliance

Compliance with Study Drug dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the Safety Management Plan and the Medical Monitoring Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

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

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations.

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

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee 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 serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

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

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

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

9.4 Monitoring and Recording Adverse Events

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

9.4.1 Serious Adverse Events

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

begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period which is defined as Study Week PT13 (Section 3.4.3). When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. The SAE should be reported using electronic SAE reporting form by scanning and emailing the form to INCDrugSafety@increresearch.com. If the electronic submission is unavailable, an Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee. The fax number for reporting SAEs can be found in the Study Reference Manual.

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

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as 13 weeks after the last dose (Study Visit PT13), see Section 3.4.3. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 484137 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 484137 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 484137 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

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

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

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

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drug (ISIS 484137 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 484137 or placebo) administration and dose
- **Permanently Discontinued:** Study Drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted:** Dosing was temporarily interrupted or delayed due to the AE and restarted

9.4.3.4 Treatment Given for Adverse Event

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

9.4.3.5 Outcome of the Adverse Event

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

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

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

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

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

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

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

9.5.3 Dosing Errors

Study Drug (ISIS 484137 or placebo) errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject takes a dose of Study Drug (ISIS 484137 or placebo) that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

There has been no occurrence of an ASO overdose in man from completed or ongoing clinical studies with ASOs.

9.5.4 Contraception and Pregnancy

Female subjects of childbearing potential are excluded from this study.

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

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

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

The progress of the pregnancy of a male subject's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records to obtain additional information.** Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Safety Endpoints

The safety and tolerability of ISIS 484137 will be accessed by determining the incidence and severity of AEs and will be evaluated by reviewing:

- AEs (including bleeding events)
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Coagulation parameters
- Use of concomitant medications

10.1.2 Primary Pharmacodynamic Endpoint

The primary PD endpoint is the absolute change in liver fat percentage as quantified by MRI-PDFF from Baseline MRI to Post-Treatment MRI.

10.1.3 Secondary Endpoints

Secondary endpoints include:

- Relative percent change in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Proportion of subjects with ≥ 30% relative reduction in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Percent change in liver volume from Baseline MRI to Post-Treatment MRI
- Percent change in plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL) from Baseline to the average of the Post-Treatment values assessed 1 and 2 weeks after the last dose (PT1 and PT2 Visits)
- Percent change in parameters of hepatic IR (FPG, insulin, and HOMA-IR) from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)
- Absolute change in HbA1c from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)

10.1.4 Exploratory Endpoints

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10.2 Sample Size Considerations

Approximately 45 subjects will be randomized (2:1 allocation ratio). With 45 subjects there will be > 90% power to detect a of 5% difference in mean absolute change in liver fat as measured by PDFF between the active and placebo groups with a 2-sided alpha of 0.05, assuming a common standard deviation of 4% and 25% non-completers.

The 5% effect size was selected based on clinical relevance with evidence that 5% PDFF reduction identified subjects with reduced steatosis grade in NASH subjects (Middleton et al. 2017).

10.3 Populations

Randomized: All subjects who are randomized into the study regardless of whether they received Study Drug.

Per-Protocol Population: Will include the subset of the Randomized Population who have received at least 10 of the prescribed doses and must receive the first 4 doses in the first 5 weeks, cannot miss 3 consecutive weekly doses and no significant protocol deviations that would be expected to impact efficacy.

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

PK Population: All subjects who have received at least 1 dose of active Study Drug (ISIS 484137), and have at least 1 PK sample collected and analyzed with evaluable results.

10.4 Definition of Baseline

- Baseline MRI hepatic fat content and volume will be from the MRI prior to and closest to randomization
- Baseline for plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL), exploratory biomarkers of DGAT2 activity (SCD-1), and biomarkers of inflammation (e.g., CK18, haptoglobin) and assessments for IR (FPG, insulin, HOMA IR) will be the average of week -1 visit (Day -7) and Day 1 pre-dose assessments
- Baseline for platelets, creatinine, ALT and AST will be the average of week -1 visit (Day -7) and Day 1 pre-dose assessments
- Baseline for HbA1c and for other routine clinical assessments of chemistry and hematology, PK assessments, vital signs and ECG for the study will be the last non-missing value prior to the first administration of Study Drug will be the last non-missing value prior to the first administration of Study Drug (ISIS 484137 or placebo; Appendix A).

10.5 Interim Analysis

No interim analysis is planned. However, during the study, an unblinded interim analysis may be conducted to assess the safety, PK/PD, and exploratory efficacy of the results. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study. Details of these controls will be described in the Statistical Analysis Plan (SAP).

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 subject data listings. Subject data listings will be presented for all subjects enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% type I error rates unless otherwise stated.

The efficacy and PD endpoints will be assessed on the Randomized Population and Per-Protocol Population. The safety analyses will be performed on the Safety Population.

10.6.1 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. Subject randomization will be summarized by cohort and treatment group. The subject disposition will be summarized. All subjects enrolled will be included in a summary of subject disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug (ISIS 484137 or placebo) received will be summarized by treatment group. Subject incidence rates of all AEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA™) system organ class, and by MedDRA™ term. Tables and/or narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug (ISIS 484137 or placebo) will be summarized.

Laboratory tests to ensure subject safety including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 484137 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

Incidence of bleeding events including the following will be tabulated by treatment for MB, CRNMB, minor bleeding, and combination of major and clinically-relevant nonmajor bleeding.

Physical examination data will be provided in the data listing. Concomitant medications will be coded using World Health Organization (WHO) Drug dictionary and summarized by treatment, ATC class and generic name.

10.6.3 Pharmacokinetic Analysis

For all evaluable subjects receiving ISIS 484137, plasma ISIS 484137 concentrations at trough during the Treatment Period and concentrations observed during the Post-Treatment Evaluation Period will be listed by dose, study day, time point, and summarized using descriptive statistics. Additional details regarding the PK analysis will be described in the SAP.

Potential relationships between selected PD and plasma exposure measures (e.g., trough concentrations) may also be explored, where deemed appropriate.

10.6.4 Pharmacodynamic/Efficacy Analysis

MRI results will be summarized and tabulated based on PDFF reductions from Baseline absolute and relative reductions and liver volume. Details of planned analysis of efficacy endpoints included PD endpoints will be provided in the SAP.

10.6.5 Additional Analyses

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11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 484137 or placebo) are administered. The subject or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

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

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

11.2 Ethical Conduct of the Study

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

11.3 Independent Ethics Committee/Institutional Review Board

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

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

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

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

11.4 Subject Confidentiality

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

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

12.3 Study Documentation and Storage

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, 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 the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

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

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

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

12.4 Study Monitoring

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

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

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 CRFs, are resolved.

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

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

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, 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 and Trade names are acceptable. Combination medications should be recorded using their trade name in English if possible.

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period	Screen	Run-In		Treatment												
Study Week	Wk -6 thru Wk -5	Wk -4 thru Wk -3	Wk -1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13
Study Day	S-42 thru S-29	D-28 thru D-15	D-7 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window (+/- days)		A	3	2												
Informed Consent	X															
Inclusion/Exclusion	X		X	X												
Medical History	X															
Physical Exam[1]	X			X					X							
Height, Body Weight and BMI[2]	X		X[7]	X					X							X
Waist/Hip Circumference	X			X					X							X
Vital Signs[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12–lead) in triplicate[15]	X			3X[6]					X							
FSH4 / Serum Pregnancy[5]	X			X[7]							X					
HIV, Hepatitis B & C	X															
Drug/Alcohol Screen	X		X[7]						X							
Chemistry Panel (Fasting)[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including P/C)[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/aPTT/INR	X															
HbA1c	X			X					X							
Fasting Plasma Glucose (FPG)[10]	X		X[7]	X		X			X			X			X	

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Run-In		Treatment												
Study Week	Wk -6 thru Wk -5	Wk -4 thru Wk -3	Wk -1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13
Study Day	S-42 thru S-29	D-28 thru D-15	D-7 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window (+/- days)		A	3	2												
Lipid Panel (serum, fasting)[10]			X	X					X			X				
Insulin (fasting)[10]			X	X					X			X				
hsCRP				X					X							
TSH	X			X					X							
Triodthyronine (T3)	X															
Thyroxine (T4) (serum)	X															
Exploratory Markers			X	X					X			X				
Archived Samples[11]				X					X			X				
PK Sampling[12]				X	X		X		X		X	X	X		X	X
Hepatic Fat Content (MRI)		X														
SC Tolerability Assessment			X													
Study Drug Administration				X	X	X	X	X	X	X	X	X	X	X	X	X
OAD Administration[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary and Exercise Counseling	X		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
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[14]					X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

Study Period	Post-Treatment Period (13 Weeks)							
Study Week	ET/PT1	PT2	PT3	PT4	PT6	PT8	ET PT12	PT13
Study Day	D92	D99	D106	D113	D127	D141	D169	D176
Visit Window (+/- days)	3				7			
Physical Exam[1]	X	X		X			X	
Body Weight and BMI[2]	X	X		X			X	
Waist/Hip Circumference	X	X		X			X	
Vital Signs[3]	X	X	X	X	X	X	X	
Blood Pressure (BP)	X	X	X	X	X	X	X	
ECG (12–lead) in triplicate[15]	X		X					
PK Sampling	X	X		X	X		X	
Archived Sample	X	X		X			X	
Chemistry Panel (serum, fasting)	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Urinalysis (including P/C ratio)[9]	X	X	X	X	X	X	X	
HbA1c (serum)	X	X		X		X		
Lipid Panel (serum, fasting)[10]	X	X		X				
Insulin (plasma, fasting)[10]	X	X		X				
Fasting Plasma Glucose (FPG)[10]	X	X	X	X	X	X	X	
hsCRP (serum)	X			X				
TSH (serum)	X						X	
Serum Pregnancy[5]	X						X	
Exploratory Markers	X	X		X			X	
Hepatic Fat Content (MRI)		X[B]						
OAD Administration[13]	X	X	X	X	X	X	X	X
Dietary & Exercise Maintenance	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Phone Contact[14]	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

Legend Text

1. Full physical exam to be given at Screening and abbreviated physical exam to be given during treatment and follow-up period as indicated to assess changes from Screening
2. Height assessed at Screening visit only
3. HR, respiratory rate (RR), temp
4. FSH: Required to confirm menopause for women ≤ 55 years who have 12 months of spontaneous amenorrhea with no alternative medical cause, and who are not surgically sterile
5. Women who are not surgically sterile. Serum test at screen, D50, D92 and D169; dipstick acceptable at Day 1 only
6. Assessments conducted at pre-dose, 1 hr and 2 hrs post-dose
7. Results required prior to randomization
8. If during the treatment period, a platelet, creatinine, or ALT result is uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) the test must be repeated and a result not meeting stopping rule must be obtained prior to next dose
9. Preferably collect specimen for analysis from the subject's second void of the day
10. Fasted samples should be taken after fasting for at least 8-10 hours. During this time the subject can drink water and they should ensure that they consume sufficient water in order to not become dehydrated
11. Stored at -70 (± 10) °C for follow-up exploration
12. During the treatment period, PK samples are collected pre-dose. During the Post-Treatment Period, PK samples are collected any time. See Appendix C
13. OAD doses are to be self-administered daily by the subject throughout the study
14. If subject misses clinic visit, a phone contact will be attempted to assess AE and conmeds
15. Triplicate ECG study procedure will consist of 3 ECGs with 2 minutes between each ECG (-1/+2 mins window between each assessment)

Notes:

All assessments should be collected pre-dose unless indicated otherwise.

Notes Regarding Timing of MRI Assessments:

A Magnetic Resonance Imaging (MRI) Assessment Windows

Baseline MRI Assessment: Week -4 or -3 (Day -28 to Day -14) + 7 days

Post-Treatment MRI Assessment: Week of PT 2 Visit (Days 99 to Day 105) +/- 7 days

B A Post-Treatment MRI to assess liver fat content and volume will occur during the week of PT2 Visit for all subjects completing 13 doses. For subjects who terminate from the treatment period early, the timing and conduct of the MRI in the Post-Treatment Period will be adjusted as follows

i. Subject received 4 or less doses, the Post-Treatment MRI Assessment will not be required

ii. Subject received 5-9 doses, the Post-Treatment MRI Assessment will occur 2 weeks after the last dose during the week of the PT2 Visit. (+/- 7 days)

iii. Subject received 10 -12 doses, the Post-Treatment MRI Assessment will be scheduled as follows:

Number of Doses Received	Post-Treatment MRI Assessment
10	5 weeks after last dose (+/- 7 days)
11	4 weeks after last dose (+/- 7 days)
12	3 weeks after last dose (+/- 7 days)

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 484137 or other similar oligonucleotides

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

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

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

PD Panel
- Fasting Glucose
- Insulin
- HbA1c

Fasting Lipid Panel
- Triglycerides
- Total Cholesterol
- ApoB
- VLDL cholesterol
- LDL cholesterol
- HDL cholesterol
- Non-HDL cholesterol

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

Thyroid Panel
- TSH
- Free T4
- Free T3

Pharmacokinetics[1]
- ISIS 484137 levels in plasma

Exploratory[3]
adiponectin
SCD-1
CK18
haptoglobin
leptin

Inflammatory
- hs-CRP [3]

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

Other[1]
- Archived serum samples

1 Serum and plasma PK samples may also be used for metabolomics/lipidomics assessments, profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assay development/testing, or to assess other actions of ISIS 484137 with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

3 Samples will be collected however may not be analyzed

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Treatment Period								
W1	W2	W4	W6	W8	W9	W10	W12	W13
D1	D8	D22	D36	D50	D57	D64	D78	D85
Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose

Post-Treatment Period (13 Weeks)				
ET/PT1	PT2	PT3	PT6	PT12
D92	D99	D113	D127	D169

Blood sample can be drawn anytime during the visit

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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

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

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

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

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

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

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

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

IONIS PHARMACEUTICALS, INC.

ISIS 484137-CS2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

Protocol Amendment 1 – 23 March 2018

EudraCT No: 2017-003197-13

Sponsor:

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

ISIS 484137-CS 2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

Protocol Amendment 1 – 23 March 2018

Protocol History:

Original Protocol: 1 August 2017

Sponsor:

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

PPD

Chief Medical Officer
Chair Drug Safety Oversight Committee
Franchise Head - CardioMetabolics

ISIS 484137

Ionis Protocol Number ISIS 484137-CS 2

Protocol Amendment 1 – 23 March 2018

EudraCT No: 2017-003197-13

Clinical Phase: 2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2$_{RX}$, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

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Key Sponsor Contact: PPD
Executive Director, Clinical Development
Phone PPD

Date: 23 March 2018

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Protocol Number:	ISIS 484137-CS2
Protocol Title:	A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2RX, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes
Amendment:	Amendment 1
Date:	23 March 2018

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2RX, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes," dated 23 March 2018, and agree to conduct the study as described herein.

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

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

_____
Investigator's Signature

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

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PROTOCOL AMENDMENT

Protocol Number: ISIS 484137-CS2

Protocol Title: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2Rx, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

Amendment Number: 1

Amendment Date: 23 March 2018

The purpose of this amendment is to clarify inconsistencies within the protocol and include flexibility with protocol procedures to improve operational logistics at the study centers. The objectives of the study remain unchanged and the updates do not impact the assessment of safety, exposure, overall study design or efficacy assessments of ISIS 484137 in T2D patients with hepatic steatosis.

Also, administrative clarifications and corrections for typographical errors have been made throughout the protocol to improve the overall clarity of the original protocol, however, these changes do not impact subject safety, exposure, or the overall study design.

The following modifications to Protocol ISIS 484137-CS2 have been made. The table below provides a list of changes to the protocol:

Protocol Section	Description of Change	Rationale
Synopsis: Study Population; Section 5.1 Inclusion Criteria #3; Appendix A Legend Foot note #4	Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea **in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea** without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved).	Definition of post-menopausal clarified for consistency throughout the protocol.

Protocol Section	Description of Change	Rationale
Synopsis: Study Population; Section 5.1 Inclusion Criteria #6	Subjects must have been on **stable mono therapy or stable combination therapy** of the following oral antidiabetic therapy: metformin, sulfonylurea (SU), dipeptidyl peptidase-IV (DPPIV inhibitor) or sodium glucose like transport protein 2 (SGLT2) inhibitor for a minimum of 3 months prior to screening evaluation and will be required to continue their stable dose of oral antidiabetic therapy throughout the study. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, glucagon-like peptide [GLP1 analogs]	Clarification of Inclusion Criteria that combination diabetic therapy is acceptable.
Synopsis: Study Population; Section 5.2 Exclusion Criteria #2	**All central laboratory** results prior to **Day 1** as follows, or any other clinically-significant abnormalities in Screening laboratory values that would render a subject unsuitable for inclusion: a. Urine protein/creatinine (P/C) ratio > 0.2 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/ 24-hr **at Screening** b. Persistently positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing < 5 red blood cells (RBC) per high power field (Persistently positive defined as 2 out of 3 that **can be confirmed during the Run-In Period** c. Serum creatinine > upper limit of normal (ULN) d. Estimated glomerular filtration rate (GFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance) e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 ULN f. Total bilirubin > ULN g. Have a current or previous diagnosis of Gilbert's disease **at Screening** h. Platelet count < 170,000/mm^3 (< 170 X 10^9/L)	Clarification that all results prior to Day1 must meet eligibility criteria.

Protocol Section	Description of Change	Rationale
Synopsis: Study Population; Section 5.2 Exclusion Criteria #6	**Was:** Subjects on lipid lowering medications must be on a stable dose and regimen for ≥ 3 months prior to Screening. Subjects receiving treatment with statins should be within the dose levels listed below. Other statin regimens should be discussed and approved with the Sponsor Medical Monitor or designee: • Simvastatin, pravastatin, atorvastatin and fluvastatin at ≤ 40 mg/day • Lovastatin or rosuvastatin at ≤ 20 mg/day • Pitavastatin up to 4 mg/day **IS:** **Subjects on HMG-CoA reductase inhibitors medications ('statins') must be on a stable dose and regimen for ≥ 3 months prior to Screening. Other lipid lowering therapies including fish oils or prescription lipid-regulating drugs (e.g., bile-acid sequestering resins, fibrates and their derivatives and ezetimibe) are not permitted. Alternate lipid lowering regimens should be discussed and approved with the Sponsor Medical Monitor or designee.**	Inclusion Criteria updated to ensure statin therapy requirements are consistent with current standard of care (The minimum doses can be higher to reach goals from new guidelines) and criteria expanded to include restrictions already outlined in the Disallowed Concomitant Therapy section.
Synopsis: Study Population; Section 5.2 Exclusion Criteria #17	Confirmed reduction in body weight of **2** kg (4.4 lbs) at the Run-In Visit (Week-1) compared to body weight taken at Screening	The "±" sign was an error, has been removed.
Synopsis: Study Visit Schedule and Procedures; Section 6.1.2.2.2 SC Tolerability	To reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will confirm tolerance of SC administration of 0.9% saline prior to randomization during the **Screening or the Run-In-Period**. This injection will follow the same procedures as injections of the Study Drug (ISIS 484137 or placebo) during the treatment period.	Clarified that this procedure can take place not only at Screening, but at any time during Screening or Run-In to improve operational logistics at the study center.

Protocol Section	Description of Change	Rationale
Section 6.1.4 Post - Treatment Period (PT1-13); Appendix A Notes Regarding Timing of MRI Assessments	A Post-Treatment MRI (See Section 6.1.2.1) to assess liver fat content and volume will occur during PT2 Visit (2 weeks after last dose) for all subjects completing 13 doses. For subjects who terminate from the treatment period early, the timing and conduct of the MRI in the Post-Treatment Period will be adjusted as follows (+/- 7-day window). **The timing of the Post-Treatment MRI should be discussed with the Ionis Study Team but may be scheduled as follows**: i. Subject received 4 or less doses, the Post-Treatment MRI Assessment will not be required ii. Subject received 5-9 doses, the Post-Treatment MRI Assessment will occur 2 weeks after last dose at the PT2 Visit iii. Subject received 10-12 doses, the Post-Treatment MRI Assessment will be scheduled as follows: • If subject received 10 doses, subject moves into Post-Treatment Period, the MRI will be conducted 5 weeks after the last dose • If subject received 11 doses, subject moves into Post-Treatment Period, the MRI will be conducted 4 weeks after the last dose If subject received 12 doses, subject moves into Post-Treatment Period, the MRI will be conducted 3 weeks after the last dose	The timing of the Post Treatment MRI should be discussed with Ionis if the patient discontinues treatment after 10, 11 or 12 doses. Language was added to improve operational logistics at the study center.
Section 8.10.1 Allowed Concomitant Therapy	Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy. **In the Post-Treatment Period, anti-diabetic agents may be added or altered for deteriorating glycemic control in consultation with the Investigator and Sponsor Medical Monitor.**	Additional language incorporated to specify that changes in antidiabetic therapy are permitted in the post treatment period in presence of deteriorating glucose control.

Protocol Section	Description of Change	Rationale
Section 8.10.1 Disallowed Concomitant Therapy	**WAS:** Use of anticoagulants/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours). These agents were to be stable prior to the first does of Study Drug. **IS:** **New or increased** use of anticoagulants/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel **unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed**; use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours) are not permitted while on Study Drug.	Language updated for consistency between eligibility criteria and Disallowed Concomitant Medications.
Section 10.6.2 Safety Analysis	**REMOVED:** Incidence of bleeding events including the following will be tabulated by treatment for MB, CRNMB, minor bleeding, and combination of major and clinically-relevant nonmajor bleeding.	Removed from Safety Analysis section and will be addressed further in the Statistical Analysis Plan, if applicable.
Appendix A Schedule of Procedures	Urinalysis (including P/C) removed at Week-1	Removed to decrease study burden on subject and study center. For most subjects only 1 urinalysis procedure will be required during Screening.
Appendix A Legend Foot note #5	Women who are not surgically sterile.	Pregnancy tests after screening are not required for post-menopausal or surgically sterile subjects during the study and have been removed.
Appendix A Legend Foot note #15	Triplicate ECG study procedure will consist of 3 ECGs with 2 minutes between each ECG (-1/+2 mins window between each assessment), **except as noted for footnote #6 where pre-dose, 1 hrs and 2 hrs post-ECGs are to be performed**	Wording added to clarify the number of ECGs to be performed during the study.

PROTOCOL SYNOPSIS

Protocol Title	A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2Rx, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes
Study Phase	2
Indication	Hepatic Steatosis in type 2 diabetes (T2DM)
Primary Objective(s)	To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with T2DM. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM.
Secondary Objective(s)	To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver fat (percent relative reduction and percent of subjects with ≥ 30% relative reduction) assessed by MRI-PDFF. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver volume assessed by MRI-PDFF. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on plasma lipoprotein profile (triglycerides [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], very low-density lipoproteins [VLDL], high density lipoprotein [HDL] and Non-HDL). To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on insulin resistance (IR) and glucose control (insulin, glucose, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c]).
Exploratory Objective(s)	To evaluate the pharmacodynamic effects of ISIS 484137 on potential biomarkers of DGAT2 activity, (e.g., stearoyl-CoA desaturase-1 [SCD-1]) and biomarkers of hepatic inflammation (e.g., cytokeratin 18 (CK 18), haptoglobin)
Study Design	Randomized, double-blind, placebo controlled, multi-center
Number of Subjects	Approximately 45 patients are planned to be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 or placebo
Study Population	**Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Males or females. Aged 18 to 75, inclusive, at the time of informed consent 3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved). Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 484137 or placebo)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Inclusion Criteria** *Continued* * 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 4. Body Mass Index (BMI) ≥ 27.0 - ≤ 39.0 kg/m^2 at Screening 5. Diagnosis of T2DM with an HbA1c ≥ 7.3% and ≤ 9.5% at Screening 6. Subjects must have been on stable mono therapy or stable combination therapy of the following oral antidiabetic therapy: metformin, sulfonylurea (SU), dipeptidyl peptidase-IV (DPPIV inhibitor) or sodium glucose like transport protein 2 (SGLT2) inhibitor for a minimum of 3 months prior to Screening evaluation and will be required to continue their stable dose of oral antidiabetic therapy throughout the study. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, glucagon-like peptide [GLP1 analogs]) 7. ≥ 10% liver fat as assessed by MRI-PDFF prior to randomization 8. Stable body weight (i.e., not varying by > 5% for at least 3 months) before Screening 9. Agree to maintain current diet and exercise regimen 10. Agree to abstain from alcoholic beverages for at least 48 hours prior to clinic visits and not increase alcohol consumption during the study **Exclusion Criteria** 1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination 2. All central laboratory results prior to Day 1 as follows, or any other clinically-significant abnormalities in Screening laboratory values that would render a subject unsuitable for inclusion: a. Urine protein/creatinine (P/C) ratio > 0.2 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr at Screening b. Persistently positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing < 5 red blood cells (RBC) per high power field (Persistently positive defined as 2 out of 3 can be confirmed during the Run-In Period c. Serum creatinine > upper limit of normal (ULN) d. Estimated glomerular filtration rate (GFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance) e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 ULN f. Total bilirubin > ULN g. Have a current or previous diagnosis of Gilbert's disease at Screening h. Platelet count < 170,000/mm^3 (< 170 X 10^9/L)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria** *Continued*
	3. Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening. Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to Screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that subject is euthyroid 4. History of solid organ transplantation or renal dialysis 5. Clinically-significant complications of diabetes (e.g., history of painful neuropathy, nephropathy, proliferative retinopathy and/or foot ulcers) 6. Subjects on HMG-CoA reductase inhibitors medications ('statins') must be on a stable dose and regimen for ≥ 3 months prior to Screening. Other lipid lowering therapies including fish oils or prescription lipid-regulating drugs (e.g., bile-acid sequestering resins, fibrates and their derivatives and ezetimibe) are not permitted. Alternate lipid lowering regimens should be discussed and approved with the Sponsor Medical Monitor or designee 7. Known history of or evidence of liver disease with a positive test for human immunodeficiency virus (HIV), hepatitis C (HCV) or chronic hepatitis B (HBV) or chronic liver disease other than NASH including alcoholic liver disease, Wilson's disease, hemochromatosis, or iron overload, Alpha-1-antitrypsin (A1AT) deficiency, prior known drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC), current placement on a liver transplant list, or MELD score > 12, established fibrosis ≥ Stage 3 fibrosis (Scale 0-4) or any cirrhosis 8. 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. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor 9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 10. Treatment with any non- ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Subjects who have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration of ≥ 4 months has elapsed since dosing 11. Recent history of, or current drug or alcohol abuse. Regular and excessive use of alcohol within 6 months prior to Screening (> 7 drinks/week for females, > 14 drinks/week 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), or use of soft drugs (such as marijuana) within 3 months prior to Screening, or hard drugs (such as cocaine and phencyclidine [PCP]) within 1-year prior to Screening, or positive urine drug screen for these drugs at Screening

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria** *Continued* 12. Concomitant medication restrictions: a. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior (e.g., sibutramine, phenetamine and orlistat) b. chronic use of systemic corticosteroids c. other antidiabetic medications not outlined in Inclusion Criteria #6 d. other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or steatosis (e.g., amiodarone, methotrexate, tamoxifen, carbamazepine) e. Use of anticoagulant/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed, use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours) f. obeticholic acid or ursodeoxycholic acid 13. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 14. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 15. Subjects with known intolerance to MRI or with conditions contraindicated for MRI Procedures: • Subjects who have any metal implant (including a heart pacemaker, rods, screws, aneurysm clip) • Subjects with claustrophobia 16. Confirmed reduction in fasting plasma glucose (FPG) of > 40 mg/dL (> 2.2 mmol/L) at the Run-In Visit (Week -1) compared to a FPG value taken at Screening 17. Confirmed reduction in body weight of 2 kg (4.4 lbs) at the Run-In Visit (Week -1) compared to body weight taken at Screening 18. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study, including unwillingness to continue with SC injections after the SC Tolerability assessment
Treatment Groups	Placebo and ISIS 484137 250 mg per week

PROTOCOL SYNOPSIS *Continued*

Study Drug Dosage and Administration	The SC tolerability assessments using 0.9% sterile saline will be administered as a 1.25 mL injection at any visit during the Screening or Run-In Periods (may also be delivered as 2 non-contiguous injection volumes of 0.75 mL and 0.50 mL). ISIS 484137 (200 mg/mL) and placebo will be supplied as 1.0 mL of solution in a 2 mL stoppered glass vial. Study Drug (ISIS 484137 or placebo) SC injection volume will be 1.25 mL (may also be delivered as two non-contiguous injection volumes of 0.75 mL and 0.50 mL). Subjects will be administered 13 weekly SC injections during the 13-week treatment period.
Rationale for Dose and Schedule Selection	The dose of 250 mg of ISIS 484137 was selected for this study based on the results of the Phase 1 trial ISIS 484137-CS1 which demonstrated an acceptable safety and tolerability profile for doses up to 300 mg after 6 weeks (8 total doses) of treatment. Additionally, several ASOs of this class have demonstrated significant efficacy and acceptable safety profiles at a similar dose level for 13 weeks and longer (Ackermann et al. 2016; Digenio et al. 2016; Duell et al. 2016). The 13-week treatment duration is supported by the ISIS 484137 nonclinical 13-week toxicology study (see Investigators Brochure) and by previous long-term weekly clinical dosing studies with several other 2'-MOE-modified ASOs. Thirteen (13) weeks of study treatment is a sufficient treatment duration to observe changes in liver fat content and improvements in IR in this patient population.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in Section 6 and Appendices A-C. The duration of subject participation in the study includes up to a 2-week Screening Period, up to a 4-week Run-In Evaluation Period, and a 13-week Treatment Period. Subjects will be required to complete a Post-Treatment Period for 13 weeks following the last dose of study medication (or early termination). The Ionis Medical Monitor or Designee will perform routine reviews of the safety results throughout the conduct of the study. To reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will confirm tolerance of SC administration of 0.9% saline prior to randomization during the Screening or the Run-In Period. This injection will follow the same procedures as injections of the Study Drug (ISIS 484137 or placebo) during the treatment period. **Screening Period: Week -6 – Week -5 (up to 2 weeks)** Laboratory and other study procedures will be performed to assess eligibility during the Screening Period. **Run-In Period: Week -4 – Week -1 (4 weeks)** Subjects will maintain his/her diet and exercise routine. During Weeks -4 and -3, subjects will have an MRI to assess liver fat content and liver volume. MRIs will be conducted using standardized procedures and settings. MRIs will be evaluated by an independent central reader, blinded to the subject's treatment assignment, to assess liver fat and liver size.

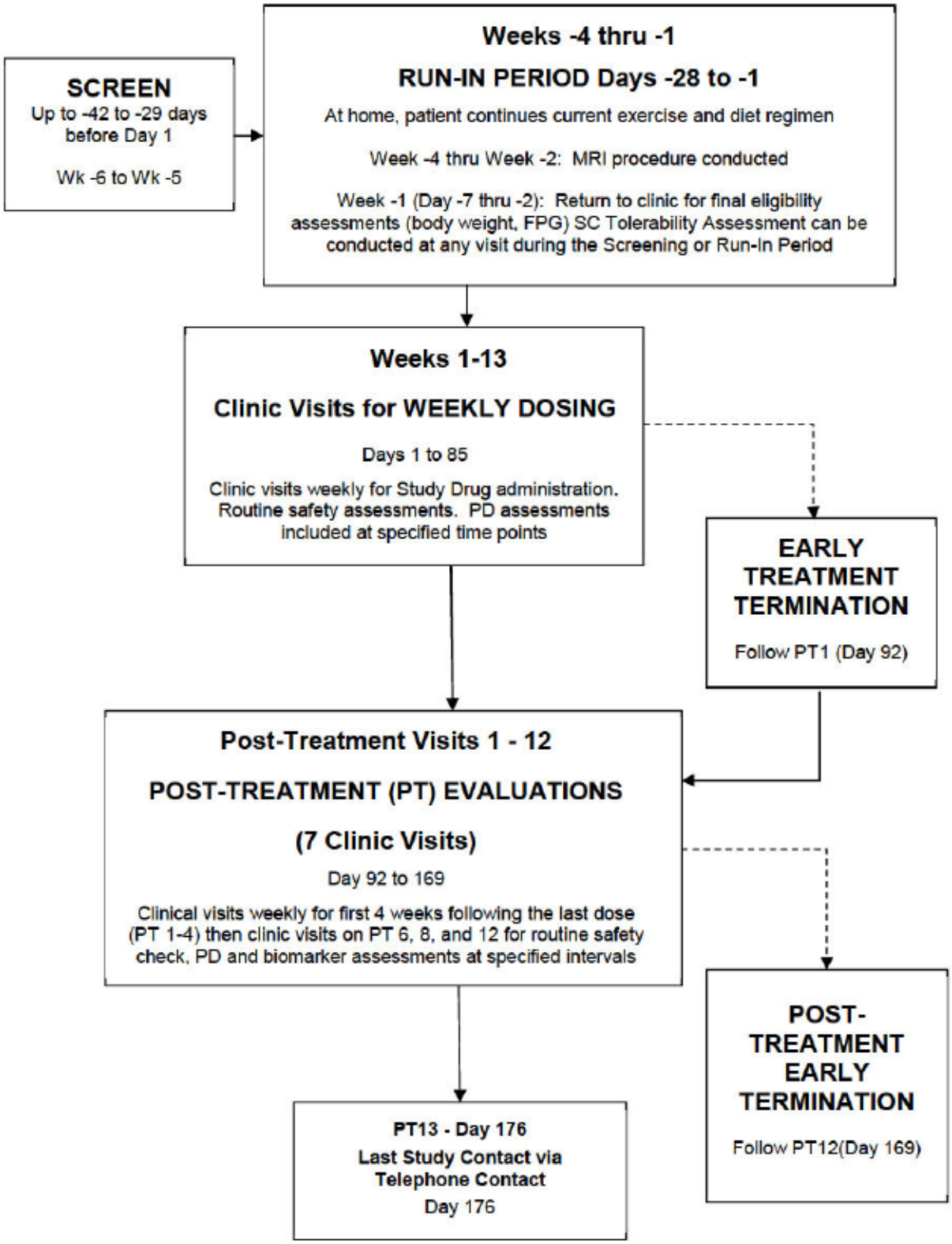
PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	**Run-In Period: Week -4 – Week -1 (4 weeks)** *Continued* Subjects with a qualifying MRI (at least 10% liver fat assessed by MRI-PDFF via central reviewer) return to clinic for Study Visit Week -1. At this visit, final qualification assessments will be conducted including body weight and FPG assessments. If it is not possible for MRI results to be available by the clinic Week -1 visit, the MRI results must be available for final qualification prior to randomization. Eligible subjects will be stratified based on MRI liver fat levels (< 20% vs. ≥ 20%) and then subjects will be randomized prior to the first dose in a 2:1 ratio to receive either ISIS 484137 or placebo. Eligible/qualified subjects will be randomized and return to clinic for the Treatment Period. **Treatment Period: Week 1 – Week 13** STUDY DRUG ADMINISTRATION: Weekly injections will be administered at the study center. SAFETY ASSESSMENTS: Weekly laboratory assessments will be obtained including chemistry, hematology, urinalysis, adverse events and concomitant medication usage. Blood samples for pharmacokinetic analysis will be drawn weekly. Additional blood tests for exploratory purposes will be collected at less frequent intervals including lipids, inflammatory markers and exploratory biomarkers. Subjects who discontinue treatment early will enter the Post-Treatment Period unless consent is withdrawn. If a subject's glycemic control deteriorates after Week 8 according to the Monitoring Rule, the oral anti-diabetic (OAD) regimen can be adjusted. **Post-Treatment Period: Week 14 – Week 26** SAFETY ASSESSMENTS: Laboratory assessments will be obtained at regular intervals throughout the 13-week Post-Treatment Period. MRI: Liver fat content and volume will be measured in the Post-Treatment Period in all subjects who complete at least 5 doses during the Treatment Period.
Safety and Tolerability Evaluations	The safety and tolerability of ISIS 484137 will be assessed by determining the incidence, severity, dose-relationship of adverse effects and changes in laboratory evaluations. Safety results in subjects dosed with ISIS 484137 will be compared with those from subjects dosed with placebo. The safety and tolerability profile of the Study Drug will be monitored weekly during the Treatment Period and at each scheduled visit in the Post-Treatment Period.
Pharmacokinetic Evaluations	Selected plasma trough and post-treatment concentrations of ISIS 484137 will be assessed in evaluable subjects receiving ISIS 484137 treatment.

PROTOCOL SYNOPSIS *Continued*

Pharmacodynamic Evaluations	The effect of ISIS 484137 on the following will be assessed • hepatic fat and liver weight content will be evaluated over time using magnetic resonance imaging that is conducted at Baseline and Post-Treatment. A central reader will calculate the percent liver fat by PDFF. MRI results in subjects dosed with ISIS 484137 will be compared with those subjects dosed with placebo • plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, ApoB, VLDL, HDL and Non-HDL) • hepatic IR and glucose control (insulin, glucose, HOMA-IR, HbA1c)
Statistical Considerations	Approximately 45 subjects will be randomized (2:1 allocation ratio) to ensure at least 33 subjects will have data on the primary study endpoint. This will result in > 90% power to detect a of 5% difference in mean absolute change in liver fat as measured by MRI-PDFF between the active and placebo groups with a 2-sided alpha of 0.05, assuming a common standard deviation of 4%.
Sponsor	Ionis Pharmaceuticals, Inc

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
apoB	apolipoprotein B
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BP	blood pressure
BUN	blood urea nitrogen
C5a	complement factor C5a (activated complement split product)
CBC	complete blood count
CK18	cytokeratin 18
CMV	Cytomegalovirus
CRF	case report form
CRNMB	clinically-relevant non-major bleeding
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAG	*sn*-1,2-diacylglycerol
DGAT	Diacylglycerol Acyltransferase
DGAT1	diacylglycerol *O*-acyltransferase 1
DGAT2	diacylglycerol *O*-acyltransferase 2
DNA	phosphorothioate modified oligodeoxynucleotides
DPPIV inhibitor	dipeptidyl peptidase-IV
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic Case Report Form

EDC	electronic data capture
FPG	fasting plasma glucose
ET PT	Early Termination patients from the Post-Treatment Period
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP1	glucagon-like peptide 1
HAV	hepatitis A virus
HbA1C	Hemoglobin A1C
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	Homeostatic model assessment- insulin resistance
HR	heart rate
hsCRP	CRP measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgM	immunoglobulin M
INR	international normalized ratio
IL6	Interleukin-6
IR	insulin resistance
IRB	Institutional Review Board
ISIS 484137	antisense inhibitor of DGAT2
IV	Intravenous(ly)
IXRS	Interactive voice/internet response system
LDH	lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol

MAG	monoacylglycerol
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
MRI	magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-estimated proton density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCS	not clinically-significant
Non-HDL	Non- high- density lipoprotein
NSAID	non-steroidal anti-inflammatory drug
OAD	oral anti-diabetic agent
P/C	urine protein/creatinine
PD	pharmacodynamic(s)
PDFF	proton density fat fraction
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
pRBC	packed red blood cells
PT	prothrombin time
RBC	red blood cells
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
siRNA	small interfering ribonucleic acid

SC	subcutaneous(ly)
SCD-1	Stearyl CoA desaturase-1
SGLT2	Sodium glucose like transport protein 2
Study Day 1	defined as the first day Study Drug product is administered to the subject
Study Drug	ISIS 484137 or placebo
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VLDL	Very low-density lipoproteins
WAT	white adipose tissue
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objective(s)

The primary objectives are:

1. To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with type 2 diabetes mellitus (T2DM)
2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM

1.2 Secondary Objective(s)

The secondary objectives are:

1. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver fat (percent relative reduction and percent of subjects with ≥ 30% relative reduction) assessed by MRI-PDFF
2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver volume assessed by MRI-PDFF
3. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on plasma lipoprotein profile (triglycerides [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], very low-density lipoproteins [VLDL], high density lipoprotein [HDL] and Non-HDL)
4. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on insulin resistance (IR) and glucose control (insulin, glucose, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c])

1.3 Exploratory Objectives

The exploratory objectives are to evaluate the pharmacodynamic (PD) effects of ISIS 484137 on potential biomarkers of DGAT2 activity (e.g., stearoyl-CoA desaturase-1 [SCD-1] and biomarker of hepatic inflammation (e.g., cytokeratin 18 [CK18], haptoglobin).

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of the metabolic syndrome (Marchesini et al. 2003) and is characterized by the accumulation of triglycerides in the liver of subjects without a history of excessive alcohol consumption. NAFLD is classified into simple steatosis, in which only hepatic steatosis is observed, and non-alcoholic steatohepatitis (NASH), in which intralobular inflammation and ballooning degeneration of hepatocytes is observed along with hepatic steatosis. Most patients with NAFLD are obese or morbidly obese and have accompanying IR (Byrne and Targher 2015) and type 2 diabetes mellitus. NASH is a progressive disease and may lead to liver cirrhosis and hepatocellular carcinoma (HCC) (Farrell and Larter 2006; Cohen et al. 2011). Twenty (20) percent of NASH patients are reported to develop cirrhosis, and 30-40% of patients with NASH cirrhosis experience liver-related death

(McCullough 2006). The incidence of NAFLD and NASH have been rapidly increasing worldwide consistent with the increased prevalence of obesity, and is currently the most common chronic liver disease. Recently, the incidence of NAFLD and NASH was reported to be 46% and 12%, respectively, in a largely middle-aged population (Williams et al. 2011). NASH has become the third most common indication for liver transplantation in the United States (Charlton et al. 2011).

Hepatic steatosis results from an imbalance between triglyceride accumulation and elimination in the liver. Insulin resistance, which is frequently seen in obese individuals, is closely linked to this process because it alters nutrient distribution among tissues and nutrient metabolism (Tomeno et al. 2013). Peripheral IR leads to an influx of free fatty acids into the liver by decreased suppression of lipolysis and increased *de novo* lipogenesis (Ibrahim et al. 2013). Although the pathogenesis of NAFLD/NASH has not been completely elucidated, the "two-hit" (Day and James 1998) and "multiple parallel hit" (Tilg and Moschen 2010) hypotheses have been proposed. In the two-hit hypothesis, hepatic steatosis occurs first through an initial metabolic disturbance and progresses to NASH by subsequent second hits derived from the gut and/or the adipose tissue such as increased levels of inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6 [IL6]), decreased levels of anti-inflammatory cytokines (e.g., adiponectin), oxidative stress, and endotoxins originating from intestinal bacterial flora. Therefore, a compound such as an antisense oligonucleotide (ASO) against Diacylglycerol Acyltransferase 2 (DGAT2) that reduces hepatic steatosis could result in prevention or attenuation of the secondary inflammation and oxidative stress thereby benefiting NAFLD and NASH patients.

2.2 Therapeutic Rationale

2.2.1 Overview of Target

Diacylglycerol acyltransferase (DGAT) catalyzes the final step in TG synthesis by facilitating the linkage of *sn*-1,2-diacylglycerols (DAG) with an acyl-CoA. DGAT has 2 isoforms, diacylglycerol *O*-acyltransferase 1 (DGAT1) and diacylglycerol *O*-acyltransferase 2 (DGAT2), and studies indicate that both DGAT1 and DGAT2 play important roles in TG synthesis. DGAT1 is most highly expressed in small intestine and white adipose tissue (WAT), whereas DGAT2 is primarily expressed in liver and WAT (Cases et al. 1998; Cases et al. 2001). The existence of DGAT2 was predicted from the finding that mice lacking DGAT1 have abundant TG in their tissues. The hDGAT2 gene is composed of 8 Exons, and spans 42.03 kb on Chromosome 11. It is located ~37.5 kb from the monoacylglycerol acyltransferase 2 (MGAT2) gene (Yen et al. 2008). In most species, the gene encodes a protein of 350-400 residues, and the calculated molecular mass for DGAT2 enzymes is in the range of 40-44 KD (Yen et al. 2008).

Although both DGAT1 and DGAT2 catalyze the same reactions in TG synthesis with DAG or monoacylglycerols (MAG) and acyl-CoA as substrates, they are functionally distinguished by their differences in catalytic properties (Cao et al. 2007; Cheng et al. 2008), subcellular localization (Stone et al. 2009), physiological regulation (Meegalla et al. 2002), and phenotypic consequences when rendered deficient (Smith et al. 2000) or overexpressed in preclinical models (Naik et al. 2014). DGAT1 null mice were found to be resistant to high-fat-diet-induced obesity because of an increased metabolic rate (partly due to increased physical activity), modestly decreased levels of tissue TGs, and increased insulin and leptin sensitivity (Smith et al. 2000).

DGAT2 null mice are lipopenic and die soon after birth because of profound reductions in substrates for energy metabolism and impaired skin permeability (Stone et al. 2004), while DGAT2 heterozygous mice are viable, healthy, and physically indistinguishable from non-deficient mice (Yu et al. 2005). The effects of specific pharmacologic antagonism of hepatic DGAT2 expression were not known until studies conducted with DGAT2 ASOs.

DGAT2 ASOs were developed to reduce the rate of TG synthesis by specifically reducing hepatic DGAT2 expression. Suppression of DGAT2, but not of DGAT1, by ASO treatment improved hepatic steatosis and blood lipid levels independent of adiposity in rodent models of obesity and data indicated that these effects were related to decreased hepatic lipid synthesis (Yu et al. 2005). In rats with diet-induced hepatic steatosis (model of human NAFLD), treatment with both DGAT1 and DGAT2 ASOs selectively reduced DGAT1 and DGAT2 ribonucleic acid (RNA) levels in liver and fat. However, only DGAT2 ASO treatment significantly reduced hepatic lipids (DAG and TG but not long chain acyl-CoAs) and reversed diet-induced hepatic IR in this rat model of diet-induced NAFLD (Choi et al. 2007). Pharmacologic effects correlated with the level of antisense inhibition of DGAT2 liver expression and > 80% decrease of DGAT2 in liver and adipose tissue did not cause any target related toxicity. These pharmacologic data indicate different functions of the two DGAT enzymes during TG biosynthesis and are consistent with those from overexpression studies. In overexpression studies in mice, DGAT2 has been identified as being more active than DGAT1, yielding a higher increase in intracellular TG that accumulates as large, centrally located cytosolic droplets (Stone et al. 2004). Furthermore, in rat hepatoma cells, DGAT1 overexpression resulted in considerably less TG accumulation than was shown by DGAT2 overexpression.

These results suggest that DGAT2 plays an important role in hepatic lipid metabolism, hepatic steatosis, hepatic insulin signaling, and hepatic insulin sensitivity and that therapeutic interventions aimed at reducing DGAT2 function in lipogenic tissues may provide clinical benefit for fatty liver disease, metabolic syndrome and cardiovascular diseases.

2.2.2 Therapeutic Rationale

ISIS 484137 is being investigated as a possible treatment for NAFLDs including NASH. Currently, the principal treatment for NAFLD/NASH is lifestyle modification by diet and exercise. There are no approved medications for these conditions. However, pharmacological therapy is indispensable because obese patients with NAFLD often have difficulty maintaining improved lifestyles. Selective inhibition of DGAT2 has been suggested as a new target for the treatment of these obesity-related metabolic diseases. Important advances have been made regarding potential applications for DGAT inhibitors, including several reports of DGAT inhibitors with improved solubility, cell-based activity, and pharmacokinetic (PK) properties. Despite strong interest and efforts of pharmaceutical companies and many academic research groups, very few compounds have reached clinical trials. Hence, the need for the development of safe and effective DGAT inhibitors remains high.

There are currently no known strategies for a small molecule approach to lower DGAT2 expression specifically in liver and/or adipose tissue. In contrast, ISIS 484137 has been shown to specifically lower hepatic DGAT2 expression and, may therefore, have the potential to reduce liver steatosis and development of NASH.

This short-term study will assess changes in hepatic steatosis over a 13-week treatment period in a patient population with higher risk for development of NAFLD and NASH, obese T2DM with elevated HbA1c. Changes in the PDFF in the liver will be estimated by MRI, referred to as MRI-PDFF. It is the fraction of the MRI visible protons bound to fat divided by all protons in the liver (bound to fat and water). The liver MRI-PDFF has been utilized as a noninvasive biomarker of hepatic steatosis as it has been strongly correlated with histologic grade of hepatic steatosis (Dulai et al. 2016; Patel et al. 2016) and has been used in trials as an objective, quantitative, precise and reproducible noninvasive imaging biomarker of liver fat content (Le et al. 2012; Kang et al. 2011). The primary endpoint is to assess absolute changes in the liver MRI-PDFF after therapy with ISIS 484137 or placebo, as longitudinal changes in PDFF have identified subjects with reduced steatosis grade with reduction of PDFF (Middleton et al. 2017).

2.3 ISIS 484137

2.3.1 Mechanism of Action

ISIS 484137 is a second-generation 2′-*O*-(2-methoxyethyl) (2′-MOE) chimeric ASO inhibitor of the molecular target DGAT2. It is complementary to a region within the non-coding region of the DGAT2 RNA and binds to the RNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 484137 to the cognate RNA results in the RNase H1-mediated degradation of the DGAT2 RNA, thus preventing production of the DGAT2 protein. Maximal antisense-mediated reduction of target RNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target RNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

ISIS 484137 is a second generation 2′-MOE chimeric antisense drug. Chemically, ISIS 484137 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of ISIS 484137 (Figure 1) is fully complementary to a 20-nucleotide stretch within the second intronic region of the DGAT2 gene at position 6–15. 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 484137 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 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 enzyme (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE

modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

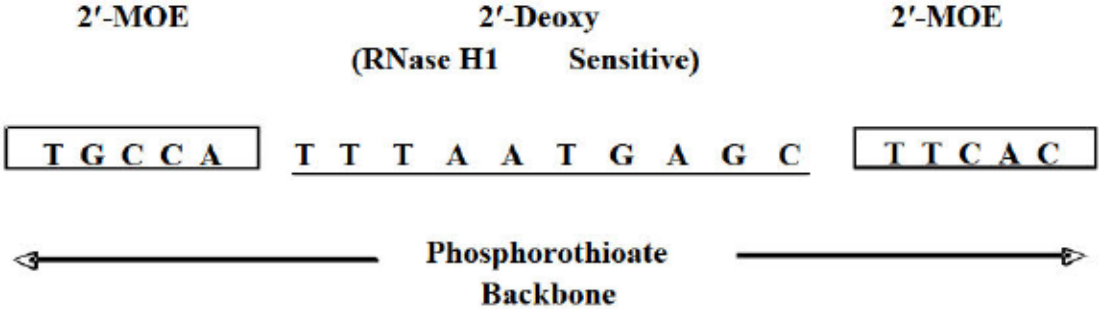


Figure 1 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence of ISIS 484137 is shown.

2.3.3 Preclinical Experience

Detailed information concerning the preclinical studies conducted with ISIS 484137 can be found in the Investigator's Brochure. A summary is included below.

Nonclinical Pharmacology

DGAT2 ASOs were developed to reduce the rate of TG synthesis by reducing liver and adipose DGAT2 expression. Treatment with DGAT2 ASOs in rodent models of obesity improved hepatic steatosis and hyperlipidemia (Yu et al. 2005) in addition to improving insulin sensitivity in a rat model of diet-induced NAFLD (Choi et al. 2007). Pharmacologic effects correlated with the level of antisense reduction of DGAT2 RNA expression. The robust and sustained improvements in hepatic TG levels and the improved plasma lipid profile were accompanied by secondary reductions in several key hepatic enzymes involved in lipid synthesis. The benefits associated with inhibiting the hepatic lipogenic pathway with DGAT2 treatment also included increased hepatic fat oxidation, improvements in hepatic insulin signaling and hepatic insulin sensitivity. More than 80% decrease of DGAT2 in liver and adipose tissue did not cause any target related toxicity. Specifically, the tissue-related skin abnormalities and dehydration associated with systemic DGAT2 deficiency was not observed.

Thus, reduction of DGAT2 expression with ISIS 484137 in animal models provided a mechanism to reduce hepatic steatosis, thereby potentially attenuating subsequent inflammation and fibrosis. This mechanism of action could offer an attractive treatment option especially for patients who have significant hepatic steatosis associated with NAFLD and NASH.

Pharmacokinetics and Product Metabolism in Animals

Dose-dependent exposures to ISIS 484137 in plasma and liver and kidney tissues were established in the 13-week mouse and monkey toxicity studies at doses between 4 and 100 mg/kg/wk and between 4 and 40 mg/kg/wk, respectively. A half-life of approximately 2 to 3 weeks was observed in monkeys. Pharmacokinetics observed in monkeys for this class of compounds typically predict the observed plasma exposure levels in humans on the basis of mg/kg equivalent doses (Geary et al. 2003; Yu et al. 2007).

ISIS 484137 was highly bound to plasma proteins, greater than 96% in mouse, monkey, and human plasma studies. The high protein binding prevents glomerular filtration and limits urinary excretion. The binding sites for these types of hydrophilic drugs differ from the binding sites of low molecular weight hydrophobic drugs; thus, few DDIs on the level of plasma protein binding are expected at clinically-relevant concentrations.

Toxicology and Safety Pharmacology

General toxicology studies were conducted with ISIS 484137 in the mouse and monkey for 13 weeks of treatment. Dose administration was by SC injection at weekly doses of 4, 12, 40, and 100 mg/kg/wk ISIS 484137 in mice or 4, 8, 12, and 40 mg/kg/wk ISIS 484137 in monkeys.

The most noteworthy findings observed in mice and monkey toxicology studies following 13-weeks of ISIS 484137 treatment were, in general, non-specific class effects that are typical for 2′-MOE ASOs (Henry et al. 2008). There was no drug-related mortality or changes in clinical signs up to the highest doses tested (100 mg/kg in mice and 40 mg/kg in monkeys). Reduction in platelet count (33,000/mm^3) was observed in a single monkey (1 of 10) in the 12 mg/kg/wk dose group on Day 93, with no clinical signs in this animal, and no microscopic evidence of hemorrhage. Since platelet reduction below 200,000/mm^3 was not observed in any other animals in the study, including the high dose of 40 mg/kg/wk, the relationship to the test article is unclear.

In vivo safety pharmacology studies conducted to date indicate that ISIS 484137 had no effects on cardiovascular parameters (blood pressure [BP], heart rate [HR] and electrocardiogram [ECG]) or pulmonary function or neurobehavior in monkeys. Genetic toxicity studies (the Ames assay and *in vitro* chromosomal aberrations in Chinese hamster lungs [CHL cells]) were negative.

There were no toxicologically significant findings at doses up to 12 mg/kg/wk for 13 weeks in the mouse and monkey studies, and therefore there is sufficient therapeutic margin to support the safe clinical use of ISIS 484137 at the proposed clinical doses and regimen.

2.3.4 Clinical Experience

The safety and tolerability of ISIS 484137 was evaluated in a total of 40 healthy overweight subjects in a double-blinded, placebo-controlled, dose-escalation Phase 1 study ISIS 484137-CS1. Of these 40 subjects, 30 received ISIS 484137 (12 in the single-dose cohorts and 18 in the multiple-dose cohorts), and 10 received placebo. ISIS 484137 was well-tolerated at doses up to 300 mg/wk for 6 weeks. There were no SAEs and all reported AEs were mild in severity. There were no dose-dependent clinically meaningful trends in laboratory assessments.

2.4 Rationale for Dose and Schedule of Administration

The safety data obtained in the Phase 1 study (ISIS 484137-CS1) as well as the clinical experience with several other 2′-MOE-modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006), supports the dosing regimen planned for this Phase 2 study. The planned regimen has been employed safely in previous clinical studies with a number of other ASOs. This class of ASOs has been safely administered intravenously (IV) and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008; Crooke et al. 2016) and treatment durations that exceed 24 months.

The currently proposed 250 mg ISIS 484137 dose level was selected based on results from the previous ISIS 484137-CS1 Phase 1 clinical study (doses 50 to 400 mg) that showed a satisfactory safety profile with these dose levels after 6 weeks (8 total doses) of treatment. Additionally, several ASOs of this class have demonstrated significant efficacy and acceptable safety profiles at a similar dose level for 13 weeks and longer (Ackermann et al. 2016; Digenio et al. 2016; Duell et al. 2016)

Weekly administration for 13-weeks is also supported by the ISIS 484137 nonclinical 13-week toxicology study (see Investigators Brochure). Kidney, liver, and adipose tissue concentrations of ISIS 484137 collected after 13 weeks of dosing during a monkey toxicology study indicate that tissue distribution for this compound is consistent with previously administered antisense oligonucleotides. Post-distribution plasma concentrations (i.e., terminal elimination phase) of ISIS 484137 are expected to be in equilibrium with tissue concentrations in humans, as was observed in monkeys, mice, and rats for similar 2′-MOE gapmers. With an estimated tissue half-life of approximately 2-3 weeks for ISIS 484137 predicted for humans based on previous experience with other second generation ASOs (Yu et al. 2009), achieving steady-state concentrations in the liver (the target organ) will be a prolonged process (e.g., time to approximately 90% of steady-state in tissues is estimated to take about 8 weeks with once-weekly dosing regimen). Thirteen (13) weeks of study treatment is a sufficient treatment duration to observe changes in liver fat content and improvements in IR in this patient population.

2.5 Risk Assessment

The known potential risks to study participants associated with ISIS 484137 are elaborated on in the Guidance to Investigator section of the ISIS 484137 Investigator's Brochure. Risks associated with DGAT2 reduction are not anticipated in this short-term trial.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study in subjects with type 2 diabetes and evidence of hepatic steatosis seen on MRI scan. Subjects will be stratified based on the liver content by MRI-PDFF during the Run-In Period (< 20% vs. ≥ 20%). Subjects will be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 250 mg or placebo (See Study Design and Treatment Schema).

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Subjects

Approximately 45 subjects are planned to be enrolled in this study, randomized 2:1 to ISIS 484137 or placebo.

3.4 Overall Study Duration and Follow-up

The study will consist of Screening and Run-In, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in Appendix A. The expected duration of the study will be up to 6 weeks of Screening with the Run-In Period, 13 weeks of Study Drug dosing, and 13 weeks of post-treatment evaluations, for a total of up to 32 weeks of participation.

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

3.4.1 Screening and Run-In

Subject eligibility for the study will be determined within 6 weeks prior to study entry, consisting of up to 2-week Screening (Week -6 to Week -5) and a 4-week Run-In Period (Week -4 to Week -1).

During the beginning of the Run-In Period (approximately Week -4 to Week -3), subjects will have a baseline hepatic MRI to assess eligibility with liver fat content. MRIs will be conducted using standardized procedures and settings. MRIs will be evaluated by a central reader, blinded to the subject's treatment assignment, to assess liver fat and liver size. Patient will also be required to complete a SC Tolerability Assessment at any visit during the Screening or Run-In Period.

3.4.2 Treatment

Eligible subjects will be randomized will report to the Study Center for study treatment every week for 13 weeks (Week 1- Week 13).

3.4.3 Post-Treatment

Subjects are to return to the Study Center for follow-up visits at the following time points after the last dose: 1 week (PT1), 2 weeks (PT2), 3 weeks (PT3), 4 weeks (PT4), 6 weeks (PT6), 8 weeks (PT8), 12 weeks (PT12). The final study visit will occur 13 weeks after the last dose and via telephone.

Completed subjects will have a Post-Treatment hepatic MRI to assess liver fat content and volume 2 weeks after the last dose. The timing of the Post-Treatment MRI for subjects who terminate early from the Treatment Period is outlined in Section 6.1.4 and Appendix A.

3.5 End-of-Study

The End-of-Study is defined as when the last subject has had their last visit.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the Study, the Sponsor and designated contract research organization (CRO) requires a copy of the Study Center's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

Subjects or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled into the Study and will be assigned a unique screening number before any Study procedures, including screening procedures, are performed. In the event the subject is re-consented or re-screened the patient must be given a new screening number. Screening numbers, once assigned, will not be re-used.

4.2 Randomization

Subjects will be randomized after all Screening and Run-In assessments through Week -1 have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

All subjects will be randomized using an automated system (IXRS). Subjects will be stratified based on liver fat content results from the MRI conducted in the Run-In Period ($< 20\%$ or $\geq 20\%$), and then subjects will be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 250 mg or placebo. The Sponsor or designee will prepare the randomization list.

4.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all subjects, monitors, and Study Center personnel related to the study will be blinded throughout the study. However, if a subject 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 subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the automated IXRS. The Sponsor or designee will be informed of the unblinding of a subject within 24 hours. An unblinded randomization schema will be maintained securely by the Sponsor's designated vendor. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for regulatory reporting (see Section 9.2).

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

In addition, the safety team assigned to review relevant Study Drug safety and tolerability data during the study in a blinded fashion will also have the ability to request the Ionis Drug Safety

Oversight Committee, chaired by the Chief Medical Officer, for unblinding the treatment assignment if needed for safety and data interpretation.

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria at Screening and through randomization or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females. Aged 18 to 75, inclusive, at the time of informed consent
3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved)

   Males must be surgically sterile, abstinent*or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 484137 or placebo)

   * 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.
4. Body Mass Index (BMI) ≥ 27.0 - ≤ 39.0 kg/m^2 at Screening
5. Diagnosis of T2DM with an HbA1c ≥ 7.3% and ≤ 9.5% at Screening
6. Subjects must have been on stable mono therapy or stable combination therapy of the following oral antidiabetic agents: metformin, sulfonylurea (SU), dipeptidyl peptidase-IV (DPPIV inhibitor) or sodium glucose like transport protein 2 (SGLT2) inhibitor for a minimum of 3 months prior to screening evaluation and will be required to continue their stable dose of oral antidiabetic therapy throughout the study. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, glucagon-like peptide [GLP1 analogs])
7. ≥ 10% liver fat as assessed by MRI-PDFF prior to randomization
8. Stable body weight (i.e., not varying by > 5% for at least 3 months) before Screening
9. Agree to maintain current diet and exercise regimen
10. Agree to abstain from alcoholic beverages for at least 48 hours prior to clinic visits and not increase alcohol consumption during the study

5.2 Exclusion Criteria

1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. All central laboratory results prior to Day 1 as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion:
   a. Urine protein/creatinine (P/C) ratio > 0.2 mg/mg. In the event of P/C ratio above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 300 mg/24-hr at Screening
   b. Persistently positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing < 5 red blood cells (RBC) per high power field (Persistently positive defined as 2 out of 3 can be confirmed during the Run-In Period)
   c. Serum creatinine > upper limit of normal (ULN)
   d. Estimated glomerular filtration rate (GFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance)
   e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 ULN
   f. Total bilirubin > ULN
   g. Have a current or previous diagnosis of Gilbert's disease at Screening
   h. Platelet count < 170,000/mm^3 (< 170 x 10^9/L)
3. Show evidence of uncorrected hypothyroidism or hyperthyroidism hormone results at Screening. Subjects receiving dose-stable thyroid replacement therapy for at least 3 months prior to Screening will be allowed to participate as long as thyroid tests (TSH/T3/T4) show that subject is euthyroid
4. History of solid organ transplantation or renal dialysis
5. Clinically-significant complications of diabetes (e.g., history of painful neuropathy, nephropathy, proliferative retinopathy and/or foot ulcers)
6. Subjects on HMG-CoA reductase inhibitors medications ('statins') must be on a stable dose and regimen for ≥ 3 months prior to Screening. Other lipid lowering therapies including fish oils or prescription lipid-regulating drugs (e.g., bile-acid sequestering resins, fibrates and their derivatives and ezetimibe) are not permitted. Alternate lipid lowering regimens should be discussed and approved with the Sponsor Medical Monitor or designee

7. Known history of or evidence of liver disease with a positive test for human immunodeficiency virus (HIV), hepatitis C (HCV) or chronic hepatitis B (HBV) or chronic liver disease other than NASH including alcoholic liver disease, Wilson's disease, hemochromatosis, or iron overload, Alpha-1-antitrypsin (A1AT) deficiency, prior known drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC), current placement on a liver transplant list, or MELD score > 12, established fibrosis ≥ Stage 3 fibrosis (Scale 0-4) or any cirrhosis
8. 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. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor
9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
10. Treatment with any non- ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Subjects who have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration of ≥ 4 months has elapsed since dosing
11. Recent history of, or current drug or alcohol abuse. Regular and excessive use of alcohol within 6 months prior to Screening (> 7 drinks/week for females, > 14 drinks/week 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), or use of soft drugs (such as marijuana) within 3 months prior to Screening, or hard drugs (such as cocaine and phencyclidine [PCP]) within 1-year prior to Screening, or positive urine drug screen for these drugs at Screening
12. Concomitant medication restrictions:
    a. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior (e.g., sibutramine, phenetamine and orlistat)
    b. chronic use of systemic corticosteroids
    c. other antidiabetic medications not outlined in Inclusion Criteria #6,
    d. other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or steatosis (e.g., amiodarone, methotrexate, tamoxifen, carbamazepine)
    e. Use of anticoagulant/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed, use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin < 160 mg/day and other short acting NSAIDS with a half-life < 20 hours)
    f. obeticholic acid or ursodeoxycholic acid

13. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
14. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
15. Subjects with known intolerance to MRI or with conditions contraindicated for MRI Procedures:
    - Subjects who have any metal implant (including a heart pacemaker, rods, screws, aneurysm clip)
    - Subjects with claustrophobia
16. Confirmed reduction in fasting plasma glucose (FPG) of > 40 mg/dL (> 2.2 mmol/L) at the Run-In Visit (Week -1) compared to a FPG value taken at Screening
17. Confirmed reduction in body weight of 2 kg (4.4 lbs) at the Run-In Visit (Week -1) compared to body weight taken at Screening
18. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study, including unwillingness to continue with SC injections after the SC Tolerability assessment

6. STUDY PROCEDURES

6.1 Study Schedule

The study period for an individual subject consists of a ≤ 6-week Screening and Run-In Period followed by a 13-week Treatment Period, and a 13-week Post-Treatment Period. Additional visits may be scheduled if required for further evaluation of an abnormal laboratory value or reported AE.

Any AEs, concomitant medications, and other safety and tolerability profiling data will be promptly reported and reviewed by Sponsor's Medical Monitor (or designee).

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

6.1.1 Screening Period (Week -6 to Week -5)

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including Screening and Run-In procedures. A ≤ 6-week period is provided to complete Screening assessments and to determine subject eligibility for the study, with Screening at Week -6 to Week -5, and the Run-In Period from Week -4 to Week -1. Subjects will be questioned for medical history, and undergo physical examination, confirmation of their diabetes status and exclude other causes of liver disease and fibrosis, 12-lead electrocardiogram (ECG) conducted in triplicate, vital signs, body weight, and height. Subjects will also be screened for infections of HIV, Hepatitis B and C, and for blood coagulation abnormalities including prolonged activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), and thyroid function tests (TSH, free T4 and free T3) levels. Follicle-stimulating hormone (FSH) will be measured to confirm menopause in

women who have not undergone surgical sterilization (females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause). Additional blood samples will be taken for routine clinical laboratory testing (Appendix A).

Individuals may be disqualified if the result of any laboratory test is outside of the range specified in the eligibility criteria (Sections 5.1 and 5.2) or, if no range is specified, is abnormal and clinically-significant as judged by the Investigator or Sponsor Medical Monitor or Designee.

During the Screening Period, screening results may be retested for assessment by the Sponsor Medical Monitor or Designee for eligibility purposes.

6.1.2 Run-In Period (Week -4 thru Week -1)

Upon completion of the Screening Period, eligible patients enter the 4-week Run-In Period for subjects to maintain their routine diet and exercise stabilization during this period and for a baseline liver MRI Assessment. Subjects will maintain their routine diet and exercise routine and continue to take their oral anti-diabetic agent (OAD) daily during this 4-week period. Substantial changes in diet and exercise activities could have an impact on liver fat content and should be avoided during study participation.

6.1.2.1 Liver MRI Assessment (Week -4 to Week -3)

An MRI of the liver will be conducted 2 times during study participation, once before treatment and once after treatment. The Baseline MRI will be conducted during the Run-In Period (Week -4 to Week -3) and the Post-Treatment MRI Assessment will be conducted during the Post-Treatment Period (Week of PT2 Visit).

These MRIs will be conducted using standardized procedures and settings and will be evaluated by a central reader, blinded to the subject's treatment assignment, to assess liver fat and liver volume.

All subjects may be required to fast for at least 4 hours before the MRI assessment.

Subjects with a qualifying Baseline MRI (at least 10% liver fat assessed by MRI-PDFF via central reviewer) will return to clinic for Run-In Week -1 Visit. If it is not possible for MRI results to be available by this visit or if it needs to be repeated, the MRI results must be available for final qualification prior to randomization. Failure to reach eligibility criteria of liver fat content by MRI is considered a screen failure and will not be repeated.

6.1.2.2 Run-In Week -1

At this visit, final qualification assessments will be conducted and confirmed according to Appendix A including body weight and FPG assessments. Subjects will maintain their routine diet and exercise routine and continue to take their OAD daily during this period. Substantial changes in either one of these activities could have an impact on liver fat content and should be avoided during study participation.

6.1.2.2.1 FPG and Body Weight Eligibility Assessments (Week -1)

Patients will be required to visit the clinic for FPG and body weight measurements in both the Screening Period (Wk-6 - Wk-4) and Run-In Period (Week -1). The FPG central lab results and

body weight clinic assessment from these 2 visits (at least 3 weeks apart) will be compared to assess the patient's eligibility for randomization.

- If a > 40 mg/dL (2.2 mmol/L) FPG reduction is observed (and confirmed with a retest) from the screening result to the Run-In Week-1, the patient cannot be randomized (Exclusion Criteria #16). If a patient is not randomized due to an observed > 40 mg/dL (2.2 mmol/L) drop in fasting glucose, the patient may be eligible for rescreening after 6 weeks have elapsed
- If a reduction in body weight of 2 kg (4.4 lbs) (and confirmed with a retest) from the screening result to the Run-In Week -1, the patient cannot be randomized (Exclusion Criteria #17)

6.1.2.2.2 SC Tolerance Assessment

To reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will confirm tolerance of SC administration of 0.9% saline prior to randomization. This injection will follow the same procedures as the injection of the Study Drug (ISIS 484137 or placebo) during the treatment period. Specifically, at any visit during the Screening or Run-In Period subjects will receive 1 SC injection of 1.25 mL of 0.9% saline (may also be delivered as 2 non-contiguous injection volumes such as 0.75 mL and 0.50 mL).

When the Screening and Run-In results are available thru Week -1, individuals will be notified of their eligibility. Qualified patients will be randomized and will proceed to the Treatment Period with Week 1, Day 1 Assessments.

6.1.3 Treatment Period (Weeks 1-13)

Enrolled subjects will be administered ISIS 484137 or placebo once each week for a total of 13 weeks of treatment. Once-weekly SC administration will occur during the visits. At each visit, subjects will be reminded to retain the same diet and exercise regimen as was followed during the Screening and Run-In Period. Substantial changes in either one of these activities could have an impact on liver fat content and should be avoided during study participation. Subjects will continue to take their OAD daily during this period.

Safety and clinical laboratory evaluations will be performed on a weekly basis. Vital signs, BP assessments, AEs and concomitant usage will be assessed during clinic visits. Other assessments will be conducted during the Treatment Period in less frequent intervals as indicated in Appendices A, B, and C include ECG, drug/alcohol screening, HbA1c, FPG, lipid panel, insulin, hsCRP, TSH, exploratory markers and PK. Any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or designee. Any questions on study procedures and visit windows may be directed to the Sponsor (or designee).

Early termination patients from the Treatment Period will be required to complete their study termination evaluations following the PT1 study procedures (see Appendix A). The timing of the Post-Treatment MRI for early termination patients from the Treatment Period is outlined in Section 6.1.4. All patients receiving at least 1 dose of study medication are required to enter the Post-Treatment Period for continuing safety evaluations.

6.1.4 Post-Treatment Period (PT 1-13)

After completing the 13 weeks of the Treatment Period, including subjects who discontinue early from the Treatment Period, subjects will return for post-treatment follow-up evaluation visits as indicated in Appendix A. All subjects will be followed for 13 weeks until the PT13 visit. During the Post-Treatment Period from PT 1- 4 (weekly visits), a visit window of ± 3 days is permitted, whereas for visits PT 6-13 a visit window of ± 7 days is permitted. Safety and clinical laboratory evaluations as well as PD markers, including those for PK analysis, will be performed as indicated in Appendices A, B, and C. Any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or designee. At each visit, subjects will be reminded to retain the same diet and exercise regimen as was followed during the Screening and Run-In Period. Subjects will continue to take their OAD daily during this period.

A Post-Treatment MRI (See Section 6.1.2.1) to assess liver fat content and volume will occur during PT2 Visit (2 weeks after last dose) for all subjects completing 13 doses. For subjects who terminate from the treatment period early, the timing and conduct of the MRI in the Post-Treatment Period will be adjusted as follows (+/- 7-day window). The timing of the Post-Treatment MRI should be discussed with the Ionis Study Team but may be scheduled as follows:

i. Subject received 4 or less doses, the Post-Treatment MRI Assessment will not be required

ii. Subject received 5-9 doses, the Post-Treatment MRI Assessment will occur 2 weeks after last dose at the PT2 Visit

iii. Subject received 10-12 doses, the Post-Treatment MRI Assessment will be scheduled as follows:

- If subject received 10 doses, subject moves into Post-Treatment Period, the MRI will be conducted 5 weeks after the last dose
- If subject received 11 doses, subject moves into Post-Treatment Period, the MRI will be conducted 4 weeks after the last dose
- If subject received 12 doses, subject moves into Post-Treatment Period, the MRI will be conducted 3 weeks after the last dose

Early termination patients from the Post-Treatment Period (ET PT) will be required to complete their End-Of-Study evaluations following the ET PT 12 Visit study procedures (see Appendix A).

6.2 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. Blood chemistry and urine samples should be taken after fasting for at least 8 hours. During the fasting period, the subject can drink water and they should ensure that they consume sufficient water to not become dehydrated.

If during the treatment period, a platelet, creatinine, or ALT result is uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) the test must be repeated and a result not meeting stopping rule must be obtained prior to next dose.

6.3 Restriction on the Lifestyle of Subjects

6.3.1 Contraception Requirements

Male subjects must refrain from sperm donation and either be abstinent† or, if engaged in sexual relations with a female of child-bearing potential, they must use effective barrier contraception with their partner from the time of signing the informed consent form until at least 13 weeks after their last dose of Study Drug. Effective contraception includes a vasectomy with negative semen analysis at Follow-up, or the use of condoms together with spermicidal foam/gel/film/cream/suppository. Male subjects engaged in sexual relations with a female of child-bearing potential must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment. Effective contraception 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 subjects with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

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

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

6.3.2 Fasting Requirements

All subjects will be required to fast for at least 8 hours before each study visit.

6.3.3 Lifestyle Restrictions

Subjects are instructed to refrain from alcohol containing beverages at least 48 hours prior to a clinic visit and should not increase alcohol consumption during the study. Additionally, subjects are requested to maintain a stable diet and exercise regimen throughout the study.

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 484137 or Placebo) characteristics are listed in Table 1.

The Study Drug (ISIS 484137 or Placebo) is contained in 2 mL stoppered glass vials. The Study Drug (ISIS 484137 or Placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 484137 or placebo) must be stored securely at 2-8 °Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	ISIS 484137	Placebo
Strength	200 mg/ mL	Not Applicable
Volume/Formulation	1 mL solution per vial	1 mL solution per vial
Route of Administration	SC	SC

* SC = subcutaneous

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 484137 or placebo) labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 484137 or placebo) supplies provided by the Sponsor.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

Study Drug administration will occur at weekly study visits from Week 1 through Week 13 by the trained personnel at the study site. ISIS 484137 or placebo will be administered subcutaneously. Study Drug (ISIS 484137 or placebo) SC injection volume will be 1.25 mL at each weekly visit (may also be delivered as 2 non-contiguous injection volumes such as -0.75 mL and 0.50 mL). Vials are for single use only.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug (ISIS 484137 or placebo) preparation and administration.

8.2 Other Protocol-Required Drugs

0.9% sterile saline will be used for a SC tolerability injection. At any visit during the Screening or Run-In Period, subjects will receive a 1.25 mL SC injection (may also be delivered as 2 non-contiguous injection volumes such as 0.75 mL and 0.50 mL).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4 Treatment Precautions

There are no specific treatment precautions required.

8.5 Safety Monitoring Rules

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

Baseline is defined as the average of week -1 visit (Day -7) and Day 1 pre-dose values.

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.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. 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 (ISIS 484137 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described in Appendix D are met, the subject will be permanently discontinued from further treatment with Study Drug (ISIS 484137 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the Protocol.

8.5.1 Safety Monitoring Rules 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.

In the event of an ALT or AST measurement that is > 3 x ULN: (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Subjects 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) should have their liver chemistry tests (ALT, AST, alkaline phosphatase [ALP], INR, and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For subjects 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] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], HCV antibody, cytomegalovirus [CMV] IgM, and Epstein-Barr virus [EBV antibody panel])
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

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

8.5.2 Safety Monitoring Rules for Platelet Count Results

If a subject's platelet count falls by 30% or greater from Baseline or the absolute platelet count is 100,000/mm^3 or less, then the subject's platelet counts should be monitored at least weekly. In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted (Table 2). The frequency of monitoring and additional lab tests will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee.

Table 2 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

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) Complete blood count (CBC) with reticulocytes and mean platelet volume (MPV)
Fibrinogen
von Willebrand factor
Total globulins, total immunoglobulin A (IgA), IgG and IgM
Complement: total C3, total C4, Bb, C5a
CRP measured by high sensitivity assay (hsCRP)
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)

Table 2 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3 *Continued*

To Be Performed at Central Lab
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 (if available)

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

8.5.3 Monitoring Rules for Deteriorating Glycemic Control

If after 8 weeks of treatment with Study Drug (ISIS 484137 or placebo), FPG levels > 270 mg/dL (or > 15 mmol/L) confirmed on 2 consecutive weekly study visits with no other explanation(s) for the elevation, additional oral glucose-lowering therapy may be started or previous therapies may be titrated up by the Investigator in consultation with the Sponsor Medical Monitor or designee. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy (e.g., insulin, GLP1 analogs) is not permitted. See Dose Adjustment Guidance in Section 8.7.

8.6 Stopping Rules

For the purposes of the stopping rules baseline is defined as the average of Day -7 and Day 1 values.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently; values that are not confirmed due failure to retest or missing lab values will be presumed confirmed:

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) with 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, and/or concomitant eosinophilia (> ULN)

8.6.2 Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a subject with Study Drug (ISIS 484137 or placebo) may be stopped temporarily:

1. Serum creatinine increase that fulfills all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) increase and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)

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 Rule for Platelet Count Results

In the event of a confirmed platelet count less than 75,000/mm^3, and in the presence of major bleeding (MB) or clinically-relevant non-major bleeding (CRNMB) (defined below; Schulman et al. 2005), dosing of a subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently. Furthermore, additional laboratory investigations will be conducted as outlined in Table 2. 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 a confirmed platelet count less than 50,000/mm^3, dosing of a subject with Study Drug (ISIS 484137 or placebo) 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 or designee.

Definitions:

Major bleeding (MB) is defined as one of the following:

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

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

8.6.4 Stopping Rules for Documented Severe Hypoglycemia

In the event of a documented severe hypoglycemic event as defined below, dosing of the subject with Study Drug (ISIS 484137 or placebo) will be stopped permanently. Also, if the Investigator considers a hypoglycemic event as clinically-significant, he/she may stop dosing at any time. Any subject with a clinically-significant event of hypoglycemia should be discussed with the Sponsor Medical Monitor or Designee.

A documented severe hypoglycemic event is defined as one in which the subject requires assistance of another person to obtain treatment for the event and has a plasma glucose level < 60 mg/dL (3.3 mmol/L). This may include treatment with IV glucose or buccal or intramuscular glucagon.

All subjects participating in the trial must be instructed to recognize the characteristic symptoms of hypoglycemia and receive detailed instructions from the Investigator on the treatment and reporting of hypoglycemic events.

The symptoms of hypoglycemia can be divided into 2 categories, neuroglycopenic and neurogenic (or autonomic) responses.

- Neuroglycopenic symptoms are the direct result of central nervous system neuronal glucose deprivation and include behavioral changes (dizziness, headaches, cloudy vision, confusion, abnormal behavior, loss of consciousness, and seizures)
- Hypoglycemia-induced neurogenic (autonomic) responses are those related to increased adrenergic activity (sweating, tremor, tachycardia, anxiety, and hunger)

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

8.7 Adjustment of Oral Antidiabetic Regimen for Subjects with Persistent Hyperglycemic

If after 8 weeks of treatment with Study Drug (ISIS 484137 or placebo), FPG levels > 270 mg/dL (or > 15 mmol/L) confirmed on 2 consecutive weekly study visits with no other explanation(s) for the elevation, additional oral glucose-lowering therapy may be started or existing therapies may be titrated in dose by the Investigator in consultation with the Sponsor Medical Monitor or designee. The use of thiazolidinediones (e.g., pioglitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, GLP1 analogs).

8.8 Discontinuation of Study Drug

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an AE that necessitates permanent discontinuation of Study Drug

- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.4
- The subject experiences an AE that necessitates unblinding of the Investigator or Sponsor to the subject's treatment assignment
- Initiation of chronic disallowed therapies which include the use of thiazolidinediones (e.g., piogitazone, rosiglitazone) and injectable antidiabetic therapy (e.g., insulin, GLP1 analogs), use of agents (including herbal or over-the counter weight loss preparations) and medications known to significantly impact body weight (e.g., sibutramine, phenetamine and orlistat)

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

Subjects who discontinue Study Drug should be encouraged to remain in the study and complete the Post-Treatment Evaluation Period and continue protocol required tests and assessments. Every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

8.9 Withdrawal of Subjects from the Study

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

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

Other reasons for withdrawal of subjects from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF as appropriate.

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

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF as appropriate.

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 the signing of the informed consent and the last protocol specified Post-Treatment Evaluation Period (Appendix A).

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy. In the Post-Treatment Period, anti-diabetic agents may be added or altered for deteriorating glycemic control in consultation with the Investigator and Sponsor Medical Monitor.

Disallowed Concomitant Therapy

The use of thiazolidinediones (e.g., piogitazone, rosiglitazone) and injectable antidiabetic therapy is not permitted (e.g., insulin, GLP1 analogs) while on Study Drug. In case a short-term insulin therapy is given when a patient is hospitalized during the study, the Investigator needs to consult with the Sponsor Medical Monitor or designee to evaluate whether the patient will be allowed to continue the study. Use of agents (including herbal or over-the counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior (e.g., sibutramine, phenetamine and orlistat) is not permitted while on Study Drug.

Initiating a new statin or increasing therapy is not permitted. Fish oils or prescription lipid-regulating drugs (e.g., bile acid analogues [e.g., obeticholic acid or ursodeoxycholic acid], bile-acid sequestering resins, fibrates and derivatives) are not permitted. If additional statin therapy or other lipid lowering therapies are required, the Investigator should discuss with the Medical Monitor whether the subject must discontinue Study Drug.

Chronic use of systemic corticosteroids and other medications, per Investigator, known to cause liver toxicity (e.g., chronic acetaminophen use) or cause steatosis (e.g., amiodarone, methotrexate) are not permitted while on Study Drug.

New or increased use of anticoagulants/antiplatelet agents (e.g., warfarin, heparin, dabigatran, rivaroxaban, clopidogrel) unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed; use of the non-steroidal anti-inflammatory drug (NSAID) nimesulide or any other drug influencing coagulation (except low dose aspirin ≤ 160 mg/day and other short acting NSAIDS with a half-life < 20 hours) are not permitted while on Study Drug.

Antineoplastic agents are not permitted while on Study Drug.

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 the informed consent and the last protocol-specified Post-Treatment Evaluation visit (Appendix A)

8.11 Treatment Compliance

Compliance with Study Drug dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the Safety Management Plan and the Medical Monitoring Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

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

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations.

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

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee 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 serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

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

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

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

9.4 Monitoring and Recording Adverse Events

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

9.4.1 Serious Adverse Events

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

subject signs the informed consent form and stop at the end of the subject's follow-up period which is defined as Study Week PT13 (Section 3.4.3). When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. The SAE should be reported using electronic SAE reporting form by scanning and emailing the form to INCDrugSafety@incresearch.com. If the electronic submission is unavailable, an Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee. The fax number for reporting SAEs can be found in the Study Reference Manual.

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

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as 13 weeks after the last dose (Study Visit PT13), see Section 3.4.3. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 484137 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 484137 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 484137 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

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

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

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

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drug (ISIS 484137 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 484137 or placebo) administration and dose
- **Permanently Discontinued:** Study Drug was discontinued and not restarted
- **Temporarily Interrupted, Restarted:** Dosing was temporarily interrupted or delayed due to the AE and restarted

9.4.3.4 Treatment Given for Adverse Event

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

9.4.3.5 Outcome of the Adverse Event

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

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

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

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

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

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

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

9.5.3 Dosing Errors

Study Drug (ISIS 484137 or placebo) errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject takes a dose of Study Drug (ISIS 484137 or placebo) that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

There has been no occurrence of an ASO overdose in man from completed or ongoing clinical studies with ASOs.

9.5.4 Contraception and Pregnancy

Female subjects of childbearing potential are excluded from this study.

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

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

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

The progress of the pregnancy of a male subject's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records to obtain additional information.** Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Safety Endpoints

The safety and tolerability of ISIS 484137 will be accessed by determining the incidence and severity of AEs and will be evaluated by reviewing:

- AEs (including bleeding events)
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Coagulation parameters
- Use of concomitant medications

10.1.2 Primary Pharmacodynamic Endpoint

The primary PD endpoint is the absolute change in liver fat percentage as quantified by MRI-PDFF from Baseline MRI to Post-Treatment MRI.

10.1.3 Secondary Endpoints

Secondary endpoints include:

- Relative percent change in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Proportion of subjects with ≥ 30% relative reduction in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Percent change in liver volume from Baseline MRI to Post-Treatment MRI
- Percent change in plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL) from Baseline to the average of the Post-Treatment values assessed 1 and 2 weeks after the last dose (PT1 and PT2 Visits)
- Percent change in parameters of hepatic IR (FPG, insulin, and HOMA-IR) from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)
- Absolute change in HbA1c from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)

10.1.4 Exploratory Endpoints

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10.2 Sample Size Considerations

Approximately 45 subjects will be randomized (2:1 allocation ratio). With 45 subjects there will be > 90% power to detect a of 5% difference in mean absolute change in liver fat as measured by PDFF between the active and placebo groups with a 2-sided alpha of 0.05, assuming a common standard deviation of 4% and 25% non-completers.

The 5% effect size was selected based on clinical relevance with evidence that 5% PDFF reduction identified subjects with reduced steatosis grade in NASH subjects (Middleton et al. 2017).

10.3 Populations

Randomized: All subjects who are randomized into the study regardless of whether they received Study Drug.

Per-Protocol Population: Will include the subset of the Randomized Population who have received at least 10 of the prescribed doses and must receive the first 4 doses in the first 5 weeks, cannot miss 3 consecutive weekly doses and no significant protocol deviations that would be expected to impact efficacy.

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

PK Population: All subjects who have received at least 1 dose of active Study Drug (ISIS 484137), and have at least 1 PK sample collected and analyzed with evaluable results.

10.4 Definition of Baseline

- Baseline MRI hepatic fat content and volume will be from the MRI prior to and closest to randomization
- Baseline for plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL), exploratory biomarkers of DGAT2 activity (SCD-1), and biomarkers of inflammation (e.g., CK18, haptoglobin) and assessments for IR (FPG, insulin, HOMA IR) will be the average of week -1 visit (Day -7) and Day 1 pre-dose assessments
- Baseline for platelets, creatinine, ALT and AST will be the average of week -1 visit (Day -7) and Day 1 pre-dose assessments
- Baseline for HbA1c and for other routine clinical assessments of chemistry and hematology, PK assessments, vital signs and ECG for the study will be the last non-missing value prior to the first administration of Study Drug will be the last non-missing value prior to the first administration of Study Drug (ISIS 484137 or placebo; Appendix A).

10.5 Interim Analysis

No interim analysis is planned. However, during the study, an unblinded interim analysis may be conducted to assess the safety, PK/PD, and exploratory efficacy of the results. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study. Details of these controls will be described in the Statistical Analysis Plan (SAP).

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 subject data listings. Subject data listings will be presented for all subjects enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% type I error rates unless otherwise stated.

The efficacy and PD endpoints will be assessed on the Randomized Population and Per-Protocol Population. The safety analyses will be performed on the Safety Population.

10.6.1 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. Subject randomization will be summarized by cohort and treatment group. The subject disposition will be summarized. All subjects enrolled will be included in a summary of subject disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug (ISIS 484137 or placebo) received will be summarized by treatment group. Subject incidence rates of all AEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA™) system organ class, and by MedDRA™ term. Tables and/or narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug (ISIS 484137 or placebo) will be summarized.

Laboratory tests to ensure subject safety including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 484137 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

Physical examination data will be provided in the data listing. Concomitant medications will be coded using World Health Organization (WHO) Drug dictionary and summarized by treatment, ATC class and generic name.

10.6.3 Pharmacokinetic Analysis

For all evaluable subjects receiving ISIS 484137, plasma ISIS 484137 concentrations at trough during the Treatment Period and concentrations observed during the Post-Treatment Evaluation Period will be listed by dose, study day, time point, and summarized using descriptive statistics. Additional details regarding the PK analysis will be described in the SAP.

Potential relationships between selected PD and plasma exposure measures (e.g., trough concentrations) may also be explored, where deemed appropriate.

10.6.4 Pharmacodynamic/Efficacy Analysis

MRI results will be summarized and tabulated based on PDFF reductions from Baseline absolute and relative reductions and liver volume. Details of planned analysis of efficacy endpoints included PD endpoints will be provided in the SAP.

10.6.5 Additional Analyses

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11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 484137 or placebo) are administered. The subject or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

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

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

11.2 Ethical Conduct of the Study

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

11.3 Independent Ethics Committee/Institutional Review Board

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

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

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

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

11.4 Subject Confidentiality

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

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

12.3 Study Documentation and Storage

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, 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 the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

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

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

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

12.4 Study Monitoring

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

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

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 CRFs, are resolved.

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

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

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, 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 and Trade names are acceptable. Combination medications should be recorded using their trade name in English if possible.

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period	Screen	Run-In		Treatment												
Study Week	Wk -6 thru Wk -5	Wk -4 thru Wk -3	Wk -1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13
Study Day	S-42 thru S-29	D-28 thru D-15	D-7 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window (+/- days)		A	3	2												
Informed Consent	X															
Inclusion/Exclusion	X		X	X												
Medical History	X															
Physical Exam[1]	X			X					X							
Height, Body Weight and BMI[2]	X		X[7]	X					X							X
Waist/Hip Circumference	X			X					X							X
Vital Signs[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12–lead) in triplicate[15]	X			X[6]					X							
FSH[4]/ Serum Pregnancy[5]	X															
HIV, Hepatitis B & C	X															
Drug/Alcohol Screen	X		X[7]						X							
Chemistry Panel (Fasting)[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[8]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including P/C)[9]	X			X	X	X	X	X	X	X	X	X	X	X	X	X
PT/aPTT/INR	X															
HbA1c	X			X					X							
Fasting Plasma Glucose (FPG)[10]	X		X[7]	X		X			X			X			X	

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Run-In		Treatment												
Study Week	Wk -6 thru Wk -5	Wk -4 thru Wk -3	Wk -1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13
Study Day	S-42 thru S-29	D-28 thru D-15	D-7 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window (+/- days)		A	3	2												
Lipid Panel (serum, fasting)[10]			X	X					X			X				
Insulin (fasting)[10]			X	X					X			X				
hsCRP				X					X							
TSH	X			X					X							
Triodthyronine (T3)	X															
Thyroxine (T4) (serum)	X															
Exploratory Markers			X	X					X			X				
Archived Samples[11]				X					X			X				
PK Sampling[12]				X	X		X		X		X	X	X		X	X
Hepatic Fat Content (MRI)		X														
SC Tolerability Assessment[16]	←	—	→													
Study Drug Administration				X	X	X	X	X	X	X	X	X	X	X	X	X
OAD Administration[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary and Exercise Maintenance	X		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
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[14]					X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

Study Period	Post-Treatment Period (13 Weeks)							
Study Week	ET/PT1	PT2	PT3	PT4	PT6	PT8	ET PT12	PT13
Study Day	D92	D99	D106	D113	D127	D141	D169	D176
Visit Window (+/- days)	3				7			
Physical Exam[1]	X	X		X			X	
Body Weight and BMI[2]	X	X		X			X	
Waist/Hip Circumference	X	X		X			X	
Vital Signs[3]	X	X	X	X	X	X	X	
Blood Pressure (BP)	X	X	X	X	X	X	X	
ECG (12–lead) in triplicate[15]	X		X					
PK Sampling	X	X		X	X		X	
Archived Sample	X	X		X			X	
Chemistry Panel (serum, fasting)	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Urinalysis (including P/C ratio)[9]	X	X	X	X	X	X	X	
HbA1c (serum)	X	X		X		X		
Lipid Panel (serum, fasting)[10]	X	X		X				
Insulin (plasma, fasting)[10]	X	X		X				
Fasting Plasma Glucose (FPG)[10]	X	X	X	X	X	X	X	
hsCRP (serum)	X			X				
TSH (serum)	X						X	
Serum Pregnancy[5]								
Exploratory Markers	X	X		X			X	
Hepatic Fat Content (MRI)		X[B]						
OAD Administration[13]	X	X	X	X	X	X	X	X
Dietary & Exercise Maintenance	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Phone Contact[14]	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

Legend Text

1. Full physical exam to be given at Screening and abbreviated physical exam to be given during treatment and follow-up period as indicated to assess changes from Screening
2. Height assessed at Screening visit only
3. HR, respiratory rate (RR), temp
4. FSH: Required as confirmation of post-menopausal status for all women ≤ 55 years who have 12 months of spontaneous amenorrhea with no alternative medical cause, and who are not surgically sterile
5. Women who are not surgically sterile
6. Assessments conducted at pre-dose, 1 hr. and 2 hrs. post-dose
7. Results required prior to randomization
8. If during the treatment period, a platelet, creatinine, or ALT result is uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) the test must be repeated and a result not meeting stopping rule must be obtained prior to next dose
9. Preferably collect specimen for analysis from the subject's second void of the day
10. Fasted samples should be taken after fasting for at least 8-10 hours. During this time the subject can drink water and they should ensure that they consume sufficient water in order to not become dehydrated
11. Stored at -70 (± 10) °C for follow-up exploration
12. During the treatment period, PK samples are collected pre-dose. During the Post-Treatment Period, PK samples are collected any time. See Appendix C
13. OAD doses are to be self-administered daily by the subject throughout the study
14. If subject is absent from a clinic visit, a phone contact will be attempted to assess AE and conmeds
15. Triplicate ECG study procedure will consist of 3 ECGs with 2 minutes between each ECG (-1/+2 mins window between each assessment), except as noted for footnote # 6 where pre-dose, 1 hrs and 2 hrs post- ECGs are to be performed
16. SC Tolerability Assessments can be conducted at any visit during the Screening or Run-In Periods

Notes:

All assessments should be collected pre-dose unless indicated otherwise.

Notes Regarding Timing of MRI Assessments:

A Magnetic Resonance Imaging (MRI) Assessment Windows

Baseline MRI Assessment: Week -4 or -3 (Day -28 to Day -14) + 7 days

Post-Treatment MRI Assessment: Week of PT 2 Visit (Days 99 to Day 105) +/- 7 days

B A Post-Treatment MRI to assess liver fat content and volume will occur during the week of PT2 Visit for all subjects completing 13 doses. The timing of the Post-Treatment MRI should be discussed with the Ionis Medical Monitor. For subjects who terminate from the treatment period early, the timing and conduct of the MRI in the Post-Treatment Period will be adjusted as follows:

i. Subject received 4 or less doses, the Post-Treatment MRI Assessment will not be required

ii. Subject received 5-9 doses, the Post-Treatment MRI Assessment will occur 2 weeks after the last dose during the week of the PT2 Visit. (+/- 7 days)

iii. Subject received 10 -12 doses, the Post-Treatment MRI Assessment will be scheduled as follows:

Number of Doses Received	Post-Treatment MRI Assessment
10	5 weeks after last dose (+/- 7 days)
11	4 weeks after last dose (+/- 7 days)
12	3 weeks after last dose (+/- 7 days)

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 484137 or other similar oligonucleotides

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

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

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

PD Panel
- Fasting Glucose
- Insulin
- HbA1c

Fasting Lipid Panel
- Triglycerides
- Total Cholesterol
- ApoB
- VLDL cholesterol
- LDL cholesterol
- HDL cholesterol
- Non-HDL cholesterol

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

Thyroid Panel
- TSH
- Free T4
- Free T3

Pharmacokinetics[1]
- ISIS 484137 levels in plasma

Exploratory[3]
adiponectin
SCD-1
CK18
haptoglobin
leptin

Inflammatory
- hs-CRP [3]

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

Other[1]
- Archived serum samples

1 Serum and plasma PK samples may also be used for metabolomics/lipidomics assessments, profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assay development/testing, or to assess other actions of ISIS 484137 with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

3 Samples will be collected however may not be analyzed

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Treatment Period								
W1	W2	W4	W6	W8	W9	W10	W12	W13
D1	D8	D22	D36	D50	D57	D64	D78	D85
Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose

Post-Treatment Period (13 Weeks)				
ET/PT1	PT2	PT3	PT6	PT12
D92	D99	D113	D127	D169

Blood sample can be drawn anytime during the visit

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

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

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

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

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

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

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

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

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

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

Statistical Analysis Plan

ISIS 484137–CS2

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2Rx, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks in Adult Patients with Type 2 Diabetes

Date: September 6, 2018

Version: 1.0

Statistical Analysis Plan Signature Page

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court Carlsbad, CA 92010

Compound Name: ISIS 484137

Protocol: ISIS 484137-CS2

Study Title: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2RX, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks in Adult Patients with Type 2 Diabetes

Protocol Version: 23 March 2018 (Protocol Amendment 1)

Signature: PPD Date: September 6, 2018

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Table of Contents

1 INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

1.1 Study Overview

This is a Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study in subjects with type 2 diabetes and evidence of hepatic steatosis seen on MRI scan. Approximately 45 subjects are planned to be randomized in this study, subjects will be randomized in a 2:1 ratio to receive SC treatment with either ISIS 484137 250 mg or placebo. Randomization will be stratified based on liver fat content results from the baseline MRI conducted in the Run-In Period (< 20% or ≥20%).

The study will consist of Screening and Run-in, Treatment, and Post-Treatment Periods. The expected duration of the study will be up to 2 weeks of Screening, up to 4 weeks of Run-In, 13 weeks of Study Drug dosing, and 13 weeks of post-treatment evaluations, for a total of up to 32 weeks of participation.

1.2 Objectives

1.2.1 Primary Objectives

The primary objectives are:

1. To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with type 2 diabetes mellitus (T2DM)

2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM

1.2.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver fat (percent relative reduction and percent of subjects with ≥30% relative reduction) assessed by MRI-PDFF

2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on liver volume assessed by MRI-PDFF

3. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on plasma lipoprotein profile (triglycerides [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], very low density lipoproteins [VLDL], high density lipoprotein [HDL] and Non-HDL)

4. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on insulin resistance (IR) and glucose control (insulin, glucose, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c])

1.2.3 Exploratory Objectives

CCI

1.3 Planned Method of Analysis

1.3.1 Safety Endpoints

The safety and tolerability of ISIS 484137 will be accessed by determining the incidence and severity of AEs and will be evaluated by reviewing:

- AEs
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Coagulation parameters
- Use of concomitant medications

1.3.2 Primary Pharmacodynamic Endpoint

The primary PD endpoint is the absolute change in liver fat percentage as quantified by MRI-PDFF from Baseline MRI to Post-Treatment MRI.

1.3.3 Secondary Endpoints

Secondary endpoints include:

- Relative percent change in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Proportion of subjects with ≥30% reduction in liver fat percentage from Baseline MRI to Post-Treatment MRI
- Percent change in liver volume from Baseline MRI to Post-Treatment MRI
- Percent change in plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL) from Baseline to the average of the Post-Treatment values assessed 1 and 2 weeks after the last dose (PT1 and PT2 Visits)
- Percent change in parameters of hepatic IR (FPG, insulin, and HOMA-IR) from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)
- Absolute change in HbA1c from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit)

1.3.4 Exploratory Endpoints

CCI

2 PROCEDURES

2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Laboratory data will be transferred electronically from Medpace Reference Laboratories to Ionis Pharmaceuticals, Inc. Hepatic fat content and volume will be transferred electronically from Medpace Imaging Core Lab to Ionis Pharmaceuticals, Inc.

2.2 Randomization & Treatment Allocation

Subjects will be randomized after all Screening and Run-In assessments through Week -1 have been completed and after the Investigator has verified that they are eligible per inclusion and exclusion criteria. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

All subjects will be randomized using an automated system (CCI). Subjects will be stratified based on liver fat content results from the MRI conducted in the Run-In Period (< 20% or ≥20%), and then subjects will be randomized in a 2:1 ratio to receive SC treatment

with either ISIS 484137 250 mg or placebo. The randomization list will be prepared by an independent external vendor.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to study site.

2.5 Data Management

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

2.5.1 Case Report Form Data

CCI (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data are entered,

reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets.

2.5.3 Pharmacokinetic Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma drug concentration data. The review process involves reconciling the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The final PK data will be stored as CSV and/or Excel files. Final data, which has been approved by Quality Assurance, will be stored in the Sponsor's document management system.

3 ANALYTICAL PLAN

3.1 General Overview of Analyses

3.1.1 General Statistical Methods

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the subject data listings. Subject data listings will be presented for all subjects enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% type I error rates unless otherwise stated. Both central and local lab data will be used in platelet analyses, including by visit summaries/figures and abnormality summary. For other lab tests, only central laboratory data will be used.

PK parameters will be summarized using number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

Individual patient data will be listed.

Baseline definition:

- Baseline MRI hepatic fat content and volume will be from the pre-dose MRI prior to and closest to randomization.

- Baseline for fasting plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL), exploratory biomarkers of DGAT2 activity (SCD-1), and biomarkers of inflammation (e.g., CK18, haptoglobin) and fasting assessments for IR (FPG, insulin, HOMA IR) will be the average of Week -1 visit and Day 1 pre-dose assessments, and any measurements between the 2 visits
- Baseline for platelets, creatinine, ALT and AST will be the average of Week -1 visit and Day 1 pre-dose assessments, and any measurements between the 2 visits
- Baseline for HbA1c and for other routine clinical assessments of chemistry and hematology, PK assessments, vital signs, weight, BMI, waist and hip circumference for the study will be the last non- missing value prior to the first administration of Study Drug
- For ECG, baseline will be defined as the last non- missing value prior to the first administration of Study Drug. If more than one time point or triplicate are taken on Day 1 pre-dose, baseline for numeric results will be defined as the average of all non-missing assessments on this day; Baseline for character results will be defined as the worst results of all values on this day.

Analytical visits:

All post-baseline data will be summarized using the visit labels provided in the data. Multiple results per subject with the same visit label will be averaged for continuous variable and the worst case result will be used for categorical variable. Results with visit labels as "Unscheduled" will not be included in the by-visit summary tables and figures except for determining baseline, but will be presented in data listings.

3.1.2 Populations

The following populations will be used in this study, and any exclusion of patients from the populations will be documented and decided upon by appropriate medical, clinical, data management, and statistical personnel at Ionis Pharmaceuticals prior to unblinding.

Randomized Population

All subjects who are randomized into the study regardless of whether they received Study Drug.

Per Protocol Population:

The subset of the Randomized Population who have received at least 10 of the prescribed doses and must receive the first 4 doses in the first 5 weeks, cannot miss 3 consecutive weekly doses and no significant protocol deviations that would be expected to impact efficacy.

Safety Population:

All subjects who are randomized and receive at least 1 dose of Study Drug

PK Population:

All subjects who have received at least 1 dose of active Study Drug (ISIS 484137), and have at least 1 PK sample collected and analyzed with evaluable results.

The efficacy and PD endpoints will be assessed on the Randomized Population and Per-Protocol Population. The safety analyses will be performed on the Safety Population.

In addition to the above analysis populations, it is recognized that some data displays will be provided for "All Screened" and "Screening Failures" patients but no data analysis will be executed in these populations except for the disposition table that includes all screened patients.

3.1.3 Sample Size Consideration

Approximately 45 subjects will be randomized (2:1 allocation ratio). With 45 subjects there will be > 90% power to detect a 5% difference in mean absolute change in liver fat as measured by PDFF between the active and placebo groups with a 2-sided alpha of 0.05, assuming a common standard deviation of 4% and 25% non-completers. The 5% effect size was selected based on clinical relevance with evidence that 5% PDFF reduction identified subjects with reduced steatosis grade in NASH subjects (Middleton et al. 2017).

3.1.4 Planned Interim Analysis

An unblinded interim analysis may be conducted to assess the safety, PK/PD, and exploratory efficacy of the results. If the interim analysis is conducted, it will be conducted by unblinded team members including a clinician and biostatistician who will not be associated with the direct conduct of the study after the unblinding occurs with interim analysis. The individuals involved in the unblinded interim analysis will be identified and documented at the time of unblinded interim analysis according to Ionis SOP.

The Investigator, study staff, patients, blinded monitors, and members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection.

3.1.5 Incomplete or Missing Data

In general, missing data values will not be imputed. Incomplete data handling rules will be described in the specified section if needed.

3.2 Demographic and Baseline Characteristics

Demographic and Baseline characteristics obtained before the first study drug administration will be summarized using descriptive statistics by treatment group for the Randomized

Population, the Per-protocol Population, and the Safety Population. Demographic including age, gender, ethnicity, race, weight, and body mass index (BMI). Baseline characteristics includes: liver fat percentage, fasting plasma lipoprotein profile (triglycerides, total cholesterol, LDL-C, apoB, VLDL, HDL, and Non-HDL), fasting assessments for IR (FPG, insulin, HOMA IR), HbA1C, and exploratory biomarkers of DGAT2 activity (SCD-1), and biomarkers of inflammation (e.g., CK18, haptoglobin) .

Age for each patient is defined as number of years between informed consent date and birth date.

For summarizing race, if multiple races are recorded in the database, then 'Multiple Race' is used in the summary table. The listing will display the specific race values.

Patient randomization and disposition will be summarized by treatment group. All patients enrolled will be included in the summary. The summaries will include: the total number of patients screened, randomized, dosed and included in each population, the number of patients completed treatment, the primary reason for terminating treatment, the number of patients completed post-treatment evaluation period, and the primary reason for terminating post-treatment evaluation period.

All protocol deviations will be listed. Protocol deviations will also be summarized by treatment group.

3.3 Safety Analyses

Safety analyses will be based on the safety population.

3.3.1 Exposure

Treatment duration, time on study, number of doses and amount and total volume of Study Drug (ISIS 484137 or placebo) received will be summarized by treatment group.

The treatment duration (days) for each patient is defined as last dose date - first dose date +1.

The time on study will be defined as the total number of days a patient is known to be followed on study calculated as follows:

Time on study = Last date on study – Date of first dose+ 1.

Where the last date on study is defined as the date of the latest visit with evaluation, or time of death from all available data for a given patient. Visits with refused or unable to contact are not visits with evaluation.

3.3.2 Adverse Events

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug and subsequently worsens, or is not present prior to receiving the first dose of study drug but subsequently appears.

If there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, the records will be compared in pair, and consider two cases, where the AE severity (mild/moderate/severe) will be compared between the two records in the pair. The 2 records will be chronologically ordered by AE start date and refer to the "first" and "second" AEs.

Case 1: The first AE record in the pair occurs before first dosing, and the second record occurs after dosing.

If the AE severity on the second record is worse than the severity on the first record, then only count the second AE as treatment-emergent. But, if the severity improves (second record severity is less severe than the first record severity), then neither record is counted as treatment-emergent.

Case 2: Both AE records in the pair occur after first dosing.

If the AE severity on the second record is worse than the severity on the first record, then count both records as treatment-emergent. But, if the severity improves, then only count the first record as treatment-emergent.

When counting the total number of treatment-emergent events, events linked together through change in severity will still be counted as separate events.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or complete missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class for:

- Any treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as "Related", "Possible", or missing relationship to study drug

- Any treatment emergent adverse events by severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported one or more events. Adverse events with missing severity will categorized as "Missing" for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

AEs that lead to study discontinuation or investigational drug discontinuation will be listed. Non-treatment emergent adverse event will be flagged in the data listing.

Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe Injection Site Erythema, Swelling, Pruritus, Pain or Tenderness that started on the day of injection, persisted for at least two days; or (B) any AE at the injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the injection site is the principal reason for discontinuation.

These events will be summarized using the MedDRA coding system, by preferred term. Patients with moderate, severe and any event will also be summarized. Discontinue due to AE at the injection site will be summarized separately.

Percentage of injections leading to those events will be summarized by preferred terms and overall using the descriptive statistics. Additionally, percentage of injections leading to events will be summarized by moderate, severe severity and overall discontinuation of study drug due to AE at injection site.

Percentage of injections leading to those events will be calculated as follows for each patient: (A/B)*100, where A=number of injections with an event, and B=total number of injections. Doses that are split across multiple injections are counted as a single injection.

Local cutaneous reactions at injection site will be listed.

Flu-like Reactions

Flu-like reactions will also be summarized using the MedDRA coding system, by preferred term.

Flu-like reactions are defined as either (A) flu-like illness or (B) Pyrexia or feeling hot or body temperature increased, plus at least two of the following: Chills, Myalgia, and Arthralgia, starting on day of injection or the next day.

Percentage of injections leading to flu-like reactions will be summarized by treatment group using the descriptive statistics.

Percentage of the injections leading to flu-like reactions will be calculated as follows for each patient: (A/B)*100, where A=number of injections leading to flu-like reactions, and B=total number of injections.

Flu-like reactions will be listed.

Bleeding Events

Treatment-emergent bleeding adverse events will be listed for patients who have platelet count reduction to < 75,000/mm^3. The bleeding events will be defined based on the Haemorrhages (SMQ) Export from MedDRA.

3.3.3 Laboratory Measurements

The following is the list of routine lab analytes that will be collected throughout the study:

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, serum glucose, blood urea nitrogen, creatinine, cholesterol, uric acid, total bilirubin, direct bilirubin, Indirect bilirubin, ALT, AST, alkaline phosphatase, creatinine kinase, GGT
- Hematology: red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC, and WBC differential (percentage and absolute) (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- Coagulation: aPTT, PT, INR
- Thyroid Panel: TSH, Free T4, Free T3
- Screening Tests: hepatitis B surface antigen, hepatitis C antibody, HIV antibody, FSH (women only, if applicable) and serum βhCG (women only). This data will only be displayed in patient listings.
- Inflammatory: hs-CRP.
- Urinalysis: color, appearance, specific gravity, PH, P/C Ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrate, microscopic examination (will be performed on abnormal findings unless otherwise specified).

Missing WBC differential absolute counts and percentages will be derived as needed:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophil counts and percentages are

missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

All lab data will be displayed in subject listings.

For platelet summaries, both central and local lab data will be used, including by visit summaries/figures and abnormality summary. For other lab tests, only central laboratory data will be used in the by-visit summaries/figures and abnormality summary. Local laboratory data will be provided in the listings only.

Chemistry, hematology, coagulation, and inflammatory will be summarized using descriptive statistics (n, mean, median, standard error, standard deviation, Q1, Q3, minimum, and maximum) by treatment group and study visit. Urinalysis data will only be listed.

For ALT and AST, the number and percent of subjects falling in each of the following categories based on the confirmed results will be tabulated by treatment group (a confirmed value is based on a consecutive lab value within 7 days. If that value is in the same or worse category the initial value is confirmed. If the consecutive value is in a better category then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days then the initial value is presumed confirmed. If there are multiple results on the same day, no matter from the same lab vendor or different lab vendors, then the worst value will be utilized in the analysis):

- ALT/AST > 3 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed

For platelet, the number and percentage of subjects falling in each of the following categories based on the confirmed results will be tabulated by treatment group: 100,000/mm^3 to <140,000/mm^3, 75,000 to <100,000/mm^3, 50,000 to <75,000/mm^3, 25,000 to <50,000/mm^3, 0 to <25,000/mm^3, decrease ≥30% and ≥50% of baseline, which is confirmed.

3.3.4 Vital Signs, Weight, BMI, Waist and Hip Circumference

Vital signs will include heart rate, respiratory rate, body temperature, and systolic and diastolic blood pressure. Summary tables will be created to present the descriptive statistics for vital sign values, weight, BMI, waist circumference, hip circumference, and waist to hip circumference ratio as well as the change and percent change from baseline at each study visits.

3.3.5 Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as adverse events. All physical examination data will be provided in a data listing.

3.3.6 12-Lead Electrocardiograms (ECG)

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTC (recorded from ECG machine).

Summary tables will be created to present the descriptive statistics for ECG parameters as well as the change and percent change from baseline at each study visits. The average of triplicates will be used in the summary.

For the categorical responses to overall interpretation, counts and percentages will be provided. For triplicates or multiple results, the worst case result will be used in the summary.

3.3.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug dictionary and summarized by ATC class, generic name and treatment group.

3.3.8 Ancillary procedures

Ancillary procedures will be provided in the listing.

3.4 Pharmacodynamic and Efficacy Analyses

3.4.1 Primary Analysis

The primary analysis will be the comparison of the absolute change in liver fat percentage between ISIS 484137 and placebo groups in the Per-protocol Population. The data will be summarized using descriptive statistics and analyzed using the ANOVA model with treatment and liver fat content stratification factor or van Elteren Test (if data departs substantially from normality, the nonparametric test, van Elteren Test, will be used), as appropriate. The normality will be tested by applying Kolmogorov-Smirnov test on the residuals. Numeric values will be rounded to 5 decimal places when applying Kolmogorov-Smirnov test. The primary analysis will be conducted when all patients complete the visit for Post-Treatment MRI.

3.4.2 Secondary Analysis

3.4.2.1 Secondary Analysis on the Primary Endpoint

As the secondary analysis of the primary endpoint, a similar analysis as the primary analysis will be repeated for the Randomized Population.

3.4.2.2 Analysis on the Secondary Endpoints

Percent change in liver fat percentage from Baseline MRI to Post-Treatment MRI will be summarized using descriptive statistics and analyzed in a similar way as the primary endpoint. The analysis will be conducted in both Per-protocol Population and Randomized Population.

The proportion of patients with ≥30% reduction in liver fat percentage from Baseline MRI to Post-Treatment MRI will be compared between ISIS 4841373 and placebo groups using the CMH test stratified by the stratification factor, the data will be analyzed in both Per-protocol Population and Randomized Population. In order to examine whether the response is consistent over a range of response thresholds, the analysis of proportion of patients with other response thresholds (e.g., 10%, 20%, 40%, 50%, etc.) will also be conducted.

The percent change in liver volume from Baseline to Post-Treatment assessment, percent change in fasting plasma lipoprotein profile from Baseline to the average of the Post-Treatment values assessed 1 and 2 weeks after the last dose (PT1 and PT2 Visits) and over time, percent change in fasting hepatic IR and absolute change in HbA1c from Baseline to the first Post-Treatment value assessed 1 week after the last dose (PT1 Visit) and over time will be summarized using descriptive statistics and analyzed in a similar way as the primary endpoint and the analyses will be conducted in both Per-protocol Population and Randomized Population. HOMA-IR will be calculated using the following formula:

HOMA-IR ($mM*mU/L^2$) = (fasting insulin concentration (μU/mL) * fasting plasma glucose (mg/dL) * 0.0555)/22.5

3.4.3 Exploratory Endpoints

CCI

3.4.4 Subgroup Analysis

To evaluate the consistency in the primary and selected secondary endpoints over baseline parameters, the following subgroup analyses will be performed in the Per-Protocol Set, if supported by data. The data will be analyzed using the ANOVA or Wilcoxon Rank Sum test, as appropriate. Additional subgroup analyses may be performed as needed.

- Baseline liver fat percentage stratum : <20%, ≥20%
- Baseline liver fat percentage : <median, ≥median
- Baseline HbA1c: <median, ≥median

- Baseline BMI: <median, ≥median

3.5 Pharmacokinetic Analysis

Pharmacokinetic (PK) analysis will be conducted in the PK Population. Plasma concentrations of ISIS 484137, along with the scheduled (nominal) and actual sampling times (i.e. time from SC dosing) will be listed (when applicable) for each patient by nominal day. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "BLQ"(below the limit of quantification). For the purpose of calculating descriptive statistics (n, mean, SD, SE, %CV, geometric mean, geometric %CV, median, minimum, and maximum for plasma concentrations) all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD, SE, and %CV will be reported as not applicable. PK concentration value(s) that are BLQ may be set at the LLOQ/2 to calculate geometric mean and geometric %CV. Summary statistics of the ISIS 484137 plasma concentrations will be tabulated by nominal day, and scheduled time point. At the discretion of the PK scientist and/or biostatistician, samples may be excluded from the summary descriptive statistics if there are large deviations between scheduled and actual sampling times.

Non-compartmental pharmacokinetic analysis of ISIS 484137 will be carried out on each individual subject plasma data set. Since only trough and post-treatment follow up PK samples will be collected, only the following PK parameters will be calculated:

- C_{trough}
- $t_{1/2\lambda z}$

Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Population PK and PKPD analysis may be performed using the PK and PD data from this study and/or combined with other ISIS 484137 clinical PK data later in the development timeline.